[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY NO. 1191]

REDUCTION PRODUCTS DERIVED FROM α-PHENACYLPYRIDINE[1]

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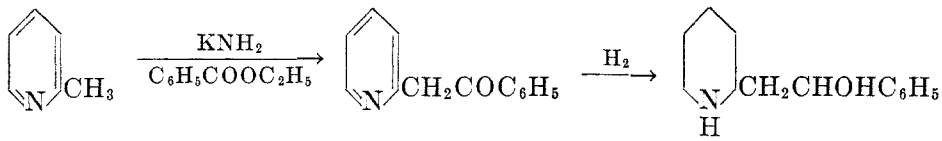
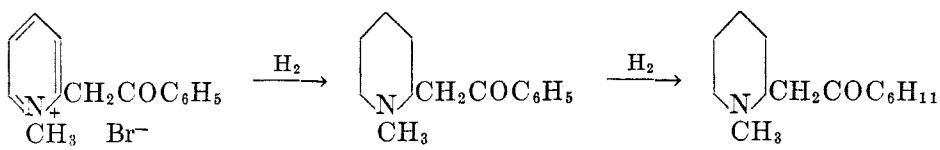
α-Phenacylpyridine (I), originally synthesized from α-picoline by a series of steps (1, *cf.* 2), has recently been obtained from this starting material in essentially a single operation (3, 4, 5). In the present work, I was conveniently prepared (6) by adding α-picoline and ethyl benzoate in that order to a solution of potassium amide in liquid ammonia.



I II

The catalytic reduction of I to 2-(β-hydroxy-β-phenylethyl)piperidine (II) had previously been reported by Scheuing and Winterhalder (2). In our experience, the reduction of I (using either platinum oxide or Raney nickel catalyst) gave the two racemic forms of II melting at 112.5° and 98.5° respectively [the carbinol, m.p. 85°, described in the literature (2) is apparently a mixture].

The platinum oxide-catalyzed reduction (terminated when the calculated amount of hydrogen had been absorbed) of α-phenacylpyridine methobromide (III) gave 1-methyl-2-phenacylpiperidine (IV)[2] in good yield.[3]



III IV V

[1] The work described in this paper was done under a Contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and the California Institute of Technology (E. R. Buchman, responsible investigator).

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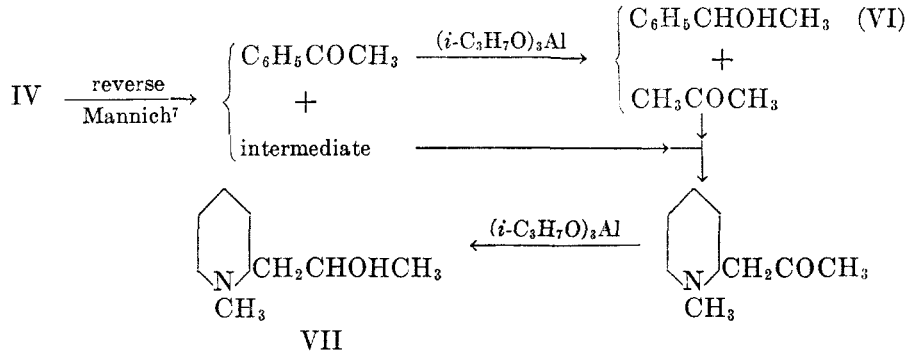
[2] Wieland and Ishimasa (7) isolated a minor lobelia alkaloid for which they suggested the structure N-methyl-II (dihydro-IV); they oxidized this carbinol to the corresponding ketone whose hydrochloride monohydrate melted at 109°; whether either of these compounds was optically active was not disclosed. Our racemic ketone (IV) gave an anhydrous hydrochloride, m.p. 172–173° dec.

[3] Compare conversion of α-acetonylpyridinemethosulfate (8) and of α,α′-diphenacylpyridine metho-*p*-toluenesulfonate (2) to the corresponding piperidine derivatives.

When the reduction was continued, hydrogen was taken up at a slower rate; there was isolated (in addition to IV) a compound tentatively formulated (on the basis of analytical results) as V.[4]

An attempted aluminum isopropoxide reduction[5] of IV gave a variety of products, among them phenylmethylcarbinol (VI) and, with reasonable certainty, 1-methyl-2-(β-hydroxypropyl)piperidine (VII)[6] [mixture of racemates (13a)]. The chart provides an explanation of the formation of these substances.



EXPERIMENTAL[8]

α-Phenacylpyridine (I). To a potassium amide solution [from 63 g. (1.6 gram-atoms) of potassium, *ca.* 1 l. of liquid ammonia, and ferric chloride catalyst] was added with stirring 80 g. (0.86 mole) of α-picoline (six minutes); to the resulting deep-red solution was added 220 g. (1.46 moles) of ethyl benzoate (eight minutes). A brick-yellow suspension formed which, during twenty minutes of stirring, lightened in color to lemon-yellow. The suspension was then diluted with 500 ml. of ether and agitation was continued for six hours (mixture warmed to room temperature) during which time ether was added to facilitate stirring. After treatment with a solution of 85 g. (1.6 moles) of ammonium chloride in 500 ml. of water (foaming!), the dark-green organic layer was separated, the aqueous phase was extracted with ether, and the combined ether extracts were extracted in turn with 1.2 l. of 1 *N* hydrochloric acid. The acid extract was then neutralized with excess potassium car-

[4] This observation is in marked contrast to the reported (2) smooth conversion of α,α′-diphenacylpyridine metho-*p*-toluenesulfonate to lobelanidine [1-methyl-2,6-di-(β-hydroxy-β-phenylethyl)piperidine]. The catalytic reduction of lobelia alkaloid analogs of IV has been little studied, *cf.* the reduction (9) of lobinin and of isolobinin. Note that Wibaut and co-workers (10) were able to effect the reduction of α-acetonylpyridine to 2-acetonylpiperidine.

[5] The aluminum isopropoxide reduction of Mannich ketones has seldom proved satisfactory (11).

[6] Wieland and Dane (12) have suggested the formula VII for a minor lobelia alkaloid, m.p. 85–87°. Our VII mixture was an oil, as were also previously reported (13) VII preparations. VII has been prepared by reduction of 1-methyl-2-acetonylpiperidine (13a), reduction of α-(β-hydroxypropyl)-pyridine methosulfate (13b), and methylation of mixed 2-(β-hydroxypropyl)piperidine racemates (13c).

[7] Compare the facile elimination of acetophenone from similarly constituted lobelia alkaloids (14).

[8] All melting points are corrected; microanalyses by Dr. G. Oppenheimer and staff of this Institute and by Huffman Microanalytical Laboratories, Denver, Colorado; spectral measurements by Miss P. Baskett and Mrs. M. Howton.

bonate and extracted with ether. The extracts were dried and distilled; the fraction b.p. 138–150° at 0.5 mm. [lit. (2) gives I, b.p. *ca.* 159° at 1 mm.] crystallized. This product (112 g.) contained benzamide; it was dissolved in 1 l. of acetone and treated with 65 ml. of 48% hydrobromic acid, giving a colorless precipitate of *I hydrobromide*, m.p. 142–147°, yield 105 g. (44% based on α-picoline). This salt crystallized from isopropyl ether-ethanol in colorless, rhombic plates, m.p. 157.2–157.9° [lit. (15) m.p. 156–157°], absorption spectrum (Fig. 1), approximate values of $\lambda_{max.}$ (aqueous solution) 255 mμ, 395 mμ (plateau). *I (free base)*, yellow needles from *n*-hexane-ether, m.p. 59.1–60.7° [lit. m.p. 50–51° (1); 59° (2, 3); 56° (4); 54° (5)] deteriorating rapidly on standing [*cf.* however (5)]; the absorption spectrum (*n*-hexane solution) is given in Fig. 1 [$\lambda_{max.}$ at 233 mμ, (254 mμ), (264 mμ), 300 mμ (plateau), 343 mμ]. A freshly prepared ethanolic solution of I exhibited three prominent maxima corresponding in position to those found in *n*-hexane but the spectrum was changing at such a rate that reproducible readings could not be obtained; the spectrum of the

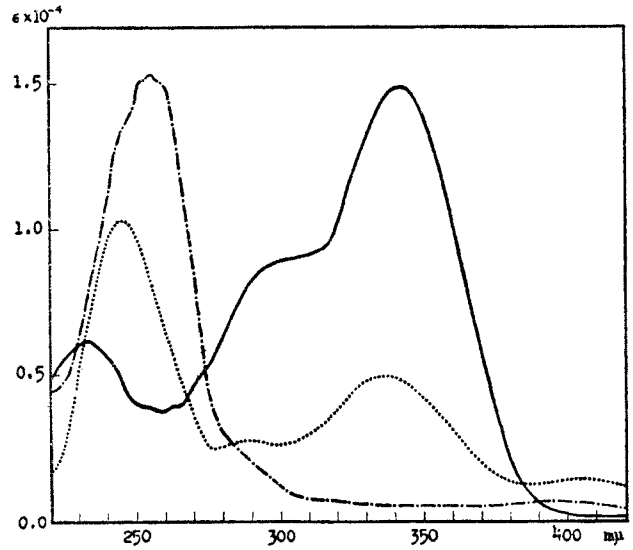


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA

——— α-Phenacylpyridine in *n*-hexane
..... α-Phenacylpyridine in 95% ethanol (solution one day old)
—·—·— α-Phenacylpyridine hydrobromide in water

ethanol solution after standing one day (not appreciably different from that of the same solution nine days later) is given in Fig. 1 ($\lambda_{max.}$ at 245 mμ, 289 mμ, 337 mμ, 404 mμ); note that this curve is in some respects intermediate between that found for I (in *n*-hexane) and that for I hydrobromide. *I oxime* melted at 116° [lit. m.p. 120° (2), 118° (16)]. *I picrate* crystallized from acetonitrile in sparse clusters of yellow, rectangular bars, some tubular, others tubes with a longitudinal opening down one face, m.p. 181.8–182.3° [lit. m.p. 176–177° (1); m.p. 179–180° (5)].

2-(β-Hydroxy-β-phenylethyl)piperidine (II). In a typical experiment, 27.7 g. of I hydrobromide, 75 ml. of ethanol, and 1 g. of Adams' platinum oxide catalyst were shaken with hydrogen at room temperature and atmospheric pressure. After thirty-one hours, the uptake was negligible and about 13.5 l. of gas had been absorbed (theory *ca.* 10.4 l.). The catalyst was filtered off and washed with ethanol; the filtrates, after evaporation to *ca.* 100 ml. and after two days in the ice-box, deposited 1.2 g. of crude α-II hydrobromide, m.p. 149–153°. Mother liquors were freed of solvent and treated with 50 ml. of acetone yielding a second crop of crystals (6.2 g)., m.p. 142°. A third crop (4.0 g.), m.p. *ca.* 134° was obtained

by again evaporating mother liquors, dissolving the residue in 25 ml. of butanone, and adding 18 ml. of isopropyl ether. A further similar treatment of the mother liquors using 15 ml. each of butanone and isopropyl ether gave 4.2 g. of hygroscopic material, m.p. *ca.* 111°. Basification of the final mother liquors gave crystalline, non-homogeneous material (4.6 g.).

A sample of crude α-II hydrobromide, m.p. 142–146°, after three recrystallizations from acetone-ethanol, had a constant m.p. 156.4–157.0°, clusters of very thin colorless blades with bluntly-pointed ends; this salt (SN 10,094) exhibited no activity when tested against avian malaria (17).

Anal. Calc'd for $C_{13}H_{19}NO \cdot HBr$: C, 54.55; H, 7.04; N, 4.89.
Found: C, 54.83; H, 7.14; N, 4.76.

The free base (α-II) was liberated from recrystallized hydrobromide and recrystallized from ligroin-isopropyl ether, sparsely-clustered colorless bars, m.p. 112.0–112.5°, analysis below. β-II was obtained from the hygroscopic mixed hydrobromides, m.p. *ca.* 111° (see above); this material was recrystallized, first by dissolving in acetone and diluting with ether and then from acetone-ethanol; basification of the mother liquors from the second recrystallization followed by five recrystallizations from 60–70° petroleum ether gave pure β-II, plates, m.p. 97.8–98.5°.

Anal. Calc'd for $C_{13}H_{19}NO$: C, 76.02; H, 9.33; N, 6.82.
Found (α-II): C, 76.16; H, 9.70; N, 6.63.
(β-II): C, 76.20; H, 9.80; N, 6.84.

The *picrates* of both forms of II were oils. Treatment of β-II with 48% hydrobromic acid under mild conditions (removal of excess acid *in vacuo*) resulted in replacement of the hydroxyl group; the product was a crystalline solid, colorless rectilinear plates from ethanol-water, m.p. 186–187° dec. (dependent on rate of heating).

Anal. Calc'd for $C_{13}H_{18}BrN \cdot HBr$: C, 44.72; H, 5.49; N, 4.01.
Found: C, 44.95; H, 5.45; N, 3.95.

An autoclave, charged with 20 g. of I (containing benzamide), 150 ml. of dioxane, 11 ml. of Raney nickel paste, and hydrogen at 140 atmospheres pressure, was heated for five hours at 85–145°. Distillation gave a mixture of oil and crystals, b.p. 100–145°/1 mm. [lit. (2) b.p. of II, 165°/4 mm.] The crystalline portion was recrystallized from benzene, m.p. 186–187°, analysis for $C_7H_{13}NO$; hexahydrobenzamide is reported (18) to melt at 184°, 185–186°. The oily portion crystallized on standing; 5 g. of this material was dissolved in 5 ml. of benzene; on cooling crude α-II separated, identified (after recrystallization from ligroin-benzene) by m.p. and mixture m.p. of the free base and of its hydrobromide. On further standing, the benzene mother liquors deposited crystals which after recrystallization from ligroin proved to be the more soluble β-II, m.p. and mixture m.p.

α-Phenacylpyridine methobromide (III). The free base liberated from 27.7 g. (0.1 mole) of I hydrobromide was dissolved in 50 ml. of ethanol and treated with 20 ml. of methyl bromide. The reaction took place at room temperature over several days; large rhomboids separated, yield, 21.6 g. (74%). A sample crystallized from ethanol in clusters of colorless plates, m.p. 214.0–214.2° dec.

Anal. Calc'd for $C_{14}H_{14}BrNO$: C, 57.55; H, 4.83; N, 4.79.
Found: C, 57.66; H, 4.89; N, 4.95.

Catalytic reduction of III. A solution of 21.6 g. (0.074 mole) of III in 250 ml. of methanol was shaken with hydrogen at room temperature and atmospheric pressure in the presence of 2 g. of Adams' catalyst. The reduction was stopped after 6.3 l. of gas (3.3 mole-equivalents) had been taken up (twenty-one minutes). After removal of catalyst, the product was freed of solvent and taken up in a small amount of ethanol. A first crop of crystalline IV hydrobromide was obtained on dilution with acetone and two additional crops resulted after evaporation of solvent and treatment with acetone; total yield, 19.4 g. (88%). First and second crop salt (18.1 g., m.p. 145–146°) was dissolved in water and basified with 4 *N* sodium hydroxide; the base was taken up in isopropyl ether and distilled at 1 mm.; yield, 12.3 g. (93% recovery) of somewhat viscous, pale yellow oil, b.p. 124°.

Anal. Calc'd for $C_{14}H_{19}NO$: C, 77.38; H, 8.81; N, 6.45.
Found: C, 77.25; H, 8.90; N, 6.42.

The following derivatives of 1-methyl-2-phenacylpiperidine (IV) were examined: the *hydrobromide* emerged slowly from the solution in a small volume of ethanol on dilution (1:1) with acetone, compact clusters of colorless granules which initially appeared cubic, m.p. 148.8–149.4°, analysis for $C_{14}H_{20}BrNO$. The *hydrochloride* crystallized slowly from the conc'd ethanolic solution on addition of about 10 volumes of ether, compact microneedle-clusters, m.p. 172–173° dec. (m.p. 166° on very slow heating), analysis for $C_{14}H_{20}ClNO$. The absorption was measured on an ethanol solution of this salt, $\lambda_{max.}$ 245 mμ ε 14500, $\lambda_{max.}$ 280 mμ ε 1350; in appearance the curve resembles that found for acetophenone (19). The *picrate* formed tiny, bright yellow or orange, granular clusters from ethanol-acetonitrile, m.p. 159.2–159.4°, analysis for $C_{20}H_{22}N_4O_8$. The *acid oxalate* formed puffballs of tiny, white, needle-clusters from isopropyl ether-ethanol, m.p. 131–133°, analysis for $C_{14}H_{19}NO \cdot C_2H_2O_4$. Addition of several drops of 48% hydrobromic acid to a mixture of IV hydrobromide and 2,4-dinitrophenylhydrazine in boiling 95% ethanol brought about solution and then separation of the difficultly soluble *hydrazone hydrobromide* as an orange crystalline solid, m.p. 237–240° dec.; *IV-2,4-dinitrophenylhydrazone* free base formed tiny clusters of orange leaves from isopropyl ether-acetonitrile, m.p. 138.1–138.6°.

The hydrogenation of 21.2 g. (0.0725 mole) of III in 60 ml. of methanol (0.3 g. of catalyst) was carried out as above except that it was allowed to continue until the rate became negligible (seven hours, 8.5 l. of hydrogen = 4.5 mole-equivalents). The regenerated crude free bases (oily) were treated with an equivalent amount of oxalic acid in isopropyl ether-ethanol; in several crops a total of 6.3 g. (28%) of crude IV oxalate (identified by analysis, conversion to hydrochloride and picrate) was obtained. The sirupy bases (12 g.) liberated from the oxalate mother liquors were then treated with 10.8 g. of picric acid in 25 ml. of boiling ethanol and the solution was allowed to cool while acetonitrile was added to maintain clarity. After seeding with IV picrate, the solution slowly deposited a small amount of this salt and, after ten days, a large quantity of bright yellow needle tufts. This crude V *picrate* (yield 6.8 g., 20%) was easily separated from traces of IV picrate since the latter emerges from solution very slowly, even when seeded, while V picrate forms relatively stable supersaturated solutions but comes out rapidly when seeded; it was recrystallized from methanol-acetonitrile, m.p. 131.4–131.8°.

Anal. Calc'd for $C_{14}H_{25}NO \cdot C_6H_3N_3O_7$: C, 53.09; H, 6.24; N, 12.38.

Found: C, 53.13, 53.19; H, 6.11, 6.18; N, 12.36, 12.50.

From the picrate the *free base* V was obtained in 82% yield, b.p. 127–132° at 1.5 mm.; the analytical figures agreed approximately with those calculated for $C_{14}H_{25}NO$. The base absorbed oxygen from the air [autoxidation of a basic ketone, *cf.* (20)]; after several weeks, careful analyses checked closely the empirical composition $C_{14}H_{25}NO_{1.3}$. Attempts to prepare the oxime, 2,4-dinitrophenylhydrazone, phenylurethan, and *p*-nitrobenzoate gave inconclusive results. The *methiodide* crystallized from ethyl acetate-ethanol in clusters of thin, colorless slats, m.p. 163.1–163.5° (sintering from 159°).

Anal. Calc'd for $C_{14}H_{25}NO \cdot CH_3I$: C, 49.32; H, 7.73; N, 3.83.

Found: C, 49.20, 49.28; H, 7.74, 7.80; N, 3.76, 3.86.

Aluminum isopropoxide reduction of IV. A mixture of 10.8 g. (0.05 mole) of freshly-distilled IV, 10 g. of aluminum isopropoxide, and 50 ml. of isopropanol was refluxed while the acetone formed was distilled off. After seven hours, when the distillate gave a negative test for acetone, the remainder of the isopropanol was removed *in vacuo* and the residue was decomposed by aqueous alkali and extracted with benzene. The benzene-soluble product, 10.0 g. of viscous oil, was only partially soluble in acid; the neutral fraction was distilled, yielding 2.6 g. of *phenylmethylcarbinol* (VI) (42%), b.p. 94° at 13 mm., m.p. between 0° and room temperature; *α-naphthylurethan*, colorless needle-clusters from ligroin-isopropyl ether, m.p. 105.6–106.0° [lit. gives for VI: b.p. 94°/12 mm. (21); m.p. 20.1° (22); α-napthylurethan, m.p. 106° (23)]. The basic fraction was liberated, taken up in ether and distilled at 1 mm.: the portion b.p. 74–105° amounted to 1.2 g. (15% calculated as VII); the portion b.p. 127–147° was 2.4 g.; and the residue was *ca.* 2.7 g. The crude VII was an oil and gave an oily picrate; the *methiodide* formed in good yield and crystallized very slowly

from ethyl acetate-ethanol in pale yellow clumps, m.p. 150–165° to cloudy melt, clear at 175° [Hess (13a) prepared two VII-methiodides, m.p. 176° and m.p. 176–177°, mixture m.p. 170–175°].

Anal. Calc'd for $C_{10}H_{22}INO$: C, 40.14; H, 7.41; N, 4.68.
Found: C, 39.79; H, 7.46; N, 4.69.

The fraction b.p. 127–147°/1 mm. was an oil which gave an oily picrate and an oily methiodide; the analysis (C, 76.79; H, 9.91; N, 8.11) indicated the possible presence of 1-methyl-2-(β-hydroxy-β-phenylethyl)piperidine racemates.

SUMMARY

An improved synthesis of α-phenacylpyridine has been described.

The catalytic reduction of α-phenacylpyridine yields the two racemic forms of 2-(β-hydroxy-β-phenylethyl)piperidine. The catalytic reduction of α-phenacylpyridine methobromide gives 1-methyl-2-phenacylpiperidine, in which on further reduction the benzene ring is hydrogenated. The reaction between 1-methyl-2-phenacylpiperidine and aluminum isopropoxide leads to the formation of methylphenylcarbinol and of 1-methyl-2-(β-hydroxypropyl)piperidine.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY AND THE PURDUE RESEARCH FOUNDATION]

NITRO ALKENE DERIVATIVES[1]

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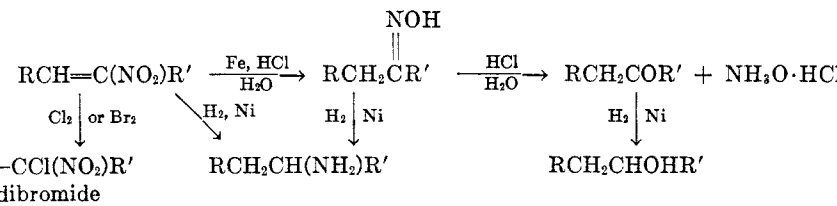
The relatively recent enhancement of the availability of the lower nitro alkanes (1) and of the nitro alcohols (2) led to the present investigation of the nitro alkenes and their derivatives. The latter are easy to synthesize in good yields and have proved to be intermediates for the facile production of higher ketones, alcohols, amines, oximes, and dihalo nitro alkanes. The highly active double bond of the nitro alkene molecule and the ease of reduction of the nitro group open the way to further syntheses still to be investigated. The accompanying diagram indicates the generic relationships involved.

ALIPHATIC: $RCHO + R'CH_2NO_2 \xrightarrow{Ca(OH)_2} RCHOHCH(NO_2)R'$

$RCHOHCH(NO_2)R' + Ac_2O \rightarrow RCH(OAc)CH(NO_2)R' + HOAc$

$2\,RCH(OAc)CH(NO_2)R' + Na_2CO_3 \rightarrow RCH{=}C(NO_2)R' + AcONa + H_2O + CO_2$

AROMATIC: $ArCHO + RCH_2NO_2 \xrightarrow[\text{amine}]{\text{Primary}} ArCH{=}C(NO_2)R$



EXPERIMENTAL

The nitro alcohols and their acetate esters were obtained in good yields using the technique of Vanderbilt and Hass (2).

The purely aliphatic nitro alkenes were produced by a slight modification of the procedure of Schmidt and Rutz (3). One mole of sodium carbonate is added to a solution of two moles of nitroalkyl acetate dissolved in 200 ml. of anhydrous benzene and refluxed in a round-bottom flask for six hours. The flask is cooled and the product decanted from solids. The residue (sodium acetate) is extracted with benzene, dissolved in water, and further extracted with small portions of benzene. The benzene solution is dried over K_2CO_3, the benzene distilled and the nitro alkene remaining is purified by distillation, usually at 10 mm., through a Podbielniak column. The nitro alkenes prepared in this way are shown in Table I.

If the aldehyde contains a formyl group attached to an aromatic nucleus the nitro alkene may be synthesized by the method of Knoevenagel and Walter (4) in a single step. This is illustrated in the preparation of *1-phenyl-2-nitropropene*. One mole each of benzaldehyde and nitroethane, 5 ml. of *n*-butylamine, and 100 ml. of absolute ethanol were refluxed

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TABLE I

PHYSICAL CONSTANTS OF THE NITRO ALKENES

NITRO ALKENE	BOILING POINT °C. (MM.)	REFRACTIVE INDEX AT 25°	d_4^{25}	CARBON, %	
				Calc'd	Found
2-Nitropropene	57.0 (100)	1.4105	1.0559	41.38	41.10
2-Nitro-2-butene	70.4 (30)	1.4584	1.0429	47.48	47.44
2-Nitro-2-hexene	82.3 (10)	1.4572	0.9824	55.77	55.74
3-Nitro-2-pentene	57.8 (10)	1.4590	1.0069	52.14	52.05
3-Nitro-3-heptene	84.4 (10)	1.4580	0.9625	58.70	58.60
3-Nitro-2-hexene	72.0 (10)	1.4572	.9833	55.77	55.70
4-Nitro-4-octene	93.0 (10)	1.4593	.9484	61.10	61.10
4-Methyl-3-nitro-2-pentene	64.0 (10)	1.4530		55.77	55.40
2-Methyl-3-nitro-3-heptene	85.5 (10)	1.4537		61.10	60.00
2-Nitro-1-butene[a]	60.5 (50)				
2-Nitro-1-pentene[a]	58.0 (20)				

[a] The other physical constants of 2-nitro-1-butene and 2-nitro-1-pentene were not determined.

TABLE II

PREPARATION OF ARYL NITRO ALKENES

ARYL NITRO ALKENES	CONVERSION, %	YIELD, %	B.P., °C. (MM.)	SP. GR.	REFR. INDEX	ANALYSES			
						Calc'd		Found	
						C, %	H, %	C, %	H, %
1-Phenyl-2-nitro-propene (4)	65 64	85 86.5	(m.p., 65)						
1-Phenyl-2-nitro-1-butene	70		125–129 (10) 121 (6) (m.p., 12)	1.1064_4^{25}	(25°) 1.5832	67.80	—	67.42	—
1-Phenyl-2-nitro-1-pentene	65–70		108–109 (3) 133–135 (6)	1.083_{25}^{25}	n_D^{25} 1.5706	69.13	6.81	68.93	6.90
1-Furyl-2-nitro-propene		85–90	(m.p., 48–49)			54.91	4.61	55.05	4.65
1-Furyl-2-nitro-1-butene (6)	70		130–131 (13) 124–125 (10)						
1-Furyl-2-nitro-1-pentene (6)			136–137 (13)						
1-Anisyl-2-nitro-1-butene	35–40	90	(m.p., 56)			63.75	6.32	63.71	6.18
1-Anisyl-2-nitro-1-pentene	35–40	90	(m.p., 35–36)			65.14	6.84	65.35	6.42

for 8 hours in a 1000-ml. round-bottom flask. When the contents were cooled and stirred a heavy, yellow, crystalline mass formed immediately. After recrystallization from absolute ethanol the product weighed 105 g. (conversion 64% of theory, yield 86.5%) with m.p. 65°.

Table II contains a list of nitro alkenes prepared thus. The method failed with ω-nitrostyrene, a poor yield of 2-nitro-1,3-diphenyl-1,3-propanediol being obtained instead. It

also failed with vanillin and nitroethane, 1-nitropropane, and 1-nitrobutane because of tar formation and with dinitroneopentane and benzaldehyde for the same reason.

REDUCTION OF NITRO ALKENES

Although nitro alkenes had been reduced by means of aluminum amalgam (5), zinc and acetic acid (5, 9) and Raney nickel and hydrogen (8), apparently no one prior to the present authors had studied the effect of cast iron turnings and dilute hydrochloric acid, which is the preferred procedure for the reduction of aromatic nitro compounds. This method proved to give good yields of either ketone or ketoxime depending upon the amount of hydrochloric acid used. The following steps are indicated.

$$RCH{=}C(NO_2)R' + Fe + H_2O \xrightarrow{HCl} [RCH{=}C(NHOH)R'] + Fe_3O_4$$

$$[RCH{=}C(NHOH)R'] \longrightarrow RCH_2\overset{\overset{NOH}{\|}}{C}R'$$

$$RCH_2\overset{\overset{NOH}{\|}}{C}R' + H_2O + HCl \longrightarrow RCH_2COR' + NH_3O\cdot HCl$$

EXPERIMENTAL

One-tenth of a mole of nitro alkene, 0.72 gram-atom (40 g.) of 40 mesh cast iron turnings, 75–100 ml. of distilled water, and 0.1 g. of ferric chloride were placed in a 500-ml. round-bottom, three-neck flask equipped with a graduated dropping-funnel, a mercury-seal stirrer, and a reflux condenser. Fifteen ml. of conc'd HCl was added dropwise for 5 to 6 hours and the temperature of the surrounding oil-bath maintained between 85 and 95°. The reaction mixture was then basified with 25% NaOH solution and distilled with steam. The distillate was extracted several times with ether, the ether distilled, and the residue rectified through a Podbielniak column at reduced pressure.

Table III indicates experiments on the reduction of 1-phenyl-2-nitropropene.

Table IV indicates the nitro alkenes reduced with iron and acid.

Table V indicates the oximes prepared either directly by reduction of nitro alkenes or by the action of hydroxylamine on ketones so prepared.

Table VI indicates the amines made by reducing the corresponding oximes with Raney nickel and hydrogen. The procedure used was as follows: A Parr hydrogenation bomb was charged with 0.04–0.06 mole of ketoxime, 6–10 g. of Raney nickel, and 75 ml. of absolute ethanol. Hydrogen was run in until the pressure was 1000–2000 p.s.i. and reduction proceeded readily at room temperature for 3–5 hours. The ethanol was distilled from the amine and this was rectified in a small modified Podbielniak column. If the hydrochloride was a crystalline solid, the amine was identified by conversion to the hydrochloride and titration with standard silver nitrate using dichlorofluorescein as an indicator.

Table VII indicates the secondary alcohols made by catalytic hydrogenation of the corresponding ketones. The procedure used was as follows: A solution of 100–150 ml. of absolute ethanol and 0.05–0.20 mole of ketone was placed in a Parr hydrogenation bomb, and freshly prepared Raney nickel (8 g. of Raney nickel per 0.1 mole of ketone) was washed into the bomb with absolute ethanol. The autoclave was then sealed and hydrogen added until the pressure was 1400–2000 p.s.i. The surrounding rocking cradle was then heated to a temperature of 125–150°, except in the case of furylacetone which was reduced at room temperature, and the rocking device started. The reduction was allowed to proceed for 5–6 hours and the contents of the bomb were washed with absolute ethanol into a beaker and the catalyst

TABLE III

SUMMARY OF EXPERIMENTS ON REDUCTION WITH IRON AND HYDROCHLORIC ACID

EXPT. NO.	MOLAR RATIO		ML./MOLE ALKENE		PRODUCT, % CONVERSION TO	
	Fe/Alkene	HCl/Alkene	Water	Solvent	Phenyl-propanone	Oxime of Phenyl propanone
101	2	0	500	0	—	20.1
102	2	0.06	500	0	5.2	49.0
103	2	0	500	0	0	0
104	2	0.10	500	0	11.3	32.5
105	2	.232	500	0	24.6	27.4
106	2	.464	500	0	36.5	23.1
108	2	0	500	0	3.7	23.8
109	2	0.06	500	0	3.7	45.0
110	2	.06	0	500[a]	0	0
111	1	.06	500	0	trace	34.6
112	2	.06	250	500[a]	10.5	62.6
113	2	.06	250	500[b]	0	0
114	2	.06	250	250[a]	10.7	45.6
116	2	.06	250	250[b]	0	0
117	1	.06	250	250[b]	0	0
123	2	.06	250	250[c]	9.9	64.2
127	2	.06	250	500[c]	9.7	63.0
128	2	1.392	500	0	41.1	20.2
129	2	1.74	500	0	56.0	13.4
130	2	1.74	1000	500[c]	41.0	30.2
131	2	1.74	1000	500[b]	18.7	40.3
II 4	7.15	1.74	750	0	75	0
RXY 24	7.15	1.97	670	0	77	0
132	2.5	2.00	500	0	44.7	20.2
136	2.5	0.52	500	0	10.5	37.5

[a] CH_3OH. [b] C_6H_6. [c] C_2H_5OH.

TABLE IV

REDUCTION OF NITRO ALKENES WITH IRON AND HCl

REDUCTION OF	PRODUCT, YIELD, %	B.P., °C. (MM.)	SP. GR. 25°/25°	n_D^{25}	ANALYSES			
					Calc'd		Found	
					C, %	H, %	C, %	H, %
1-Phenyl-2-nitro-propene	Phenylacetone, 75–77	215–216						
1-Phenyl-2-nitro-1-butene	1-Phenyl-2-butanone, 68	101–102 (10)						
1-Phenyl-2-nitro-1-pentene	1-Phenyl-2-pentanone, 45–50	107 (10)						
1-Furyl-2-nitro-propene	Furylacetone, 35–40	179–180						
1-Furyl-2-nitro-1-butene[a]	1-Furyl-2-butanone, 65–70	76 (11–12) 99 (27)	1.032	1.4680	69.55	7.29	69.45	7.40
1-Furyl-2-nitro-1-pentene	1-Furyl-2-pentanone, 64	95 (15)	0.999	1.4629	71.02	7.95	70.95	8.03
1-Anisyl-2-nitro-1-butene	1-Anisyl-2-butanone, 60	132 (5)	1.039	1.5101	74.14	7.92	74.33	7.92
1-Anisyl-2-nitro-1-pentene[b]	1-Anisyl-2-pentanone, 60–62	120–122 (3)	1.025	1.5120	74.99	8.39	74.92	8.12

[a] 1-Furyl-2-alkanones, colorless liquids with peculiar odors, tend to become reddish brown on standing. [b] 1-Anisyl-2-alkanones are colorless liquids, stable on standing, and have characteristic, pleasant odors.

filtered from the solution. Most of the ethanol distilled from the reduction products and purification of the secondary alcohol was effected by distillation through a modified Podbielniak column under reduced pressure.

If nitro alkenes are reduced directly with Raney nickel and hydrogen, saturated amines are obtained in a single step. The reduction of 3-nitro-2-pentene in this way using 1-butanol as solvent gave a 55% yield of 3-pentylamine, identified by boiling point and m.p. of hydrochloride [217.5° (Literature, 216°)]. Some ammonium chloride was formed simultaneously.

TABLE V

PREPARATION OF OXIMES

OXIME	B.P., °C. (MM.)	SP. GR. 25°/25°	n^{25}	ANALYSES			
				Calc'd		Found	
				C, %	H, %	C, %	H, %
1-Phenyl-2-propanone oxime (60–65%) plus 8–12% 1-phenyl-2-propanone, from reduction of 1-phenyl-2-nitropropene	99 (2) (m.p., 68–70)						
1-Phenyl-2-butanone oxime	117–118 (2)	1.036	1.5363	73.60	8.03	74.00	7.88
1-Phenyl-2-pentanone oxime	116 (1–2)	1.017	1.5292	74.54	8.53	74.47	8.54
1-Furyl-2-propanone oxime (7)	95 (5)						
1-Furyl-2-butanone oxime	119–120 (10)	1.082	1.4980	62.72	7.23	62.82	6.83
1-Furyl-2-pentanone oxime	118 (4)	1.054	1.4935	64.66	7.84	64.66	7.92
1-Anisyl-2-butanone oxime	(m.p., 75)			68.38	7.83	68.00	7.97
1-Anisyl-2-pentanone oxime	*ca.* 135 (1–2) (m.p., 58–59)			69.51	8.27	69.49	8.18

TABLE VI

PREPARATION OF AMINES

Compound reduced	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)
Ketoxime, mole	0.058	0.05	0.065	0.05	0.05	0.057	0.042	0.041
Raney nickel, grams	8	8	10	6	10	10	10	10
Ethanol, ml	150	75	150	75	125	125	125	100
Initial H pressure, p.s.i.	1800	810	1900	1900	1440	1900	1240	1240
Time of reduction, hours	2	4–5	5	3	5	5½	5	5
Temperature, °C	80	Room	Room	Room	Room	Room	Room	Room
Yield of amine, %	55	75	70	90	50	60	40	70

(1) 1-Phenyl-2-propanone oxime
(2) 1-Phenyl-2-butanone oxime
(3) 1-Phenyl-2-pentanone oxime
(4) 1-Furyl-2-propanone oxime
(5) 1-Furyl-2-butanone oxime
(6) 1-Furyl-2-pentanone oxime
(7) 1-Anisyl-2-butanone oxime
(8) 1-Anisyl-2-pentanone oxime

Table VIII indicates the dihalides formed by addition of chlorine or bromine to various nitro alkenes. Nitro alkenes add the halogens readily giving the dihalide derivatives. These are stable, high-boiling liquids which possess an odor much milder than that of the parent nitro alkene. The dichlorides were prepared by absorbing the mole-equivalent of chlorine in a carbon tetrachloride-nitro alkene solution. The following method was employed in the preparation of the dibromides of nitro alkenes.

Two-tenths mole of bromine dissolved in 75 ml. of carbon tetrachloride was added slowly to a solution of two-tenths mole of 3-nitro-2-pentene in 25 ml. of carbon tetrachloride. The

solution was shaken vigorously and kept cool during the addition of bromine. At the end of the addition the solution had a pronounced bromine color. After standing for one day the unreacted bromine was extracted with 5% sodium hydroxide solution. The oily layer was washed with water and dried over calcium chloride. The dried sample was analyzed by distillation on a modified Podbielniak column. The dibromide fraction was collected between 98–101°/10 mm. The purified 2,3-dibromo-3-nitropentene had b.p. 100°/10 mm. Yield, 87.5%.

The dibromides of 3-nitro-3-heptene and 4-nitro-4-octene decomposed slightly upon distillation, giving off hydrogen bromide. The dichloride of 3-nitro-3-heptene, however, was quite stable at its boiling point.

TABLE VII

PREPARATION OF *sec*-ALCOHOLS

Compound reduced	(1)	(2)	(3)	(4)	(5)	(6)
Ketone, mole	0.20	0.20	0.043	0.157	0.10	0.048
Raney nickel, grams	15	15	6	8	8	4
Ethanol, ml	150	150	100	100	100	100
Initial H pressure, p.s.i.	1800	1800	1900	1400	1600	1620
Time of reduction, hours	5	5	5	6	6	6
Temperature, °C.	140	90	150	Room	125	125
Yield of *sec*-alcohol, %	95	80	60	55+	83+	80+

(1) Phenylacetone
(2) 1-Phenyl-2-butanone
(3) 1-Phenyl-2-pentanone
(4) Furylacetone
(5) 1-Furyl-2-butanone
(6) 1-Furyl-2-pentanone

+ Represents yield of tetrahydrofuryl-*sec*-alcohol.

TABLE VIII

PHYSICAL CONSTANTS OF THE DIHALIDES

COMPOUND	B.P., °C. (10 MM.)	REFRACTIVE INDEX (25°)	d_4^{25}	HALOGEN, %	
				Calc'd	Found
1,2-Dibromo-2-nitrobutane	98.4	1.5217	1.9151	61.27	61.37
2,3-Dibromo-2-nitrobutane	60.0 (m.p.)			61.27	61.15
2,3-Dibromo-3-nitropentane	102.8	1.5169	1.8097	58.14	58.12
2,3-Dibromo-2-nitrohexane	113.0	1.5112		55.32	55.15
2,3-Dibromo-3-nitrohexane	111.8	1.5101	1.7057	55.32	55.37
3,4-Dibromo-3-nitroheptane	115.5	1.5062		52.76	51.78
4,5-Dibromo-4-nitrooctane	122–124	1.5018		50.44	49.90
2,3-Dichloro-3-nitropentane	69.4	1.4621		38.12	37.85
2,3-Dichloro-2-nitrohexane	89.6	1.4617	1.2170	35.46	35.53
3,4-Dichloro-3-nitroheptane	90.5	1.4630	1.1916	33.14	33.25

The halogen content of the dihalides was determined by the Carius sealed-tube method. Ten new dihalides of nitro alkenes are reported in Table VIII.

Hydrolysis of Nitro Alkenes

It was found that the nitro alkenes dissolve readily in sulfuric acid (3:1, H_2SO_4:H_2O by volume) with decomposition. In all cases the nitro alkene was cleaved at the double bond with the simultaneous formation of an aldehyde fragment. This may be interpreted as follows:

$$RCH{=}C(NO_2)R' + H_2O \xrightarrow{H^+} RCHOHCH(NO_2)R'$$

$$RCHOHCH(NO_2)R' \rightleftarrows RCHO + R'CH_2NO_2$$

$$R'CH_2NO_2 + H_2O + H_2SO_4 \longrightarrow R'CO_2H + NH_3OH \cdot HSO_4$$

Polymerization of nitro alkenes. All nitro alkenes polymerize with more or less rapidity. For this reason they should be used promptly after synthesis. The polymerization products are black, viscous materials readily soluble in acetone and benzene.

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WEST LAFAYETTE, INDIANA

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

THE REACTION OF PROPENYLPHENOL ETHER DIBROMIDES WITH SODIUM IODIDE

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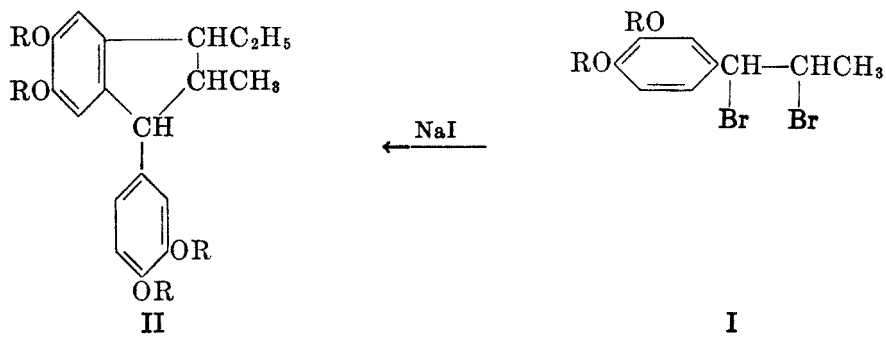
Sodium iodide has been used in the past to some extent as an agent for removal of halogen from certain dibromo and dichloro compounds. For example, the geminal dihalogen compound, benzophenone dichloride, was converted into tetraphenylethylene in acetone solution with sodium iodide, with separation of iodine (1). From ethylene dibromide under similar conditions ethylene is formed. Other vicinal dibromides and dichlorides react in the same manner to form a double bond (2).

This communication deals with the reaction of one of the vicinal dibromide groups, namely the reaction of propenylphenol ether dibromides with sodium iodide. The reaction proceeds in anhydrous acetone and can be well controlled by titration of the iodine formed.[1] The experimental results show that some of the propenylphenol ether dibromides, the dibromides of anethole, isosafrole, isoeugenol benzyl ether, and 3-benzyloxy-4-ethoxypropenylbenzene react with sodium iodide to regenerate the double bond. The dibromides of isoeugenol methyl ether, 3,4-diethoxypropenylbenzene, and 3,4-dibenzyloxypropenylbenzene, on the other hand, react under similar conditions unexpectedly with formation of dimeric compounds. Besides the dimeric compound, usually, more or less propenylphenol ether is also formed. The dimerization proceeds most readily with 3,4-diethoxypropenylbenzene.



II I

(a) R = CH_3 (c) R = $CH_2C_6H_5$
(b) R = C_2H_5 (d) R = H

The dimeric compound of m.p. 99–100°, formed from isoeugenol methyl ether dibromide (Ia) in mixture with the dimer of isoeugenol methyl ether (IIa) m.p.

[1] Davis and Heggie (3) examined the reactions of α,β-dibromides, *e.g.*, benzalacetophenone dibromide with sodium iodide, from the point of view of the reaction rate, but did not examine the structure of the compound formed.

100–101° [from isoeugenol methyl ether by the action of hydrogen chloride (4, 5)], showed no melting point depression. Müller and co-workers (5) suggested the IIa hydrindene structure for diisoeugenol dimethyl ether on the basis of oxidative degradation. Cartwright and Haworth are also of Müller's opinion (6). Both groups synthesized diisoeugenol methyl ether. Although its melting point is identical with the melting point of the dimer prepared from isoeugenol methyl ether by the action of hydrogen chloride, nevertheless the melting point of a mixture of these two specimens was depressed. In their opinion, however, this does not signify that the hydrindene structure is incorrect, as four racemic modifications are possible.

Based on analogy, the dimeric 3,4-diethoxypropenylbenzene (IIb) arising from 1-(3,4-diethoxyphenyl)-1,2-dibromopropane (Ib) (7) may also be considered to have a hydrindene structure, as it showed no depression with the dimeric compound obtained from 3,4-diethoxypropenylbenzene by the action of hydrogen chloride. To decide whether the iodine formed is a dimerizing agent, the 3,4-diethoxypropenylbenzene was treated under these conditions for forty-eight hours in acetone solution with iodine (8). No dimerization took place, as only the unchanged starting compound was isolated.

The dimeric compound of m.p. 116° (IIc), formed from 1-(3,4-dibenzyloxyphenyl)-1,2-dibromopropane (9, 10) (Ic), was converted into 1-(3,4-dihydroxyphenyl)-2-methyl-3-ethyl-5,6-dihydroxyindane (IId) by catalytic debenzylation. As was to be expected, the compound is very readily oxidized. It was converted by the action of diazomethane into IIa. The resulting compound of m.p. 106° (though it crystallized from alcohol like diisoeugenol dimethyl ether) showed a melting point depression with an authentic specimen of diisoeugenol dimethyl ether. It can nevertheless be assumed that the difference between the two compounds is also stereochemical, as we suggest for Müller's and Haworth's compounds.

All these dimeric compounds react with bromine, forming a monobromo derivative, like diisoeugenol dimethyl ether.

Concerning the reaction mechanism, it is most probable that dibromide is first converted into diiodide, and the unstable diiodide gives off iodine. The remaining radicals, or the intermediate containing the activated ethylenic double bond, stabilize through dimerization.

Experiments are in progress to decide how the different radicals influence the reaction resulting in the formation of a double bond or dimeric compound.

EXPERIMENTAL

Diisoeugenol dimethyl ether (IIa). A solution of 3.4 g. of 1-(3,4-dimethoxyphenyl)-1,2-dibromopropane (Ia) in 15 ml. of anhydrous acetone was treated with a solution of 3 g. of sodium iodide in 30 ml. of acetone. Free iodine formed immediately. After twenty-four hours at room temperature, the mixture was treated with a solution of sodium bisulfite, or sodium thiosulfate, to remove iodine. Dilution with water gave an oily product, which was brought into ether. The ether layer was washed with water, dried, and evaporated. The resulting pale yellow oil crystallized from methanol, yielding 0.4 g. of colorless needles, m.p. 99–100°. Mixed melting point with an authentic sample of diisoeugenol dimethyl ether m.p. 101° [prepared according to the method of Széki (4b) with hydrogen chloride from iso-

eugenol methyl ether] showed no depression. In some cases the oily product did not crystallize. It was treated with bromine in ether solution. The crystals melted at 100° and showed no depression with the starting dibromide.

1-(3,4-Diethoxyphenyl)-1,2-dibromopropane (Ib). A solution of 8 g. of 3,4-diethoxypropenylbenzene (7) in 20 ml. of dry chloroform was cooled to −5°. On adding a mixture of 6.2 g. of bromine and 10 ml. of dry chloroform dropwise, colorless crystals deposited. These were recrystallized from ligroin (with charcoal), plates, m.p. 116°, yield 10 g.

Anal. Calc'd for $C_{13}H_{18}Br_2O_2$: C, 42.6; H, 5.1.
Found: C, 42.6; H, 5.0.

Dimeric 3,4-diethoxypropenylbenzene (IIb) [*1-(3,4-diethoxyphenyl)-2-methyl-3-ethyl-5,6-diethoxyindane*]. (a) One gram of 1-(3,4-diethoxyphenyl)-1,2-dibromopropane (Ib) was treated with sodium iodide as described above. The method was simplified by pouring off the solvent from the oily product after diluting the acetone solution with water. The oil was covered with water; it solidified in twenty-four hours. This product was crystallized from ethanol, m.p. 99°, yield 0.3 g. (53.3%). Molecular weight (acetone), 379.

Anal. Calc'd for $C_{26}H_{36}O_4$: C, 75.7; H, 8.8.
Found: C, 75.3; H, 8.6.

(b) *From diethoxypropenylbenzene.* A solution of 1 g. of 3,4-diethoxypropenylbenzene in 5 ml. of ether was saturated with hydrogen chloride. After standing overnight, the ether was removed in a vacuum. The residue was crystallized from methanol; colorless needles, m.p. 99°, undepressed by mixture with a specimen of dimeric diethoxypropenylbenzene prepared according to method (a).

Bromo derivative of the dimeric 3,4-diethoxypropenylbenzene. A solution of dimeric 3,4-diethoxypropenylbenzene (method a) in abs. ether was allowed to stand overnight with an excess of bromine. On removing the solvent, a crystalline residue was obtained, which recrystallized from alcohol in long needles, m.p. 114°. Molecular weight (acetone), 471, 507. In the dimeric compound one hydrogen atom was replaced by bromine.

Anal. Calc'd for $C_{26}H_{35}BrO_4$: C, 63.5; H, 7.2.
Found: C, 63.3, 63.2; H, 7.0, 7.2.

Dimeric 3,4-dibenzyloxypropenylbenzene (IIc) [*1-(3,4-dibenzyloxyphenyl)-2-methyl-3-ethyl-5,6-dibenzyloxyindane*]. A solution of 4.5 g. of Ic (9, 10) and 3 g. of sodium iodide in 30 ml. of acetone was allowed to stand two days. The iodine was removed with sodium thiosulfate, 150 ml. of 0.1 *N*. The oily product solidified on standing overnight, 1.5 g. After two recrystallizations (charcoal) from alcohol, it had m.p. 114–116°, colorless needles, yield 0.5 g. It can also be crystallized from ether.

Anal. Calc'd for $C_{46}H_{44}O_4$: C, 83.6; H, 6.7.
Found: C, 83.5; H, 6.4.

In some cases, nevertheless, from the semisolid oily product only 3,4-dibenzyloxypropenylbenzene was isolated. Three recrystallizations from ether-alcohol gave colorless needles, m.p. 70–71°. Bruckner's 3,4-dibenzyloxypropenylbenzene (9) melts at 64°, but a mixture showed no depression (65–66°). The compound of m.p. 70–71° was converted into its dibromide in ether solution (10). The crystalline product was recrystallized from ligroin, m.p. 120°, undepressed by mixture with a specimen of Ic (10) of m.p. 116°.

Dimeric 3,4-dibenzyloxypropenylbenzene, 0.08 g., in 50 ml. of alcohol was hydrogenated in the presence of previously hydrogenated Pd-charcoal. The calculated four moles of hydrogen was taken up in 15 minutes. The catalyst-free solution was treated with excess diazomethane, and removal of solvent left a brown oil which crystallized from alcohol. Two recrystallizations gave colorless needles, m.p. 106°, depressed to 85–95° by mixture with a specimen of IIa prepared from isoeugenol methyl ether according to the hydrogen chloride method. The debenzylated dimeric compound is very easily oxidized; removal of methanol gave a dark oil, which did not solidify.

Bromo derivative of dimeric 3,4-dibenzyloxypropenylbenzene. IIc was treated with bromine as described above, m.p. 141°.

Anal. Calc'd for $C_{46}H_{43}BrO_4$: C, 75.1; H, 6.0.
Found: C, 75.0; H, 6.2.

3-Benzyloxy-4-ethoxypropenylbenzene. To a solution of 0.6 g. of sodium in 25 ml. of abs. alcohol, 4.5 g. of 3-hydroxy-4-ethoxypropenylbenzene and 3.3 ml. of benzyl chloride were added. The mixture was refluxed for three hours. On standing at room temperature, long flat needles deposited. The crystals were washed with water and dil. sodium hydroxide; recrystallized from alcohol, yield 5 g., m.p. 75°.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.5; H, 7.5.
Found: C, 80.3; H, 7.5.

1-(3-Benzyloxy-4-ethoxyphenyl)-1,2-dibromopropane. A solution of 2.7 g. of 3-benzyloxy-4-ethoxypropenylbenzene was treated with bromine as described above; yield of dibromide compound 3.5 g., m.p. 114°, from ligroin.

Anal. Calc'd for $C_{18}H_{20}Br_2O_2$: C, 50.5; H, 4.7.
Found: C, 50.4; H, 4.6.

The reaction of 1-(3-benzyloxy-4-ethoxyphenyl)-1,2-dibromopropane with sodium iodide was carried out as above. The crystals melted at 75°, not depressed by mixture with a specimen of 3-benzyloxy-4-ethoxypropenylbenzene.

Isoeugenol benzyl ether. The reaction of 1-(3-methoxy-4-benzyloxyphenyl)-1,2-dibromopropane (11) with sodium iodide gave isoeugenol benzyl ether, m.p. 58°. It was converted into its dibromide, which showed no depression with the starting dibromide, m.p. 122°.

Isosafrole. The reaction of 1-(3,4-methylenedioxyphenyl)-1,2-dibromopropane with sodium iodide was carried out as described above. The oil was purified by distillation in steam. Its dibromide showed no depression with the starting dibromide.

Anethole. Anethole was prepared from 1-(4-methoxyphenyl)-1,2-dibromopropane as described for isosafrole, m.p. 21°.

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[CONTRIBUTION FROM JESUS COLLEGE, OXFORD]

A CALCULATION OF THE NUMBER OF POSITIONAL ISOMERS IN SOME AROMATIC SYSTEMS

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Hill (1, 2, 3) and Polya (4, 5, 6) have given detailed mathematical treatments of position isomerism in simple ring compounds. With the exception of a short table (5), the present authors do not believe that the results for aromatic systems have been published. Part II of this paper is devoted to tables of isomers for all possible modes of substitution in the benzene, naphthalene, anthracene, and phenanthrene systems, together with a table showing only the number of isomers, with all the substituents identical, in a number of more complicated aromatic hydrocarbons. Since the calculations were made before the attention of the authors was drawn to the work of Hill and Polya, a résumé of our treatment of this particular problem is given below.

Method of calculation: The substituents in the aromatic systems to be considered may be either single atoms or univalent groupings, though for ease of explanation, the word "grouping" is used below. Any question, therefore, of isomerism in the side chain is excluded from this discussion. Optical isomers due to restricted rotation are also not counted.

It will be obvious that the number of dimethylnaphthalenes will be the same as that of the hexamethyl compounds: both of these are referred to as the A_6B_2 naphthalenes. The lettering in the final table is arranged so that in the expression $A_aB_bC_c \cdots$, $a \geq b \geq c$, etc. The sum of a, b, c, etc. is equal to n, the number of replaceable hydrogen atoms in the original hydrocarbon.

In every case, the parent hydrocarbon is planar and the symmetry elements within the plane are considered. A symmetry factor S is defined as follows:—

(a) If the hydrocarbon molecule has one or more axes of two-fold symmetry, S is equal to twice the number of such axes.

(b) If the hydrocarbon molecule has a center of two-fold symmetry but no axis, $S = 2$ (for one of three-fold symmetry, $S = 3$).

(c) If the hydrocarbon molecule has neither a center nor an axis of symmetry, $S = 1$.

Thus, for example:—

	TWO-FOLD AXES	TWO-FOLD CENTRE	S
Benzene	6	(1)	12
Coronene	6	(1)	12
Triphenylene	3	—	6
Naphthalene	2	(1)	4
Anthracene	2	(1)	4
Phenanthrene	1	—	2
Chrysene (1:2-Benzphenanthrene)	—	1	2
1:2-Benzanthracene	—	—	1

Now the number of ways in which b groupings of type B can be arranged in n positions, while a groupings of type A fill the remaining $(n - b)$ positions, is

$$C = \frac{n!}{a!\,b!}$$

This would be the number of A_aB_b isomers if the parent hydrocarbon had no elements of symmetry.

For the $A_aB_bC_cD_d \cdots$ isomers, this formula becomes

$$C = \frac{n!}{a!\,b!\,c!\,d! \cdots}$$

If the symmetry factor of the parent hydrocarbon is S, and none of the $A_aB_bC_cD_d \cdots$ isomers derived from it has an element of symmetry, the number of such isomers is given by

$$C = \frac{1}{S} \times \frac{n!}{a!\,b!\,c!\,d! \cdots}$$

In cases where none of the axes of symmetry of the original hydrocarbon passes through a substitutable CH group, the above condition is satisfied if any of the numbers a, b, c, d, etc. is odd. In cases such as benzene or anthracene, where an axis of symmetry can pass through a pair of CH positions, more than two of these numbers must be odd. Another exception must be made in cases such as triphenylene and coronene, where three-fold symmetry is possible if the number of groups of each substituent is a multiple of three.

If all of the $A_aB_bC_cD_d \cdots$ isomers had the same symmetry factor S' (defined in the same way as S for the parent hydrocarbon) then equation [1] would be

$$C = \frac{S'}{S} \times \frac{n!}{a!\,b!\,c!\,d! \cdots}$$

i.e.,

$$\frac{S}{S'}\,C = \frac{n!}{a!\,b!\,c!\,d! \cdots} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots [2]$$

Unless $S' = 1$, the isomers will not, in fact, all have the same symmetry factor S'. There will be C_1 isomers of symmetry factor S_1', C_2 isomers of symmetry factor S_2', and so on. Hence the left hand side of equation [2] is actually the sum of terms of the type $\frac{S}{S_1'}\,C_1$. In other words

$$\sum \frac{S_1'}{S}\,C_1 = \frac{n!}{a!\,b!\,c!\,d! \cdots} \quad \ldots\ldots\ldots\ldots\ldots\ldots\ldots\ldots [3]$$

The numbers of symmetrical $A_aB_bC_cD_d \cdots$ isomers were found by drawing or inspection, and application of equation [3] gave the number of asymmetrical

compounds. Thus where two of the numbers a, b, $c \cdots$ etc. in the $A_aB_bC_c \cdots$ substituted anthracenes are odd, $S' = 2$ for the symmetrical cases and application of equation [3] shows that the number of $A_aB_bC_c \cdots$ compounds exceeds that given by equation [1] by half the number of symmetrical isomers.

Another equation of some value is the following: if the number of $A_aB_bC_c \cdots$ isomers is N that of $A_{a-1}B_bC_cX \cdots$ is N_1 and that of $A_{a-2}B_bC_cX_2 \cdots$ is N_2

then
$$N_2 = \left(\frac{a}{2} - 1\right) N_1 + \frac{aN}{2} \quad \ldots\ldots\ldots\ldots\ldots\ldots [4]$$

This relation, however, only holds for cases where the quantity N_1 can be obtained from equation [1]. In addition, it is inapplicable to benzene, triphenylene or coronene derivatives, since in these compounds certain arrangements become identical on rotation through 60° or 120° about the centre of symmetry.

However, the phenanthrene system may be quoted as one where equation [4] has been useful. Thus, for example,

Number of A_8B_2 = 4 × (Number of A_9B) + 5 × (Number of A_{10})

Number of $A_6B_2C_2$ = 3 × (Number of A_7B_2C) + 4 × (Number of A_8B_2) and Number of $A_6B_2C_2$ = (Number of A_6B_3C) + 2 × (Number of A_6B_4) the third equation being used to obtain the value for A_6B_4.

PART II. RESULTS

TABLE I

NUMBERS OF ISOMERS IN THE BENZENE SERIES

A_6	1						
A_5B	1						
A_4BC	3	A_4B_2	3				
A_3BCD	10	A_3B_2C	6	A_3B_3	3		
A_2BCDE	30	A_2B_2CD	16	$A_2B_2C_2$	11		
$ABCDEF$	60						

TABLE II

NUMBERS OF ISOMERS IN THE NAPHTHALENE SERIES

A_8	1						
A_7B	2						
A_6BC	14	A_6B_2	10				
A_5BCD	84	A_5B_2C	42	A_5B_3	14		
A_4BCDE	420	A_4B_2CD	210	A_4B_3C	70	A_4B_4	22
A_3BCDEF	1,680	A_3B_2CDE	840	A_3B_3CD	280		
$A_2BCDEFG$	5,040	A_2B_2CDEF	2,520				
$ABCDEFGH$	10,080						
		$A_4B_2C_2$	114				
		$A_3B_2C_2D$	420	$A_3B_3C_2$	140		
		$A_2B_2C_2DE$	1,260				
		$A_2B_2C_2D_2$	648				

TABLE III

NUMBERS OF ISOMERS IN THE ANTHRACENE[a] SERIES

A_{10}	1						
A_9B	3						
A_8BC	23	A_8B_2	15				
A_7BCD	180	A_7B_2C	92	A_7B_3	32		
A_6BCDE	1,260	A_6B_2CD	632	A_6B_3C	212	A_6B_4	60
A_5BCDEF	7,560	A_5B_2CDE	3,780	A_5B_3CD	1,260	A_5B_4C	318
$A_4BCDEFG$	37,800	A_4B_2CDEF	18,900	A_4B_3CDE	6,300	A_4B_4CD	1,578
$A_3BCDEFGH$	151,200	A_3B_2CDEFG	75,600	A_3B_3CDEF	25,200		
$A_2BCDEFGHI$	453,600	$A_2B_2CDEFGH$	226,800				
ABCDEFGHIJ	907,200					A_5B_5	66
		$A_6B_2C_2$	330				
		$A_5B_2C_2D$	1,896	$A_5B_3C_2$	636		
$A_4B_2C_2D_2$	4,770	$A_4B_2C_2DE$	9,456	$A_4B_3C_2D$	3,156	$A_4B_4C_2$	810
$A_3B_2C_2D_2E$	18,912	$A_3B_2C_2DEF$	37,800	$A_3B_3C_2DE$	12,600		
$A_2B_2C_2D_2EF$	56,712	$A_2B_2C_2DEFG$	113,400				
		$A_4B_3C_3$	1,056				
$A_3B_3C_2D_2$	6,312	$A_3B_3C_3D$	4,200	$A_2B_2C_2D_2E_2$	28,440		

[a] Since the symmetry properties of pyrene and diphenyl are identical with those of anthracene, this table also applies to them.

TABLE IV

NUMBERS OF ISOMERS IN THE PHENANTHRENE SERIES

A_{10}	1						
A_9B	5						
A_8BC	45	A_8B_2	25				
A_7BCD	360	A_7B_2C	180	A_7B_3	60		
A_6BCDE	2,520	A_6B_2CD	1,260	A_6B_3C	420	A_6B_4	110
A_5BCDEF	15,120	A_5B_2CDE	7,560	A_5B_3CD	2,520	A_5B_4C	630
$A_4BCDEFG$	75,600	A_4B_2CDEF	37,800	A_4B_3CDE	12,600	A_4B_4CD	3,150
$A_3BCDEFGH$	302,400	A_3B_2CDEFG	151,200	A_3B_3CDEF	50,400		
$A_2BCDEFGHI$	907,200	$A_2B_2CDEFGH$	453,600				
ABCDEFGHIJ	1,814,400					A_5B_5	126
$A_6B_2C_2$	640						
$A_5B_2C_2D$	3,780	$A_5B_3C_2$	1,260			$A_4B_2C_2D_2$	9,480
$A_4B_2C_2DE$	18,900	$A_4B_3C_2D$	6,300	$A_4B_4C_2$	1,590	$A_3B_2C_2D_2E$	37,800
$A_3B_2C_2DEF$	75,600	$A_3B_3C_2DE$	25,200			$A_2B_2C_2D_2EF$	113,400
$A_2B_2C_2DEFG$	226,800						
		$A_4B_3C_3$	2,100				
$A_3B_3C_2D_2$	12,600	$A_3B_3C_3D$	8,400			$A_2B_2C_2D_2E_2$	56,760

TABLE V

OTHER AROMATIC SYSTEMS

	A_{12}	$A_{11}B$	$A_{10}B_2$	A_9B_3	A_8B_4	A_7B_5	A_6B_6
Naphthacene and perylene	1	3	21	55	135	198	246
Triphenylene	1	2	14	38	90	132	166
3:4-Benzphenanthrene, 3:4-benzpyrene, and chrysene	1	6	36	110	255	396	472
1:2-Benzanthracene and 1:2-benzpyrene	1	12	66	220	495	792	924
Coronene	1	1	9	19	50	66	90
	A_{14}	$A_{13}B$	$A_{12}B_2$	$A_{11}B_3$	$A_{10}B_4$	A_9B_5	A_8B_6	A_7B_7
2:3-Benznaphthacene and *p*-Diphenylbenzene (Terphenyl)	1	4	28	94	266	508	777	868

OXFORD, ENGLAND

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[CONTRIBUTION FROM THE NATIONAL INSTITUTES OF HEALTH AND THE NATIONAL INSTITUTE OF MEDICAL RESEARCH]

THE STEREOCHEMICAL FORMULAS OF THE HYDROXYPROLINE AND ALLOHYDROXYPROLINE ENANTIOMORPHS AND SOME RELATED SUBSTANCES

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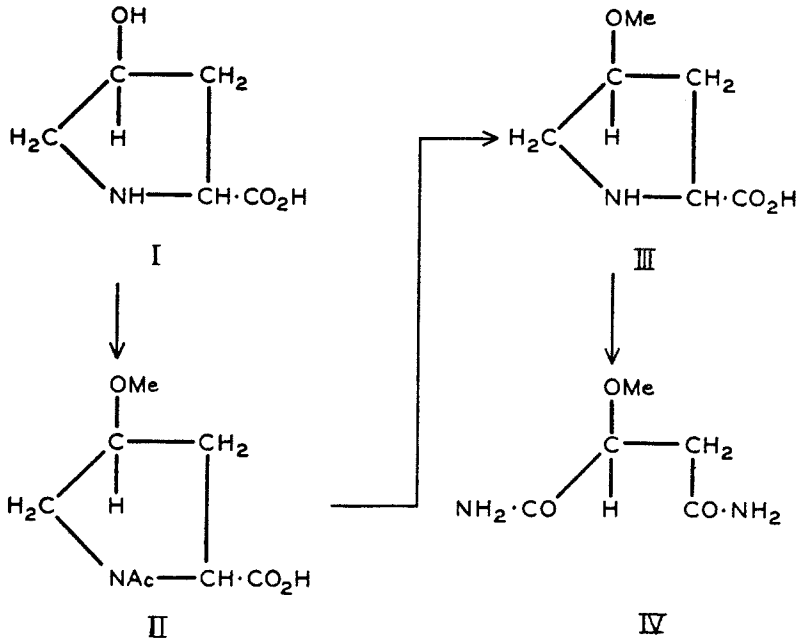
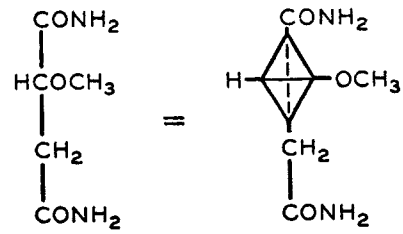
In 1945 one of us reported (1) experimental data of a conclusive nature which disclose the configuration of the asymmetric γ-carbon atom of the naturally occurring α-amino acid hydroxyproline and its enantiomorph, and supplementary data which allow extension of these determinations to the enantiomorphs of allohydroxyproline. Starting with natural hydroxyproline ($[\alpha]_D$ $-76.3°$), its O-

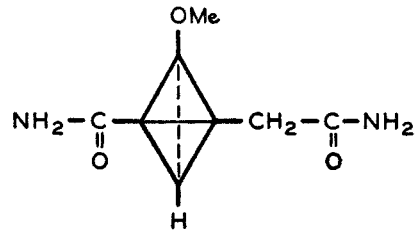


methyl ether was prepared and from this substance there was obtained in a series of degradation reactions the crystalline dextrorotatory diamide of methoxysuccinic acid, the configuration of which had been previously established as

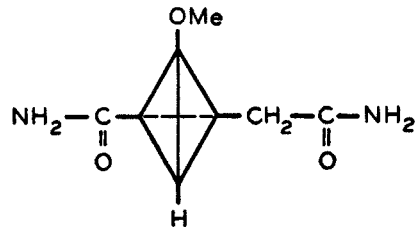


in the configurational system that was originally instituted by Emil Fischer. There was then deduced from these experimental data a perspective partial stereo-formula of natural hydroxyproline through the sequence of formulas shown here as I–IV.

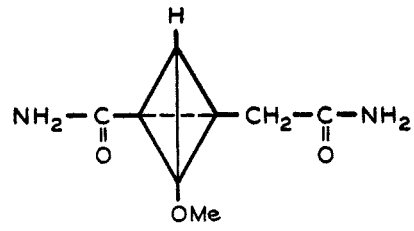
Subsequent to the publication of formula I it has been recognized by each of us independently that this formula does not represent correctly the configuration of the asymmetric γ-carbon atom. If one constructs the customary mechanical model of I by the use of a tetrahedron for its asymmetric γ-carbon atom it becomes apparent that IV must be interpreted as



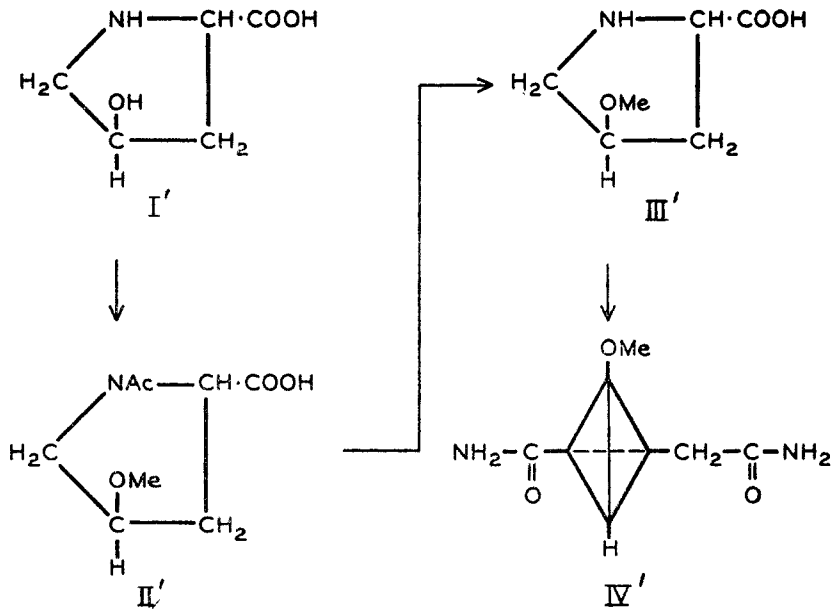
which is not the stereo-formula for the dextrorotatory diamide of methoxy-succinic acid in the Fischer system; the correct stereo-formula for this dextrorotatory diamide is



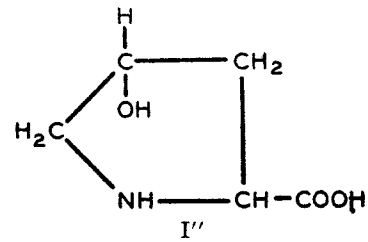
and formula IV really represents the levorotatory diamide, the formula of which by the Fischer conventions is



If one wishes to express the sequence I–IV in the universally accepted conventional system of Fischer, the development is correctly shown by the formulas I′–IV′. It will be seen that formulas I and I′ are enantiomorphous as respects the

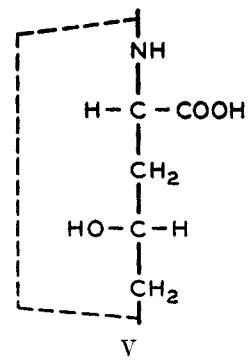


asymmetric γ-carbon atom, a relationship that may be visualized more readily if one turns the mechanical model of I′ so that its perspective picture is I″; in I″ the ring lies in the plane of the paper, the OH group lies below this plane and the



I″

H attachment to the γ-carbon atom lies above this plane. In a review article (2) of recent date the new formula V for natural hydroxyproline was deduced and it was stated that "this formula in which the plane of the ring is perpendicular

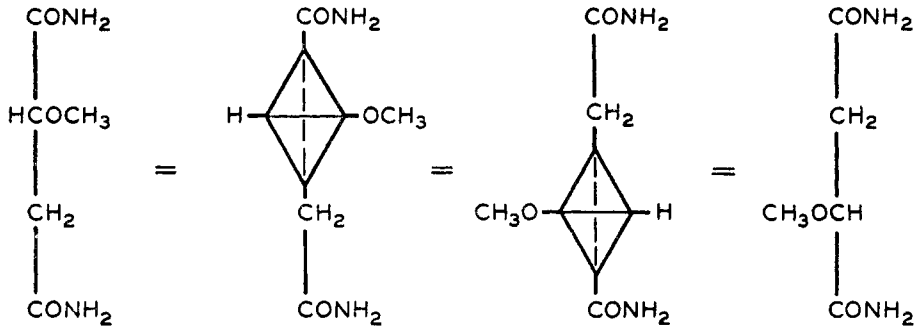


V

to the plane of the paper shows very clearly the *trans* position of the two substituents [OH and COOH] in hydroxyproline." This formula V conforms with the formula I′ as respects the asymmetric γ-carbon atom provided that the reader observes the usual convention that the dotted line lies below the plane of the paper.

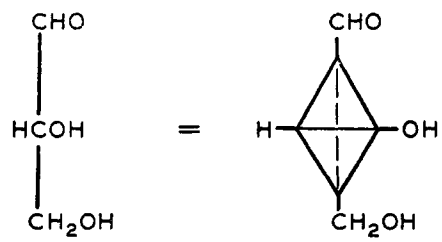
We believe it advisable for the sake of full clarity that the development of the stereo-formula for natural hydroxyproline ($[\alpha]_D$ −76.3°) should be presented anew, with particular attention at all steps to the observance of the two conventions that were established by Emil Fischer for writing the stereo-formulas of organic chemistry in a plane.[1]

The stereo-formula of the dextrorotatory diamide of methoxysuccinic acid is VI, which may also be written as VII, VIII or IX.



VI VII VIII IX

These equivalent formulas are all of the Fischer system and they preserve his two conventions. The first convention specifies the mechanical model that is represented by such a formula as VI; a straight line joining the connecting apices of the four carbon atoms (tetrahedra) lies in the plane of the paper and the H and OCH_3 attachments to the asymmetric carbon atom lie above the plane of the paper. Formula VII is a representation of the model in such a way that this first convention is indicated graphically; the dotted (invisible) back edge of the tetrahedron lies in the straight line of the four carbon atoms in the plane of the paper and the visible edge connecting H and OCH_3 lies above the plane of the paper. In present day practice Fischer's second convention selects as reference substance the



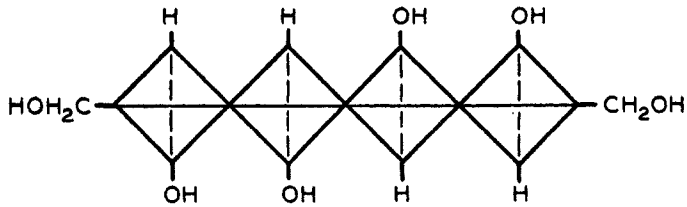
X XI

[1] These conventions are the subject of a review article by one of us (H) in *Advances in Carbohydrate Chem.*, **3**, 1 (1948).

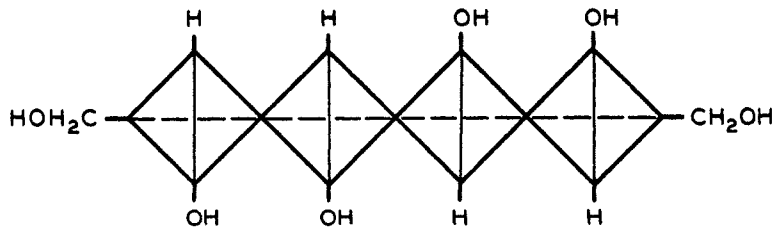
dextrorotatory enantiomorph of glyceraldehyde, arbitrarily assigns to it the configuration X and designates it as D$_g$-glyceraldehyde.

The subscript g in the prefix D$_g$ indicates that the D is being used in the sense of carbohydrate nomenclature. Later, the prefixes D$_s$ and L$_s$ will appear in designation of the enantiomorphs of some α-amino acids. The subscript g stands for glyceraldehyde as the reference substance of the carbohydrate nomenclature and s is the analogous abbreviation for serine, the reference substance of the α-amino acid system of nomenclature. The conclusive correlation of the enantiomorphs of these two reference substances through precise chemical transformations depends upon the following observations: (a) carbon atom 2 in chitosamine was correlated in configuration with one of the enantiomorphs of glyceraldehyde by Haworth, Lake, and Peat (3), who proved that chitosamine is 2-desoxy-2-amino-D-glucose; (b) carbon atom 2 of chitosamine was correlated in configuration with one of the enantiomorphs of alanine by Wolfrom, Lemieux, and Olin (4); the enantiomorphs of alanine and serine were correlated by Fischer and Raske (5). The need for some method of distinguishing between the D and L nomenclatures of carbohydrates and α-amino acids in cases where confusion can arise, and the use of g and s subscripts to meet this need, were proposed by one of us (H) in January 1947; see a report by H. B. Vickery, *J. Biol. Chem.*, **169**, 242 (1947) and *Chem. Eng. News*, **25**, 1365 (1947). The D and L symbols are often the same in the carbohydrate and α-amino acid nomenclatures but this is not always the case; thus D$_g$-glucosaminic acid is a D$_s$-α-amino acid but D$_g$-mannosaminic acid is an L$_s$-α-amino acid, and natural threonine is an L$_s$-α-amino acid although it is configurationally related closely to D$_g$-threonic acid.

The earliest use that is known to us of graphic formulas of the type of VII and VIII to represent the two Fischer conventions is the formula of D$_g$-mannitol that was published by L. Maquenne in his textbook "Les Sucres et Leurs Principaux Dérivés" (Carré and Naud, Paris, 1900). Maquenne's formula (p. 13) is



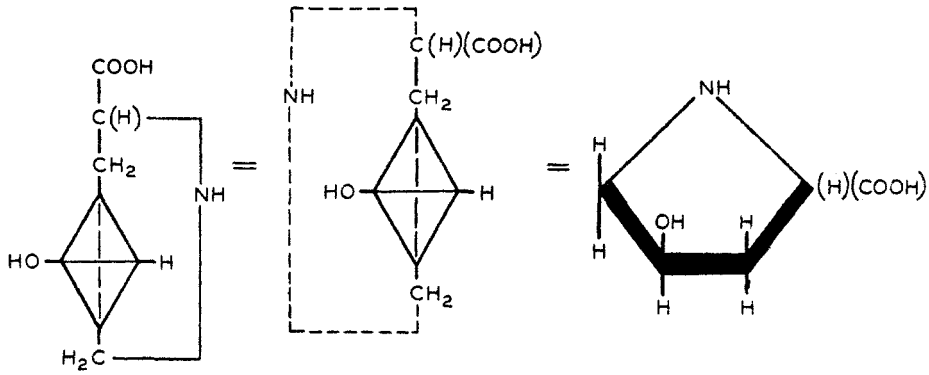
but it is incorrectly drawn as it does not follow Fischer's first convention and the mechanical model which it represents is really that of L$_g$-mannitol. The correct formula for D$_g$-mannitol is



which preserves Fischer's first and second conventions.

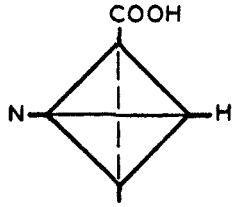
The configuration VIII for the dextrorotatory diamide of methoxysuccinic acid leads to the partial stereo-formula XII for natural hydroxyproline ($[\alpha]_D$ −76.3°);

in this formula the arrangements for the asymmetric γ-carbon atom are specified through Fischer's two conventions but the arrangements for the asymmetric α-carbon atom are left unspecified. To change formula XII to a perspective formula XIV of the type that was introduced by Drew and Haworth (6) for cyclic carbohydrate structures, one observes with a mechanical model that the tetrahedron representing the α-carbon atom must be turned 120° in order that the ring may be represented as in a plane perpendicular to the plane of the paper and lying below the paper; this is represented in XIII. Formula XIV is then readily visualized as a perspective view of XIII. Referring back to formulas I and I′ one recognizes that XIV is in agreement with I′ but not with I.



XII XIII XIV

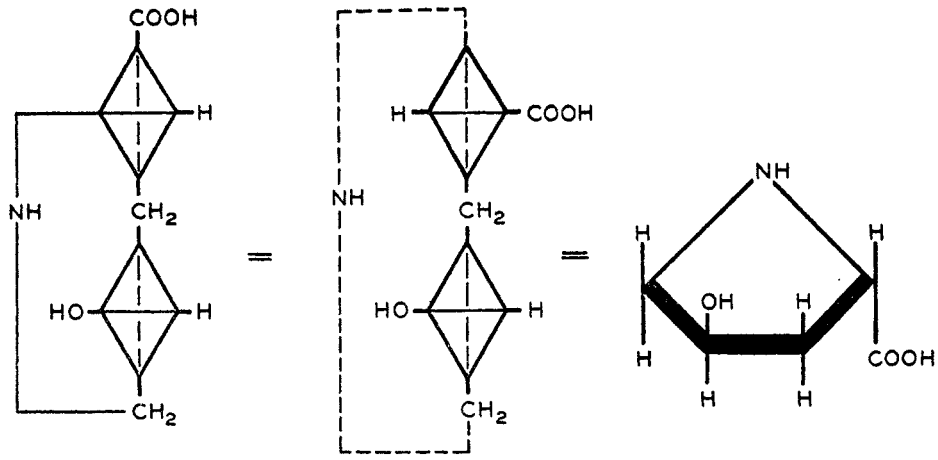
Formulas I′ and XIV leave unspecified the stereo arrangement for the α-carbon atom. The article (1) by one of us (N) summarizes the strong evidence from several earlier sources that in natural hydroxyproline ($[\alpha]_D$ −76.3°) this atom has the L$_s$ configuration XV, namely that of L$_s$-serine. When this arrangement is supplied to I′ and XII, the full configurational formula of natural L$_s$-



XV

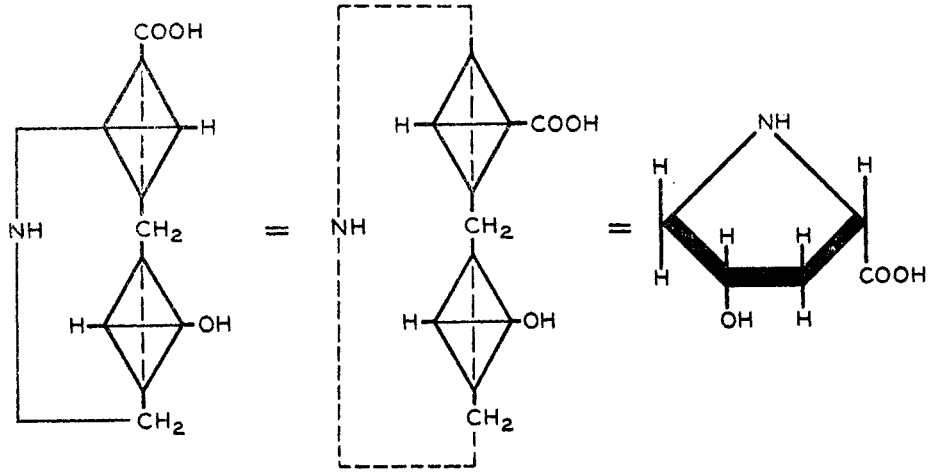
hydroxyproline becomes XVI in the Fischer system, and the equivalent in the Haworth perspective representation becomes XVIII, through XVII. Formulas V and XVII are in agreement.

In the research (1) by one of us (N) L$_s$-hydroxyproline (XVIII) was converted to one of the enantiomorphs of its diastereomer by a Walden inversion of the arrangement of the γ-carbon atom; this enantiomorph is accordingly named L$_s$-



XVI XVII XVIII

allohydroxyproline ($[\alpha]_D$ −58.1°), and its stereo-formula is obviously XIX and the equivalent XXI, through XX.



XIX XX XXI

The stereo-formulas that have now been established for the enantiomorphs of hydroxyproline and allohydroxyproline through the experimental data (1) of one of us (N) regarding the γ-carbon atom and the earlier evidence concerning the α-carbon atom are summarized in Table I.

The perspective formulas of the table can be extended to several other substances, including some alkaloids.

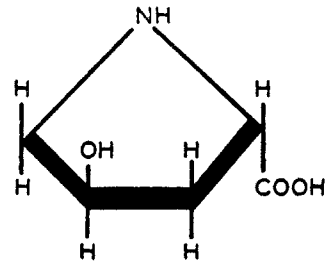
L$_s$-Hydroxyproline was converted by Kaneko (9) to a γ-chloroproline which could be reduced to natural (levorotatory) proline, which accordingly can be assigned the formula XXVI. The formula of its enantiomorph becomes XXVII.

The earlier evidence that natural proline and natural hydroxyproline are sterically related to L$_s$-serine involved some uncertainty because of the fact that

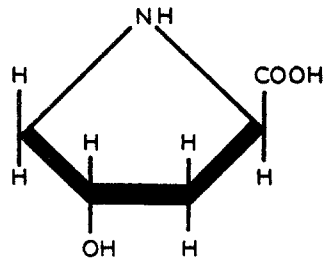
TABLE I

THE ENANTIOMORPHS OF HYDROXYPROLINE AND ALLOHYDROXYPROLINE

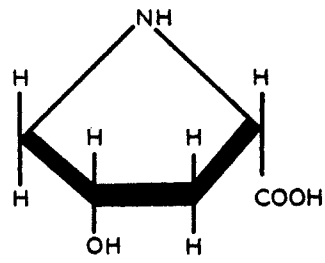
L_3-Hydroxyproline, $[\alpha]_D$ −76.3° (XXII) (Occurs in proteins)



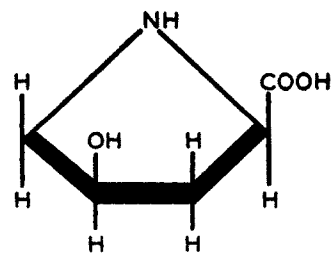
D_3-Hydroxyproline, $[\alpha]_D$ +75.2° (XXIII) (Natural occurrence unknown)

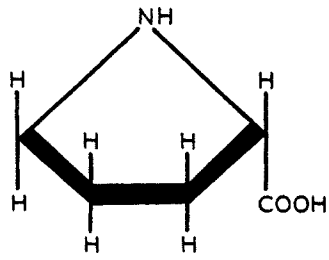


L_3-Allohydroxyproline (7), $[\alpha]_D$ −58.1° (XXIV) [Occurs in phalloidine, a toxic peptide from *Amanita phalloides* (8)]

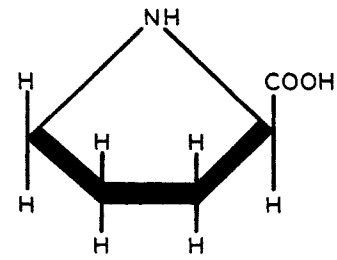


D_3-Allohydroxyproline (7), $[\alpha]_D$ +58.6° (XXV) (Natural occurrence unknown)





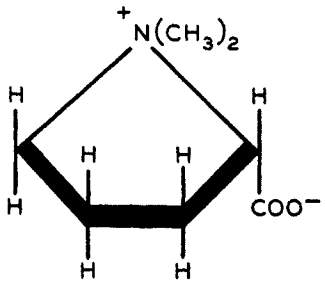
XXVI
L_s-Proline
(Levorotatory, occurs in proteins)



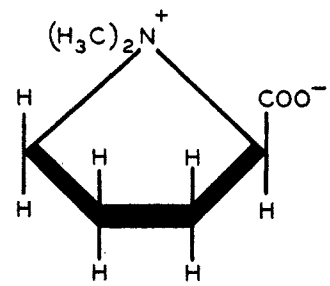
XXVII
D_s-Proline
(Dextrorotatory, natural occurrence unknown)

the nitrogen atom of proline is a member of the pyrrolidine ring. The recent experimental work of Karrer and Portmann (10b) in chemically correlating natural proline with natural glutamic acid, which possesses no ring and is believed on very strong evidence to be sterically related to L_s-serine, gives a more secure foundation to the older inference that natural proline is L_s-proline.

The levorotatory enantiomorph of stachydrine has been correlated sterically with L_s-proline (10); the perspective formula for this enantiomorph thus becomes XXVIII and that of its mirror image becomes XXIX.



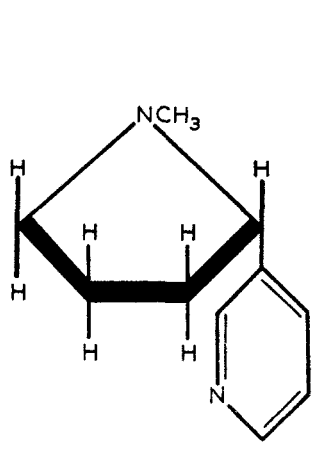
XXVIII
L_s-Stachydrine
(Levorotatory hydrochloride)



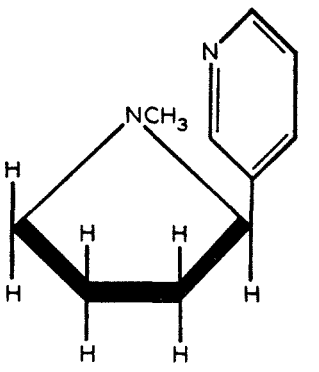
XXIX
D_s-Stachydrine

Since the naturally occurring levorotatory enantiomorph of nicotine has been shown by Karrer and Widmer (10a) to be sterically related to L_s-proline, natural nicotine is to be given the perspective formula XXX and its enantiomorph the formula XXXI.

The mechanical model that is represented by XXX is that of natural nicotine through Fischer's second convention (*i.e.*, that XI is the model of D_g-glyceraldehyde and in consequence XV the analog for L_s-serine). While there is thus no ambiguity with respect to the correlation of actual models, the use of an L or D symbol for natural nicotine becomes a matter of convention in nomenclature. Nicotine possesses no carboxyl or carbonyl group and thus one must select some other similarity between the formulas for nicotine and serine (or glyceraldehyde) as an arbitrary basis for L and D nomenclature. Fortunately, the selection in this



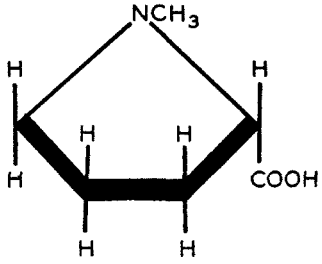
XXX
L$_S$-Nicotine
(Naturally occurring, levorotatory)



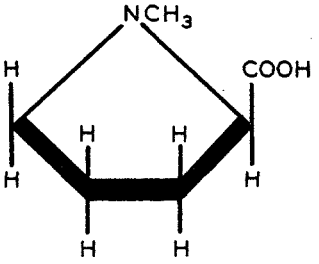
XXXI
D$_S$-Nicotine

instance is readily made through the close similarity of formulas XXVI for L$_S$-proline and XXX for natural nicotine. Natural nicotine appears to us to be best designated L$_S$-nicotine because it can be regarded as derivable, at least in principle, by the replacement of the COOH group of N-methyl-L$_S$-proline by a proper pyridine residue.

Levorotatory hygric acid has been correlated chemically with natural L$_S$-proline by Karrer and Widmer (10a); accordingly, the perspective formulas of the enantiomorphs of hygric acid are XXXII and XXXIII.



XXXII
L$_S$-Hygric Acid
(levorotatory)



XXXIII
D$_S$-Hygric Acid

It is important to observe that Emil Fischer's second convention is maintained in all the formulas XXII–XXXIII and that their derivation has included his first convention. The mechanical models that are specified by these stereo-formulas through his first and second conventions are entirely independent of all nomenclature, a matter that was emphasized by Fischer (11).

BETHESDA, MARYLAND AND HAMPSTEAD, LONDON

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(11) FISCHER, *Ber.*, **40**, 102 (1907); ["Untersuchungen über Kohlenhydrate und Fermente," Verlag Julius Springer, Berlin, vol. 1, p. 893 (1909)].

[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

THE CONFIGURATION OF CHOLESTEROL DIHALIDES

D. E. A. RIVETT[1] AND EVERETT S. WALLIS

Received June 13, 1949

The addition of halogen to the double bond of cholesterol can theoretically give rise to four stereoisomers, two of which possess the *cis* or coprostane skeleton and two the *trans* or cholestane arrangement. However, only one isomer has as yet been isolated from the direct bromination or chlorination of the free sterol.

On the basis of earlier observations that saturated 3-keto steroids with rings A and B fused in the *cis* position are brominated at C_4 and those with an A/B: *trans*-ring-union are brominated at C_2 (1), Butenandt and Schramm (2) and Inhoffen (3) showed that dibromocholestan-3-one, and hence dibromocholesterol, possesses a *cis* or coprostane structure. The validity of this work rests on the assumption that the same directive influences are present when hydrogen at C_5 is replaced by halogen. This assumption appears to be well-founded, since bromination of a 3-keto-cholestane-5,6(β)-diol, the configuration of whose hydroxyl group at C_5 is known (4), yields 2-bromo-3-ketocholestane-5,6(β)-diol (5).

In this connection it is interesting to note that Décombe and Rabinowitch (6) have advanced a *trans* or cholestane structure for dichlorocholesterol because it yields 3(β)-hydroxycholestane on catalytic hydrogenation. It must be noted, however, that these authors provide no evidence to support this assumption, and as will be shown later in this paper, this assignment of a *trans* configuration is incorrect.

That there is the possibility of the formation of isomeric dihalides of $\Delta^{5,6}$-sterols was first shown by Berg and Wallis (7), who obtained two isomeric dichlorides by the action of iodobenzene dichloride on certain $\Delta^{5,6}$-sterol esters. This phenomenon was observed with cholesteryl benzoate and *p*-toluenesulfonate, β-sitosteryl benzoate, and stigmasteryl benzoate.

In this paper we wish to describe the results of our investigations on the determination of the configurations of the two chlorine atoms at C_5 and C_6 of one of these dichloro esters, namely the lower-melting isomer of 3-benzoxy-5,6-dichlorocholestane (m.p. 120°). This compound on hydrolysis with alkali yields a 5,6-dichlorocholesterol identical with the cholesterol dichloride obtained in poor yield by direct chlorination of cholesterol. It is also identical with the cholesterol dichloride obtained in good yield by the action of iodobenzene dichloride on the free sterol. This dichlorocholesterol was oxidized to the corresponding 3-keto compound and treated with one mole of bromine in acetic acid solution. We submit the following evidence as indicative that the bromine atom in the resulting bromo compound is situated at C_4. Dehalogenation with zinc and acetic acid yields cholestene-4-one-3. Treatment with potassium acetate in boiling ethanol yields a compound which Inhoffen (3), who obtained it from the corresponding

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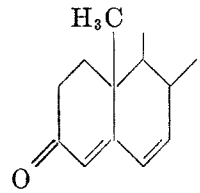
tribromo compound, has formulated as (I) but which has recently been shown by spectroscopic means to be (II).



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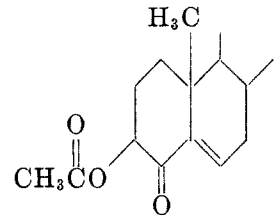
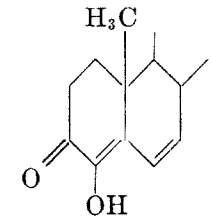


II



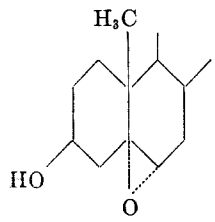
III

With hot hydrochloric acid (II) was converted to 4-hydroxy-4,6-cholestadiene-3-one (III). The products (II) and (III) which had previously been obtained from 4,5,6-tribromocholestan-3-one are identical with those which we prepared from bromodichlorocholestan-3-one.

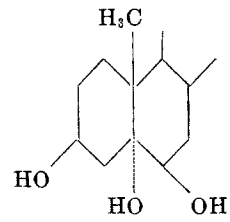
It should be noted, however, that the stability of the bromodichlorocholestan-3-one is far greater than that of the corresponding tribromo compound, for whereas 4,5,6-tribromocholestan-3-one on heating with sodium iodide in ethanol yields the enol ethyl ether of 4-cholestene-3,6-dione, 4-bromo-5,6-dichlorocholestan-3-one under the same conditions is recovered largely unchanged.

Accordingly we must conclude that rings A and B in dichlorocholesterol are fused in the *cis* position in the same way as in dibromocholesterol and in cholesterol hydrochloride (8) and not in the *trans* position as assumed by Décombe and Rabinowitch (6).

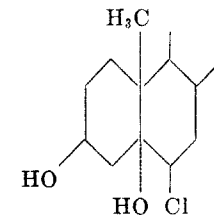
Our next experiments were directed to the solution of the problem of determining the configuration of the halogen atom in the 6-position of the cholesterol dihalide molecule. To our knowledge no attempt has as yet been made to determine the stereochemical configuration of the halogen atom in this position in either dibromo- or dichloro-cholesterol. Any methods involving substitution of this halogen atom at C_6 are liable to doubt because of uncertainty in establishing whether *cis* or *trans* elimination has occurred. However, we have succeeded in determining the arrangement of this halogen atom in the following manner. When "α"-cholesterol oxide, which has been shown to be 5,6(α)-oxidocholestane-3-ol (IV) (4), is treated in the form of its acetate with aqueous dioxane at 150°, or with acetic acid, it forms the 3-acetoxy, or the 3,6-diacetoxy derivative respectively, of the so-called "trans triol" (9, 4), the configuration of which has been established as cholestane-3(β),5,6(β)-triol (V) (4, 5). Similar treatment of the 3-acetoxy or the 3-benzoxy derivatives of (IV) with hydrochloric acid yields a product which has been shown to possess a tertiary hydroxyl group and which on hydrolysis with quinoline or sodium carbonate again yields (IV) (9, 10, 11). This product is therefore the 3-acetoxy or the 3-benzoxy derivative of 6(β)-chlorocholestane-3,5(β)-diol (VI), inversion having as before occurred at C_6 (4). Treatment of the corresponding derivatives of "β"-cholesterol oxide (VII) with hydrochloric acid gives derivatives of 5-chlorocholestane-3(β),6(β)-diol (VIII) with inversion at C_5 (4, 12).



IV



V



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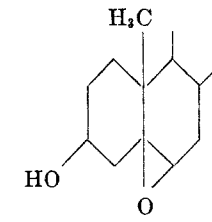

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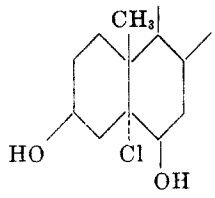

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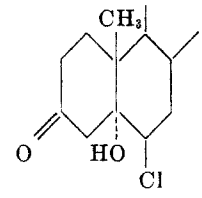

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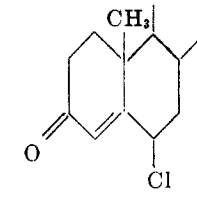

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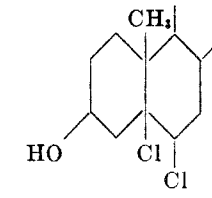

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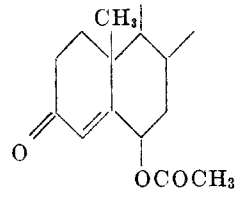
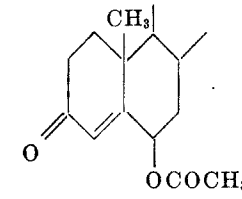


XII



XIII

We have obtained (VI) by reacting the *free* sterol "α"–oxide with hydrochloric acid. This compound (VI) was oxidized with chromic acid to the corresponding 3-keto steroid (IX). Dehydration with thionyl chloride and pyridine gave 6(β)-chloro-4-cholestene-3-one (X). Dichlorocholesterol on oxidation to the ketone followed by dehydrochlorination with potassium acetate in ethanol yielded a product identical in optical rotation, ultra-violet absorption spectrum, melting point, and mixed melting point with this compound. Thus both chlorine atoms in the particular dichlorocholesterol under discussion are on the same side of the molecule and configurationally the compound has the structure (XI).

When both 6(β)-chloro-4-cholestene-3-one (X) and the corresponding 6-bromo compound, obtained by oxidation and dehydrobromination of dibromocholesterol (13), were allowed to react with acetate ions the same product was obtained. It possessed an ultra-violet absorption band similar to the starting materials and analyzed correctly for the corresponding acetate. However, it differs both in melting point and rotation from the known 6(β)-acetoxy-4-cholestene-3-one (XII). We believe that it is 6(α)-acetoxy-4-cholestene-3-one (XIII) which as yet has not been reported. The appearance of the same 6-acetoxy compound from both the 6-bromo and the 6-chloro compounds indicates that the stereochemical arrangement of the halogen atoms in both these steroids is the same. Accordingly, dibromocholesterol is correctly designated as 5,6(β)-dibromocoprostan-3-ol.

Experiments are now in progress designed to determine the configuration of the two halogen atoms in the higher-melting isomer of 3-benzoxy-5,6-dichlorochol-

estane (m.p. 251°), originally prepared by Berg and Wallis (7) by the action of iodobenzene dichloride on cholesteryl benzoate, and in the free sterol dichloride corresponding to this benzoate subsequently prepared by Décombe and Rabinowitch (14), by the action of the same reagent on cholesteryl formate followed by gentle hydrolysis. The results of these investigations will be reported at a later date.

Perhaps in this connection it should be noted that it has been reported (15) that two isomeric bromides are obtained on direct bromination of cholesteryl benzoate. Evidence, however, submitted to substantiate this claim is weak and the problem needs further investigation.

EXPERIMENTAL[2]

Preparation of 4-bromo-5,6-dichlorocholestan-3-one. Dichlorocholesterol, m.p. 138°, prepared by the method of Berg and Wallis (7), was oxidized with chromic acid according to the directions of Décombe and Rabinowitch (6) to yield 5,6-dichlorocholestan-3-one, m.p. 97° (dec.), softening at 94°; $(\alpha)_D^{22}$ −27° (*c*, 4.9).

To a solution of 1.90 g. of 5,6-dichlorocholestan-3-one in 150 ml. of acetic acid was added a few drops of a 50% mixture of hydrobromic and acetic acids followed by 1 mole of bromine dissolved in acetic acid (5.9 ml., 0.707 *M*.). The solution was decolorized almost immediately. After the solution stood at room temperature for a half-hour 300 ml. of water was added and the resulting precipitate filtered off, washed with water, and dried. Recrystallization from 60 ml. of a 1:1 mixture of ethyl acetate and ethanol gave 1.25 g. of feathery needles, m.p. 163–165° (dec.). Repeated recrystallization from aqueous acetone gave material which melted constantly at 166–167° (dec.); $(\alpha)_D^{22}$ −20.5° (*c*, 2.9).

Anal. Calc'd for $C_{27}H_{43}BrCl_2O$: C, 60.7; H, 8.11.
Found: C, 61.0; H, 8.24.

Reactions of 4-bromo-5,6-dichlorocholestan-3-one. (a) A mixture of 0.20 g. of 4-bromo-5,6-dichlorocholestan-3-one, 0.5 g. of zinc dust, and 10 ml. of acetic acid was refluxed for 2½ hours. It was then poured into water, extracted with ether, the ethereal solution washed with aqueous bicarbonate, dried, and evaporated. The residue was dissolved in ethyl acetate, the solution decolorized with Darco and methanol added until an incipient turbidity occurred. After ice-box storage, crystals were obtained which on further recrystallization from the same solvent had m.p. 80°, undepressed in admixture with an authentic specimen of cholestene-4-one-3, m.p. 80°.

(b) Hot solutions of 1.00 g. of 4-bromo-5,6-dichlorocholestan-3-one in 4 ml. of benzene and of 0.70 g. of potassium acetate in 25 ml. of ethanol were combined and the mixture gently boiled in an open flask for 20 minutes. There occurred a rapid separation of inorganic material from the solution. Water was added until a faint turbidity formed, the solution was cooled, and the resulting crystalline precipitate filtered off. Recrystallization from 25 ml. of ethanol gave 0.57 g. of 3-acetoxy-2,5-cholestadiene-4-one (II) as prisms, m.p. 158–159°; $(\alpha)_D^{24}$ +11.9° (*c*, 3.1). A mixed melting point with a specimen, m.p. 158–159°, prepared from 4,5,6-tribromocholestan-3-one, was 158–159°. As a further means of identification II was hydrolyzed with ethanolic hydrochloric acid by Inhoffen's procedure (3) to 4-hydroxy-4,6-cholestadiene-3-one (III), m.p. 159–160°, undepressed in admixture with an authentic specimen, m.p. 158–159°; $(\alpha)_D^{24}$ +39.7° (*c*, 2.1).

(c) A solution of 200 mg. of 4-bromo-5,6-dichlorocholestan-3-one in 1 ml. of benzene was refluxed with 160 mg. of sodium iodide and 10 ml. of ethanol for 2½ hours. Water was added and the solution extracted with ether. The ethereal solution was washed with aqueous

[2] All melting points are uncorrected. All rotations were taken in chloroform with a 1-dm. semimicro tube and light-absorption data were determined in ethanolic solutions with a Beckman spectrophotometer.

sodium bisulfite, water, and evaporated. The residue, recrystallized once from ethanol, gave 110 mg. of material melting at 158–159°, and a mixed melting point determination with starting material showed no depression.

Preparation of 6(β)-chlorocholestane-3,5(β)-diol (VI). "α"-Cholesterol oxide (3.2 g.) m.p. 139–140°, prepared by the method Ruzicka and Bosshard (16) was dissolved in 150 ml. of dry chloroform and a steady stream of dry hydrogen chloride was passed through the solution for a half-hour. A crystalline precipitate formed after about 5 minutes. The solution was kept overnight at room temperature and then this precipitate was filtered off. Recrystallization from 150 ml. of ethyl acetate-methanol (1:1) gave 2.5 g. of felted needles, m.p. 163–164° (dec.). Further recrystallization from hexane gave material melting at 164–165° (dec.); $(\alpha)_D^{23}$ −10° (*c*, 2.7).

Anal. Calc'd for $C_{27}H_{47}ClO_2$: C, 73.8; H, 10.8.
Found: C, 73.5; H, 10.9.

Acetylation of this compound with acetic anhydride gave 6(β)-chloro-5-hydroxy-3(β)-acetoxycholestane, m.p. 190–191°; $(\alpha)_D^{22}$ −29.5° (*c*, 1.9). A mixed melting point determination with an authentic specimen, m.p. 190–191°, prepared from "α"-cholesterol oxide acetate by the method of Baxter and Spring (12) showed no depression. These authors report $(\alpha)_D^{18}$ −26.7° and m.p. 186–187°.

Preparation of 6(β)-chloro-5-hydroxy-cholestan-3-one (IX). A solution of 1.9 g. of chromic acid in 50 ml. of acetic acid was added during 1.5 hours with continuous stirring to a solution of 6.2 g. of 6(β)-chlorocholestane-3,5(β)-diol in 850 ml. of acetic acid. The mixture, in which a crystalline precipitate had formed, was allowed to stand at room temperature overnight. Excess chromic acid was then destroyed by the addition of a little ethanol and 2 liters of water was added with stirring. The precipitate was washed with water, and dried. Recrystallization from 330 ml. of ethyl acetate gave 4.2 g. of needles, m.p. 190° (dec.), which on further recrystallization from the same solvent melted at 193° (dec.); $(\alpha)_D^{22}$ +3° (*c*, 0.9). These needles are only slightly soluble in ether, chloroform, and ethanol but are moderately soluble in hot ethyl acetate.

Anal. Calc'd for $C_{27}H_{45}ClO_2$: C, 74.2; H, 10.38.
Found: C, 74.6, H, 10.48.

Preparation of 6(β)-chloro-4-cholestene-3-one (X). A solution of 0.30 g. of 6(β)-chloro-5-hydroxycholestan-3-one in 6 ml. of dry pyridine was treated dropwise at 0° with 0.15 ml. of thionyl chloride. The mixture was kept at this temperature for 20 minutes and then poured into ice-water. The solution was made acid to Congo Red with hydrochloric acid and extracted with ether. The ethereal solution was washed twice with water, filtered from some gelatinous material, and evaporated. The residue crystallized spontaneously on the addition of a little methanol. Two crystallizations from ethyl acetate-methanol gave 80 mg. of short needles, m.p. 127–128°; $(\alpha)_D^{25}$ +13° (*c*, 2.7); λ_{max} (ultra-violet) 2410 Å (ε 14,000).

Preparation of 6(β)-chloro-4-cholestene-3-one (X) *from 5,6-dichlorocholestan-3-one.* Three and seven-tenths grams (8.2×10^{-3} mole) of 5,6-dichlorocholestan-3-one, m.p. 97° (dec.), was refluxed in a solution of 2.4 g. (25×10^{-3} mole) of freshly fused potassium acetate and 150 ml. of ethanol for 2 hours. Potassium chloride began to separate from the solution after about 10 minutes. Water (300 ml.) was carefully added, the solution cooled, and the resulting crystalline precipitate washed with water. The filtrate was analyzed for chloride ion by the Volhard method. It contained 8.2×10^{-3} mole of chloride ion. The precipitate was recrystallized from 80 ml. of aqueous acetone to give 1.95 g. of short needles, m.p. 124–126°. One crystallization from ethyl acetate-methanol gave material which melted constantly at 125–127°; $(\alpha)_D^{26}$ +14.0 (*c*, 2.6); λ_{max} (ultra-violet) 2410 Å (ε 14,000). A mixed melting point determination with the 6(β)-chloro-4-cholestene-3-one, m.p. 127–128°, prepared from 6(β)-chloro-5-hydroxycholestan-3-one showed no depression.

Anal. Calc'd for $C_{27}H_{43}ClO$: C, 77.4; H, 10.34.
Found: C, 77.6; H, 10.16.

Ruzicka (17) mentions the preparation of this compound but gives no details of its properties.

Preparation of 6(α)-acetoxy-4-cholestene-3-one (XIII). To a solution of 6.0 g. of freshly fused potassium acetate in 25 ml. of dry acetic acid was added 1.12 g. (2.67×10^{-3} mole) of 6(β)-chlorocholestene-4-one-3, m.p. 124–126° and the mixture was refluxed gently for 80 minutes with the exclusion of moisture. Water was added and the solution extracted with ether. The aqueous solution contained 2.60×10^{-3} mole of chloride ion as determined by the Volhard method. The ethereal solution was washed thoroughly with dilute sodium bicarbonate solution, water, and dried. The ether was removed and the remaining oil dissolved in a little acetone. This solution was decolorized with Darco and methanol was added until a slight turbidity formed. The crude crystalline product (90 mg.), m.p. 134–136°, which slowly formed was recrystallized twice from acetone-methanol to give long colorless needles which melted constantly at 139–139.5°; $(\alpha)_D^{25}$ +62°; λ_{max} (ultra-violet) 2420 Å (ε 14,500).

Anal. Calc'd for $C_{29}H_{46}O_3$: C, 78.7; H, 10.47.
Found: C, 78.4; H, 10.37.

When 6-bromocholestene-4-one-3, m.p. 131°, prepared by the method of Dane, Wang, and Schulte (13), was treated with potassium acetate and acetic acid as above, the same product, m.p. 139–139.5°, was obtained and in similar yield. A mixed melting point determination with the material, m.p. 139–139.5°, obtained from the 6-chlorocholestene-4-one-3 showed no depression. Attempts to improve the yield of this product were fruitless. Ellis and Petrow (5) record for 6(β)-acetoxycholestene-4-one-3, m.p. 101.5° and $(\alpha)_D^{19}$ +36°.

Preparation of 6(α)-hydroxy-4-cholestene-3-one. A solution of 50 mg. of 6(α)-acetoxy-4-cholestene-3-one in 4 ml. of 0.2 *N* ethanolic sodium hydroxide was kept at room temperature overnight and acidified. Isolation of the product with ether followed by three crystallizations from ether-methanol gave needles m.p. 116–118°. A mixed melting point determination with starting material showed a depression to 90–100°.

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 81.1; H, 11.08.
Found: C, 81.4; H, 11.31.

In ethanolic solution this material gives a purple coloration with ferric chloride. The mother liquors from this product, m.p. 115–118°, were worked up to yield crude material m.p. 106–109°. This was acetylated with acetic anhydride and pyridine at room temperature to yield material identical with the 6(α)-acetoxy-4-cholestene-3-one described above. 6(β)-Hydroxy-4-cholestene-3-one has m.p. 192°.

Acknowledgment. We wish to take this opportunity to express our thanks to the Rockefeller Foundation, New York City, for a grant in aid, and to Merck and Company, Inc., Rahway, New Jersey, for the analyses published in this paper.

SUMMARY

Cholesterol dichloride prepared either by the action of iodobenzene dichloride on cholesterol or by direct chlorination of cholesterol, has been shown to possess the *cis* or coprostane structure and not the *trans* or cholestane arrangement as previously reported. The halogen atom at C_6 in the above cholesterol dichloride and also in cholesterol dibromide has been proved to possess the (β)-configuration.

PRINCETON, NEW JERSEY

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

5-(α-PHENYLETHYL)SEMIOXAMAZIDE AS A CARBONYL REAGENT

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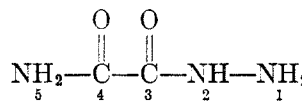
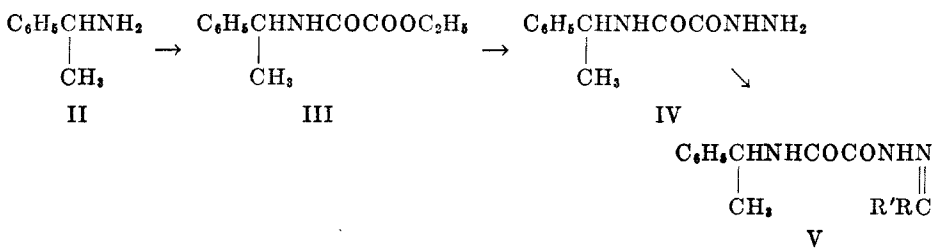
Derivatives (1) of semioxamazide (I) with carbonyl compounds possess the advantage of facile hydrolysis, thus permitting easy regeneration of the aldehyde or ketone. 5-Substituted semioxamazides have been suggested as reagents



I

for the identification of carbonyl compounds, but 5-phenylsemioxamazide (2, 3) and 5-methylsemioxamazide (4) formed derivatives which had uniformly high melting points. We have found that representative carbonyl derivatives of 5-(α-phenylethyl)semioxamazide (IV) possess more satisfactory melting points. Optically active forms of this carbonyl reagent have also been obtained and the utilization of the asymmetric form in the resolution of carbonyl compounds has been demonstrated with 3-methylcyclohexanone.

5-(α-Phenylethyl)semioxamazide (IV) was readily prepared from α-phenylethylamine (II), ethyl oxalate, and hydrazine. The reaction between α-phenyl-



II III IV

V

ethylamine and ethyl oxalate at room temperature gave ethyl N-(α-phenylethyl)oxamide (III) in 91% yield, and that between III and hydrazine gave IV in 93% yield. 5-(α-Phenylethyl)semioxamazide formed derivatives (V) with numerous aldehydes and ketones, and the wide differences in the melting points of these derivatives suggest the feasibility of using this reagent for characterization purposes (see Table I).

The optically active forms of 5-(α-phenylethyl)semioxamazide were readily obtained by the same process starting with *d*- and *l*-α-phenylethylamine. *l*-5-(α-Phenylethyl)semioxamazide was employed successfully for the resolution of 3-methylcyclohexanone. An optically pure derivative was obtained after five recrystallizations. This derivative was readily hydrolyzed to give *l*-3-methylcyclohexanone, which was characterized as the optically pure form by conversion to the semicarbazone (5). Other reagents which have been employed for

the resolution of carbonyl compounds were mentioned by Woodward, Kohman and Harris (6) when they initiated the use of *l*-menthydrazide. Recently, Adams, and Garber (7) have introduced the bisulfites of optically active amines as aldehyde and ketone resolving agents. The *d* and *l* forms of 5-(α-phenylethyl)semioxamazide can now be added to those reagents which are applicable to carbonyl compound resolution.

EXPERIMENTAL

Ethyl N-(α-phenylethyl)oxamide. The preparation of this compound was carried out according to the method which Tierie (4) employed for the formation of ethyl N-methyloxamide. To 15 g. (0.12 mole) of distilled α-phenylethylamine in 150 cc. of absolute ethanol at room temperature was added slowly with stirring 38 cc. (0.25 mole) of distilled ethyl oxalate. The reaction mixture was allowed to stand for twenty-four hours, and a small amount of diamide was removed by filtration. Ethanol was removed by distillation, and unreacted ethyl oxalate, by vacuum-distillation. The residue, which solidified, was purified by recrystallization from absolute ethanol to give 23.2 g. (91%) of glistening colorless needles, m.p. 54°.

Anal. Calc'd for $C_{12}H_{15}NO_3$: C, 65.14; H, 6.83.
Found: C, 64.86; H, 6.68.

5-(α-Phenylethyl)semioxamazide. The method of preparation was similar to that employed by Tierie (4). To a solution of 20 g. (0.10 mol) of ethyl N-(α-phenylethyl)oxamide in 200 cc. of absolute ethanol was added with stirring 6.0 g. (0.10 mole) of 85% hydrazine hydrate. A precipitate formed immediately and the entire contents of the reaction flask became a semi-solid mass. The crude product was dissolved in the minimum amount of hot 95% ethanol, and the solution was filtered to remove traces of the dihydrazide of oxalic acid. The very fine needles which separated from the filtrate were recrystallized from ethanol to give 20.5 g. (93%) of 5-(α-phenylethyl)semioxamazide, m.p. 157°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32; N, 20.28.
Found: C, 58.09; H, 6.27; N, 20.04.

Condensation of 5-(α-phenylethyl)semioxamazide with aldehydes and ketones. The procedure used by Wilson and Pickering (1) for preparing ketonic semioxamazones was found most successful. To 0.1 g. of the aldehyde or ketone in 20 cc. of anhydrous benzene was added 0.2–0.5 g. of the reagent. A crystal of iodine was added and the reaction mixture was refluxed for five to ten minutes (or until the disappearance of undissolved 5-(α-phenylethyl)semioxamazide). Rigorously anhydrous conditions were necessary for success in the formation of the ketone derivatives. The derivative usually crystallized out when the benzene solution was cooled. If the derivative was too soluble in benzene, the addition of low-boiling petroleum ether was used to cause precipitation. Aqueous ethanol was a satisfactory solvent for recrystallization of the aldehyde derivatives, but benzene or benzene-petroleum ether was necessary for the ketone derivatives, all of which were readily susceptible to hydrolysis. In Table I are recorded a number of representative products (all colorless needles) of 5-(α-phenylethyl)semioxamazide with aldehydes and ketones, formed under the conditions described above. It should be pointed out that under these conditions, a number of complex carbonyl compounds *failed* to give derivatives: benzoin, benzalacetophenone, benzil, mesityl oxide, acetoacetic ester, and levulinic acid.

Resolution of α-phenylethylamine. The method outlined briefly by Betti (8) and described in detail by Campbell, Houston, and Kenyon (9) was utilized for obtaining *l*-α-phenylethylamine. The directions given in "Organic Syntheses" (10) for the resolution of racemic α-phenylethylamine were used to obtain the *d* isomer.

d- and l-5-(α-Phenylethyl)semioxamazide. Following the procedure for the preparation of racemic 5-(α-phenylethyl)semioxamazide, the *d* and *l* forms were obtained from the corresponding optically pure forms of α-phenylethylamine in yields identical with those reported for the racemate.

d-5-(α-Phenylethyl)semioxamazide, m.p. 167–168°. A solution containing 1.0395 g. of the reagent in 100 cc. of chloroform gave α_D^{23} + 1.06° (*l*, 1), or $[\alpha]_D^{25}$ + 102.0°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32.
Found: C, 57.99; H, 6.51.

l-5-(α-Phenylethyl)semioxamazide, m.p. 167–168°. A solution containing 0.6249 g. of the reagent in 100 cc. of chloroform gave α_D^{25} −0.64° (*l*, 1), or $[\alpha]_D^{25}$ −102.5°.

Anal. Calc'd for $C_{10}H_{13}N_3O_2$: C, 57.96; H, 6.32.
Found: C, 57.98; H, 6.35.

Resolution of 3-methylcyclohexanone with l-5-(α-phenylethyl)semioxamazide. To a solution of 25 g. (0.2 mole) of 3-methylcyclohexanone in 50 cc. of benzene was added 21 g. (0.1 mole) of *l*-5-(α-phenylethyl)semioxamazide and a crystal of iodine. The mixture was refluxed a few minutes, or until a clear solution was obtained. The solution was concentrated and cooled, and the solid product thus obtained was recrystallized five times from ben-

TABLE I

CARBONYL COMPOUND	M.P., °C.	RECRYST. SOLVENT	MOLECULAR FORMULA	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
Derivatives of 5-(α-Phenylethyl)semioxamazide							
n-Butyraldehyde	154–155	ethanol	$C_{14}H_{19}N_3O_2$	64.37	7.33	64.30	7.60
Isovaleraldehyde	161–162	ethanol	$C_{15}H_{21}N_3O_2$	65.43	7.69	65.24	7.69
Furfural	221–222	ethanol	$C_{15}H_{15}N_3O_3$	63.15	5.30	63.44	5.47
Benzaldehyde	237	ethanol	$C_{17}H_{17}N_3O_2$	69.12	5.80	69.39	5.83
Cinnamaldehyde	248–249	ethanol	$C_{19}H_{19}N_3O_2$	71.01	5.96	70.97	6.19
Biacetyl	126–127	benzene	$C_{14}H_{17}N_3O_3$	61.07	6.23	61.60	6.37
Acetophenone	187	methanol	$C_{18}H_{19}N_3O_2$	69.88	6.19	69.82	6.00
Cyclohexanone	173–174	benzene	$C_{16}H_{21}N_3O_2$	66.88	7.37	67.04	7.45
Derivatives of *l*-5-(α-Phenylethyl)semioxamazide							
l-3-Methylcyclohexanone	179–180	benzene	$C_{17}H_{23}N_3O_2$	67.74	7.69	67.75	7.88
Cyclopentanone	161–162	benzene-pet. ether	$C_{15}H_{19}N_3O_2$	65.91	7.01	66.20	7.17
Cycloheptanone	142–143	benzene-pet. ether	$C_{17}H_{23}N_3O_2$	67.74	7.69	67.82	7.76
Formaldehyde	199–200	benzene-pet. ether	$C_{11}H_{13}N_3O_2$	60.26	5.98	60.22	6.04

zene. The colorless needles melted at 179–180°, and the melting point did not change on further recrystallization. The yield of optically pure product was 4.1 g. (27%). A solution of 1.264 g. in 100 cc. of purified chloroform gave an initial reading of α_D^{25} −1.75° (*l*, 1), or $[\alpha]_D^{25}$ −139.0°. While the solution remained in the stoppered polarimeter tube, the rotation was observed to change gradually to a constant reading, after eight hours, of α_D^{25} −1.45°, or $[\alpha]_D^{25}$ −114.7°. Evaporation of this chloroform solution gave a solid, m. p. 179–180°, identical with the original derivative. When the solid was redissolved in chloroform, the shift in rotation during eight hours was again observed from $[\alpha]_D^{25}$ −139.0° to a constant value of −115.0°. Further recrystallization failed to eliminate this shift in rotation. The infrared absorption spectrum of the derivative was identical with that of the material which had remained eight hours in chloroform solution.

Hydrolysis of the pure condensation product proceeded rapidly (a few minutes) when 0.8 g. was refluxed in an excess of 20% sulfuric acid. The solution was cooled and filtered

free from hydrazine sulfate. The filtrate was extracted several times with 5-cc. portions of ether. The combined ethereal extracts were dried and the ether was removed. The residual oil was converted to the semicarbazone in the usual manner. After one recrystallization from ethanol, the *semicarbazone of l-3-methylcyclohexanone* melted at 179–180°. A solution in absolute ethanol gave $[\alpha]_D^{25}$ +20.6°. Adams, Smith, and Loewe (5) and Adams and Garber (7) reported $[\alpha]_D^{20}$ +20.8° for the semicarbazone of *l-3*-methylcyclohexanone.

SUMMARY

5-(α-Phenylethyl)semioxamazide has been investigated in its racemic form as a reagent for the characterization of aldehydes and ketones and in its optically active form as a resolving agent for carbonyl compounds possessing an asymmetric carbon atom.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY AND THE BERSWORTH LABORATORIES]

THE CARBOXYMETHYLATION OF AMINES. II. TRIGLYCINE

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It is the purpose of this paper to report a new and improved method for the preparation of triglycine through the use of sodium cyanide and formaldehyde. This reaction represents an extension of the carboxymethylation reaction previously described (1).

In 1912 Polstorff (2), investigating the reaction between equimolar parts of sodium cyanide and formaldehyde, isolated a little triglycine and a smaller amount of diglycine. From the filtrate glycollic acid was obtained as the zinc salt. The combined products accounted for only about 42% of the cyanide used in the reaction. As a synthesis of triglycine, the method of Polstorff is unsatisfactory, since a large proportion of other products, such as glycollic acid, diglycine, and no doubt glycine itself, is formed. Under conditions which were substantially the same as those used by Polstorff, Kohn (3) found the main products to be hexamethylenetetramine and glycollic acid. He stated that glyconitrile, though probably formed as an intermediate, was too unstable to exist more than momentarily, and that it hydrolyzed to glycollic acid and ammonia, which in turn combined with formaldehyde to produce hexamethylenetetramine. Kohn attempted to isolate the nitrile, as prepared from calcium cyanide and formaldehyde, but was not successful. On the other hand, Romijin (4) suggested that the reaction between an alkali cyanide and formaldehyde takes place quantitatively with the formation of the alcoholate salt of glyconitrile. Although Polstorff assumed that the alcoholate salt of the nitrile was formed, the existence of this substance was not considered certain. As recently as 1944, Mowry (5) stated "In aqueous solution, a mixture of formaldehyde and sodium cyanide reacts like glyconitrile and sodium hydroxide."

Mutschin (6) found that at room temperature very little decomposition of the nitrile took place after 50 hours, and that in the presence of sodium hydroxide, it remained unchanged up to one hundred hours. The work done in this laboratory shows that the nitrile, though fairly stable at room temperature, decomposes rapidly above 30°. The authors have succeeded in isolating both the free nitrile and its alcoholate salts, and its use in the carboxymethylation reaction has already been reported.

Polstorff assumed that the formation of triglycine took place through hydrolysis of the alcoholate salt of glyconitrile, with the formation of ammonia and glycollic acid, subsequent reaction of ammonia with free glyconitrile to form by dehydration the nitriles of glycine, diglycine, and triglycine and formation of triglycine itself in the same reaction mixture by final hydrolysis of the corresponding trinitrile. It is to be noted that he postulated dehydration and hydrolysis as taking place in the same solution at the same time.

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In a previous publication (1) we have shown that the carboxymethylation reaction does not take place with the formation of an intermediate nitrile, but goes directly to the amino acid salt. The formation of triglycine, therefore, probably did not take place by the method indicated by Polstorff but rather by the following steps:

$$CH_2O + NaCN \rightarrow NaOCH_2CN \xrightarrow{2\,H_2O} HOCH_2COONa + NH_3$$

$$H_2NCH_2COONa + NaOCH_2CN + H_2O \rightarrow HN(CH_2COONa)_2 + NH_3$$

$$NH(CH_2COONa)_2 + NaOCH_2CN + H_2O \rightarrow N(CH_2COONa)_3 + NH_3$$

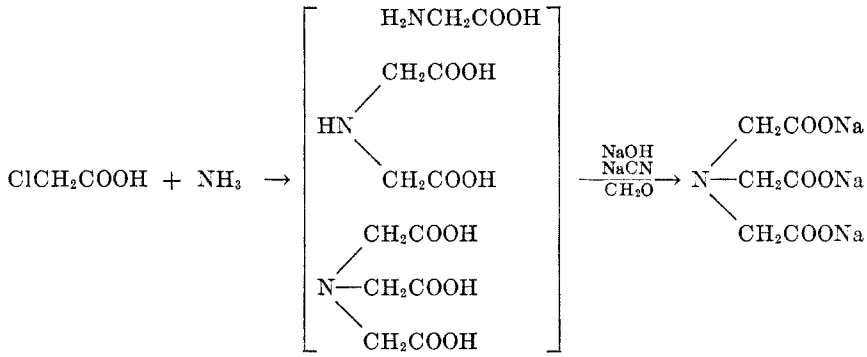
We have previously shown that high alkalinity favors the carboxymethylation reaction, partly because ammonia is more rapidly evolved and partly because the reaction is speeded up. The conditions used by Polstorff are not satisfactory for maintaining high alkalinity. This leads to a lowered rate of evolution of ammonia and gives an opportunity for the reaction of ammonia with the alcoholate of glyconitrile to form triglycine. The yield of this product is very low, as would be expected under these conditions. We have found that attempts to improve the yield by increasing the alkalinity, however, are fruitless, since this increases the tendency of ammonia to escape from the reaction mixture before it has an opportunity to react.

On further study of these reactions, we found two methods of getting around these difficulties. The first involves the use of a non-volatile amine, glycine itself, as a starting material. The use of glycine in the carboxymethylation reaction according to the method already outlined, however, is unsatisfactory since here again the alkalinity is not sufficiently great to remove the ammonia as soon as it is formed. One might be inclined to suppose that the evolution of ammonia is not a serious matter since the reaction of ammonia with sodium cyanide and formaldehyde would lead to the production of triglycine. We have found, however, that this leads to the formation of considerable amounts of glycine and diglycine as well and makes it impossible to obtain a high yield of the desired product. Also, under these conditions, a large proportion of colored by-products is formed. On the other hand, when the sodium salt of glycine was treated by the carboxymethylation reaction at high temperature, and in the presence of excess alkali, it was found that the reaction rapidly went to completion and that the triglycine obtained was not contaminated with by-products.

The disadvantage of this process lies in its restriction to glycine as a starting material, since it is not readily obtained in the pure state from the ammonolysis of a halogenated acid. In this connection it is interesting to note the findings of Robertson (7) who reported the recovery of 63% of the theoretical amount of

glycine when one mole of chloroacetic acid was treated with four liters of concentrated ammonia, but obtained a very low yield when the ammonia was cut down to about a liter or less. The use of a small amount of ammonia with a relatively large amount of chloroacetic acid, however, does not produce a satisfactory yield of triglycine. Usually a sirupy mixture is produced from which it is impossible to separate any products in appreciable amounts. This was mentioned by Robertson and by many other workers.

It is to be noted that the same end-product of the carboxymethylation reaction is obtained whether the starting material is glycine or a mixture of glycine, diglycine, and triglycine. It was therefore decided to investigate the carboxymethylation of the reaction mixture formed on the ammonolysis of chloroacetic acid. However, if the amount of sodium cyanide and formaldehyde needed is to be determined, it is necessary to know roughly how far the ammonolysis has proceeded toward the formation of secondary and tertiary amines. Conversely, since the conversion of glycine and diglycine to triglycine by the carboxymethylation reaction is practically quantitative, it is possible to determine roughly the extent of ammonolysis of the halogen acid from the yield of triglycine based on the halogen acid when an excess of sodium cyanide and formaldehyde is employed. The higher the proportion of glycine as the result of ammonolysis of the halo acid, the greater will be the amounts of sodium cyanide and formaldehyde required, and the greater will be the yield of the desired product. The overall synthesis can be represented schematically by the following reactions:



Two sets of reaction conditions were employed. First, the recommendations of Robertson for obtaining the highest possible yield of glycine were followed. Four liters of concentrated ammonia were used at room temperature per mole of chloroacetic acid. Under these conditions he isolated only 63% of the theoretical amount of glycine but estimated that 86% was present in the reaction mixture. The sodium cyanide and formaldehyde used in the subsequent step was based on the production of the maximum amount (one mole) of glycine, and 0.83 mole of triglycine was isolated. The large amount formed indicates not only that more than 60% of glycine was formed by ammonolysis of chloroacetic acid, but also, that a considerable amount of the by-products must have been in the form of diglycine which was subsequently converted to triglycine *via* carboxy-

methylation. It is also possible that a small amount of triglycine was formed directly from the chloroacetic acid and ammonia.

A second procedure was worked out using one liter of concentrated ammonia water per mole of chloroacetic acid, under conditions which Robertson found resulted in a negligible yield of glycine. The amount of sodium cyanide and formaldehyde needed for carboxymethylation of the reaction mixture was calculated assuming 50% conversion of chloroacetic acid to glycine and 50% to diglycine. As a result of the over-all process, 0.63 mole of triglycine was obtained, a surprisingly large amount in view of the low yields resulting from ammonolysis under the conditions employed in the first part of the synthesis. The method shows considerable promise as a convenient and inexpensive process for the preparation of triglycine.

Although it is not possible to calculate the theoretical yield, it is obviously considerably higher than 83% in the first case and very much higher than 63% in the second. It is probable that the sodium cyanide and formaldehyde were in considerable excess in both cases and may be cut down appreciably without notably decreasing the yield. A further advantage of this method is that the starting materials are ammonia and a halo acid and that the desired substance is obtained in high yield free from by-products without isolation or separation of the intermediates.

The laboratory procedure employed and the isolation and identification of the product are described below.

EXPERIMENTAL PART

Triglycine from glycine. Glycine (75 g.) was dissolved in 200 cc. of a solution containing 43 g. of sodium hydroxide and was treated with 300 cc. of a solution containing 103 g. of sodium cyanide and 3 g. of sodium hydroxide, and with 180 cc. of 37% formaldehyde solution, in a 2-liter reaction flask equipped with a dropping-funnel, reflux condenser, and mercury-seal stirrer. About 60% of the sodium cyanide solution was added at once and the reaction mixture heated to 80° with a water-bath and stirred vigorously. One-half of the formaldehyde was then added slowly from the dropping-funnel over a period of four hours. The remainder of the sodium cyanide was then added through the reflux condenser and the remaining formaldehyde was added over an additional four-hour period. The evolution of ammonia began almost immediately after addition of the formaldehyde was begun, and became more rapid as the reaction proceeded. After it had stood overnight, the reaction mixture was heated on the water-bath to 100° and stirred for a two-hour period. The resulting pale yellow solution was then cooled and brought to *p*H 1.2 with sulfuric acid. Crystallization took place immediately but the product was allowed to stand overnight to insure complete precipitation. It was then filtered, washed thoroughly with water, and recrystallized from boiling water, giving 89 g. of pure *triglycine;* yield 93%. The product was identified by carbon, hydrogen, and nitrogen analyses.

Triglycine from chloroacetic acid. A. Chloroacetic acid (47.5 g.) was dissolved in two liters of concentrated (28%) aqueous ammonia and allowed to stand for 24 hours at about 30°. Water and ammonia were then distilled off until the volume of the residue was about 250 cc. Sodium hydroxide (44 g.) was then added (with cooling) and the volume of the resulting solution was reduced to 200 cc. by further distillation. A solution containing 54 g. of sodium cyanide and 1 g. of NaOH was prepared and 60 cc. of this solution was added to the reaction mixture, which was then heated to 80° (water-bath) and stirred vigorously while 50 cc. of 37% formaldehyde solution (containing 0.575 mole) was added dropwise over a period of four

hours. The remainder of the sodium cyanide solution was then added, and another 50 cc. of formaldehyde solution was added in the same manner. After the pale yellow product had stood overnight, it was heated by a boiling-water bath for two hours and stirred vigorously to remove ammonia. The solution was adjusted to *p*H 1.2 with sulfuric acid and the white precipitate which formed was allowed to stand for an hour before filtering The colorless crystalline triglycine, after filtration and thorough washing with water, weighed 78 g. (0.83 mole) and was analytically pure, based on C, H, and N.

B. Chloroacetic acid (95 g.) was dissolved in 1 liter of concentrated (28%) aqueous ammonia, and allowed to stand for 24 hours at about 30°. The excess ammonia was removed by distillation of the solution to a volume of about 250 cc.; 44 g. of sodium hydroxide was then added with cooling and an additional 50 cc. of water was distilled off. The pale yellow solution was then placed in a 2-liter round-bottom flask equipped with a reflux condenser, dropping-funnel, and mercury-seal stirrer. A solution containing 75 g. of sodium cyanide and 2 g. of sodium hydroxide was added and the reaction mixture was heated to 80° (water-bath) and stirred vigorously while a 37% formaldehyde solution containing 1.58 moles of formaldehyde was added dropwise over a period of seven hours. After the product had stood overnight, it was heated and stirred on a boiling-water bath for two hours, cooled, and acidified to *p*H 1.2 with sulfuric acid. A white precipitate of triglycine formed immediately. It was allowed to stand for one hour, and was filtered and washed thoroughly with water giving 124 g. (0.63 mole) of triglycine which was sufficiently pure to give a correct elementary analysis.

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PREPARATION OF TRIMETHYLENEDIAMINES

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The purpose of this paper is to report on the preparation of a number of β-alkylaminopropionitriles and the conversion of some of these to the corresponding monoalkyltrimethylenediamines. The by-products obtained in the synthesis of both classes of substances are also described.

The reaction between acrylonitrile and primary amines was carried out according to the method of Holcomb and Hamilton (1). When an excess of amine is used, the main product of the reaction is the monosubstituted amine. A small yield of the disubstituted amine is also obtained in most cases. Catalytic reduction of the monosubstituted product results in the formation of the monoalkyltrimethylenediamine in good yield as well as a small amount of the secondary amine in accordance with the mechanism of von Braun, *et al.* (2).

In the present research the mononitrile was prepared from cyclohexylamine and both mono- and di-nitriles were prepared from *n*-dodecylamine, *n*-butylamine, and benzylamine. The monocyclohexyl and dodecyl derivatives were reduced to the corresponding primary and secondary amines. Of the compounds prepared, β-cyclohexylaminopropionitrile, β-dodecylaminopropionitrile, and β-butylaminopropionitrile have been reported by Hoffman and Jacobi (3); γ-cyclohexylaminopropylamine has been described by Tarbell, *et al.* (4), and the β-benzylaminopropionitrile has been reported by King and MacMillan (5). These workers give substantially the same physical properties for the nitriles and amines as those obtained in the present work, but did not report on the by-products of their reactions.

In this investigation, the mononitriles were obtained as colorless liquids while the dinitriles were isolated as pale yellow liquids. The nitriles were reduced with Raney nickel catalyst prepared according to the procedure of Covert and Adkins (6). Methanol saturated with ammonia was used as a solvent in order to repress formation of the secondary amine, according to the suggestion of Schwoegler and Adkins (7). The experimental results and analytical data are given in Table I for the nitriles and in Table II for the amines. The methods used for preparation of these substances are described below.

EXPERIMENTAL PART

N-(γ-Cyclohexylaminopropyl)-N'-phenyl urea. The phenyl urea derivative of cyclohexylaminopropylamine was prepared in the usual manner and recrystallized twice from ethanol. Colorless crystals, m.p. 202–203°, were obtained.

Anal. Calc'd for $C_{16}H_{25}N_3O$: N, 15.26. Found: N, 15.07.

Bis-γ-cyclohexylaminopropylamine. This substance was obtained as a higher-boiling fraction in the preparation of cyclohexylaminopropylamine. The product was isolated as a small amount of pale yellow liquid, boiling range 210–224° at 11 mm.

β-Dodecylaminobispropionitrile. This substance was obtained as a high-boiling fraction in

the preparation of β-dodecylaminopropionitrile. It was isolated as a colorless liquid boiling at 182–184° at 1 mm.

γ-Dodecylaminopropylamine. To 40 ml. of methanol which had been saturated with ammonia at 0° was added 40 g. of β-dodecylaminopropionitrile. The solution was reduced in the presence of Raney nickel at 1400 lbs. of hydrogen and at 120–130° for four hours. After filtration and removal of the volatile components, the residue was distilled under diminished pressure. Yield, 35 g. (86%) of N-dodecyltrimethylenediamine, b.p. 137–141° at 1 mm. The product was a colorless liquid which solidified in the receiver to a colorless waxy solid, m.p. 24.5–25.5°.

Bis-γ-dodecylaminopropylamine. This substance was obtained as a higher-boiling fraction in the preparation of γ-dodecylaminopropylamine. It was isolated as a pale yellow liquid, boiling range 190–210° at 1 mm.

TABLE I

NITRILES

SUBSTANCE	B.P., °C./MM.	YIELD, %	LIT. REF.	ANALYSES N, %	
				Calc'd	Found
β-Cyclohexylaminopropionitrile	144–145/11	70	(3)	18.41	18.30
β-*n*-Dodecylaminopropionitrile	152–156/2	91	(3)	11.75	11.41
β-*n*-Dodecylaminobispropionitrile	182–184/1	—	—	14.42	14.20
β-*n*-Butylaminopropionitrile	102–105/10	70	(3)	22.20	22.00
β-*n*-Butylaminobispropionitrile	120–128/10	—	—	23.45	23.33
β-Benzylaminopropionitrile	181–184/24	84	(5)	17.50	17.34
β-Benzylaminobispropionitrile	173–175/3–4	—	—	19.70	19.49

TABLE II

AMINES

SUBSTANCES	B.P., °C./MM.	YIELD, %	LIT. REF.	MOL. WT.		ANALYSES N, %	
				Calc'd	Found	Calc'd	Found
γ-Cyclohexylaminopropylamine	85–89/2	74	(4)	156	165	17.93	17.68
Bis-γ-cyclohexylaminopropylamine	210–224/11	—	—	296	300	14.22	14.05
γ-Dodecylaminopropylamine	137–141/1	86	—	242	237	11.55	11.76
Bis-γ-dodecylaminopropylamine	182–184/1	—	—	468	457	8.98	9.29

β-Butylaminobispropionitrile. The dinitrile was isolated as a high-boiling fraction from the residue remaining after the distillation of β-butylaminopropionitrile. A small amount of a pale yellow liquid, boiling range 120–128° at 10 mm., was obtained.

β-Benzylaminobispropionitrile. A small yield of the disubstituted amine, β-benzylaminobispropionitrile, boiling at 173–175° at 4 mm., was obtained on further distillation of the residue obtained from the distillation of β-benzylaminopropionitrile.

SUMMARY

The preparation of β-alkylaminopropionitriles and β-alkylaminobispropionitriles by the reactions of amines with acrylonitrile and the preparation of γ-alkylaminopropylamines and of bis-γ-alkylaminopropylamines by reduction

of the corresponding β-alkylaminopropionitriles are described. Of the substances discussed, β-dodecylaminobispropionitrile, β-butylaminobispropionitrile, β-benzylaminobispropionitrile, N-(γ-cyclohexylaminopropyl)-N′-phenyl urea, bis-γ-cyclohexylaminopropylamine, γ-dodecylaminopropylamine, and bis-γ-dodecylaminopropylamine have not been reported previously.

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FURTHER OBSERVATIONS ON THE GUERBET REACTION

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In previous papers (1, 2) the "Guerbet Reaction" which, *e.g.*, converts butyl alcohol into 2-ethylhexanol (and butyric acid) was formulated as follows:

A. $2\ CH_3CH_2CH_2CH_2OH \rightarrow 2\ CH_3CH_2CH_2CHO$

B. $2\ CH_3CH_2CH_2CHO \rightarrow CH_3CH_2CH_2CH{=}C(C_2H_5)CHO$

C. $3\ CH_3CH_2CH_2CH{=}C(C_2H_5)CHO \rightarrow CH_3CH_2CH_2CH_2OH + CH_3CH_2CH_2COOH + CH_3CH_2CH_2CH_2CH(C_2H_5)CH_2OH.$

Primary alcohols, which are branched in α-position, should, therefore, be incapable of this reaction (incapable of step B). We have observed that 2-ethylhexanol $C_8H_{18}O$ gives, when heated with its sodium derivative, a compound of the expected formula $C_{16}H_{34}O$. This, however, is not a higher alcohol, but *bis*-2-ethylhexyl ether, as it contains no hydroxyl group and is split by hydriodic acid into 2-ethylhexane and 2-ethylhexyl iodide. A similar reaction was observed before (1) for cinnamyl alcohol, which has also no methylene group in the immediate vicinity of the hydroxyl. These observations recall the occasional formation of isopropyl ethers in the reduction of ketones with aluminum isopropoxide (3). In contradistinction to 2-ethylhexanol, the isomeric 1-octanol undergoes the Guerbet reaction to give an alcohol $C_{16}H_{34}O$ which is assumed to be 2-hexyldecanol, and caprylic acid.

"Mixed" Guerbet reactions between a primary alcohol carrying an α-methylene group, and a primary alcohol which does not conform to this requirement, take place as expected, according to the following scheme:

A′. $R_1CH_2OH \rightarrow R_1CHO$
$R_2CH_2CH_2OH \rightarrow R_2CH_2CHO$
B′. $R_1CHO + R_2CH_2CHO \rightarrow R_1CH{=}C(R_2)CHO$
C′. $R_1CH{=}C(R_2)CHO \rightarrow R_1CH_2CH(R_2)CH_2OH$

To the examples reported previously (1), we have added the condensation between benzyl and β-phenylethyl alcohols which leads to 2,3-diphenylpropanol, $C_6H_5CH_2CH(C_6H_5)CH_2OH$. In this case, the benzoic acid formed in step C′ was not isolated as such, but in the form of its reduction product, toluene. A similar method of synthesis of this alcohol has been described by Mastagli (4).

Likewise, the course of the Guerbet reaction between a primary and a secondary alcohol is predetermined by the fact that an aldehyde condenses with a ketone always to give an alkylidene-ketone [for a remarkable exception, see Kuzin and Nevraeva (5)]. Primary alcohols and cyclohexanol, therefore, give 2-alkylcyclohexanols. This fact, established previously (1), has now been confirmed for the

pair isobutyl alcohol-cyclohexanol, which condense to give 2-isobutylcyclohexanol.

Guerbet (6) already has observed that two molecules of secondary alcohols react analogously. In this case, the third molecule of the alcohol cannot supply the four hydrogen atoms required in step C in the same manner as a primary alcohol. As a matter of fact, a deep-seated destruction occurs, reminiscent of the oxidative splitting of the corresponding ketone (from isopropanol, isovaleric, acetic, and formic acids and from *sec*-butanol, propionic and formic acids were obtained).

In the Experimental part some data are reported showing the beneficial effect of small amounts of copper-bronze on the course of the Guerbet reaction, which has been mentioned previously (1). It helps to suppress the undesirable oxidation of the alcohol to the corresponding acid under the influence of the sodium alkoxide.

EXPERIMENTAL

All experiments were carried out in an autoclave. The reaction mixture was heated to the desired temperature; then the excess pressure was released and the mixture heated for the time required at a pressure of about 50–60 atm.

1. *Butyl alcohol.* Table I shows the effect of small amounts of copper-bronze on the product obtained from 2 moles of butyl alcohol and 0.67 atom of sodium.

2. *Isoamyl alcohol.* Table II refers to experiments with 2 moles of the alcohol and 0.67 atom of sodium. The structure of the C_{10} alcohol has been determined by Nef (7); the C_{10} acid which is obtained in small quantities and for which b.p. 249°/760; 135–136°/13 has been observed, is therefore, most proabably 2,6-dimethylheptane-5-carboxylic acid, $(CH_3)_2CHCH_2CH_2CH(COOH)CH(CH_3)_2$.

3. *2-Ethylhexanol.* When 1 mole (130 g.) of 2-ethylhexanol was heated at 300° for six hours with 0.3 mole of sodium and 0.7 g. of copper-bronze, 20% of the starting material was recovered unchanged. The neutral product weighed 45 g., and boiled at 144–146°/13. It is di-2-ethylhexyl ether.

The acidic reaction product (48 g.) was mainly 2-ethylhexoic acid, b.p. 118°/14, formed by oxidation of the starting material. The neutral product (5 g.) was boiled for four hours with 50 cc. of hydriodic acid (b.p. 127°). After dilution with water, the product was extracted with ether and the ethereal solution washed with sodium carbonate and sodium thiosulfate. Fractionation *in vacuo* gave a low-boiling liquid and a fraction which boiled at 122°/13 with some decomposition (liberation of iodine).

The first fraction boiled under atmospheric pressure at 120° and was saturated and halogen-free; it was 2-ethylhexane. The second fraction was 2-ethylhexyl iodide.

Anal. Calc'd for $C_8H_{17}I$: C, 40.0; H, 7.1; I, 52.9.
Found: C, 40.6; H, 7.3; I, 52.4.

It was identified by conversion into the crystalline trimethyl-(2-ethylhexyl)ammonium iodide, m.p. 208° (1).

4. *1-Octyl alcohol.* A batch of 130 g. of octyl alcohol (1 mole), in which 7.6 g. of sodium (0.33 mole) had been dissolved, was heated in the presence of 0.6 g. of copper-bronze at 295° for five hours. The reaction set in at 210°, as indicated by the sudden pressure rise in the autoclave when this temperature was reached. Treatment with water gave an organic layer, consisting of (a) 45.0 g. of octyl alcohol, b.p. 195° (34.6% recovery), (b) 42.0 g. of 2-hexyldecanol, b.p. 170–180°/24 (52%), and an aqueous layer from which (c) 34.0 g. of *n*-caprylic acid, b.p. 120–125°/10 (70.8%) was isolated. Practically no higher-boiling acidic product (hexyloctylacetic acid) was observed.

2-Hexyldecanol is a colorless, viscous oil which did not solidify at room temperature; the caprylic acid crystallized, upon cooling, and had the correct m.p., 16°.

5. *Condensation of benzyl and β-phenylethyl alcohol.* When 1.5 moles (162 g.) of benzyl alcohol and 1.5 moles (183 g.) of β-phenylethyl alcohol were heated for six hours at 310° with 1 mole of sodium metal and 1.2 g. of copper-bronze, exactly one-third of each alcohol was recovered unchanged. The β-phenylethyl alcohol was converted into polystyrene (90 g., 57.7%) [see (1)]. 2,3-Diphenylpropanol (8), b.p. 186°/14, was isolated in an amount of 25 g. (11.8%), while 32 g. (17.5%) of benzoic acid, and 10 g. of toluene (21.7%) were formed. A small amount of 2,4-diphenylbutanol, the expected Guerbet product from β-phenylethyl alcohol, was also isolated.

6. *Condensation of isobutyl alcohol and cyclohexanol.* Isobutyl alcohol (93 cc.) and 100 cc. of cyclohexanol were heated at 280° for twelve hours with 8 g. of sodium metal and 2 g.

TABLE I

GUERBET REACTION WITH BUTYL ALCOHOL

EXPT.	TEMP., °C.	TIME, HRS.	COPPER ADDED, G.	BUTYL ALCOHOL RECOVERED G.	2-ETHYLHEXANOL		BUTYRIC ACID		2-ETHYLHEXOIC ACID G.
					G.	%	G.	%	
1	270	10	—	15	55	63.4	55	93.7	5
2	300	6	0.75	9	79	91.0	50	85.1	10
3	300	6	1.5	20	78	89.9	40	68.1	5

The % yields are calculated on the basis of the amount of sodium used without considering the recovered butyl alcohol.

TABLE II

GUERBET REACTION WITH ISOAMYL ALCOHOL

EXPT.	TEMP., °C.	TIME, HRS.	COPPER ADDED, G.	ISOAMYL ALCOHOL RECOVERED, G.	C_{10} ALCOHOL		ISOVALERIC ACID		C_{10} ACID G.
					g.	%	G.	%	
1	290	6	—	22	65	61.7	65	95.6	7
2	300	5	—	11	55	52.2	65	95.6	12
3	300	6	0.9	20	79	75.0	50	73.5	12
4	300	6	1.8	20	80	76.0	48	70.6	12
5	295	6	3.6	20	75	71.2	48	70.6	12

of copper-bronze. Repeated fractionation gave as a neutral product 2-isobutylcyclohexanol, b.p. 118°/22, 111°/15; yield, 56 g. (36%).

Anal. Calc'd for $C_{10}H_{20}O$: C, 76.9; H, 12.8.
Found: C, 77.0; H, 13.1.

The acid formed in the reaction was identified as isobutyric acid.

7. *Guerbet condensation of propyl alcohol.* In this (and the following) case, too, the addition of copper has proved beneficial. In an autoclave, 180 g. of propyl alcohol (3 moles) and 23 g. of sodium (1 mole) were refluxed until all the metal had dissolved. The solution was allowed to cool to 60°, 0.9 g. of copper-bronze was added and the mixture heated at 295° for five hours. The usual treatment of the reaction product gave as neutral products: propyl alcohol, 39.6 g. (22% recovery) and C_6 alcohol, b.p. 148°, 73.2 g. (71.7%) and as acidic products: propionic acid, b.p. 140–142°, 59.4 g. (80.2%) and residue, presumably C_6 acid. It can be assumed that the C_6 alcohol is 2-methylpentanol (9)[1] and the C_6 acid is methylpropylacetic acid.

[1] Terentjew (9) found b.p. 147–149° for 2-methylpentanol.

8. *Guerbet condensation of pentanol-1.* In the above-described manner, 176 g. of pentanol-1, (2 moles), 15.4 g. of sodium (0.67 mole) and 0.9 g. of copper-bronze were heated at 300° for five hours. It was interesting to note that the reaction set in (rise in pressure) at 210°, *i.e.*, at a temperature 30° lower than that required for butyl alcohol. Neutral products: pentanol-1, 35.0 g. (19.9% recovery) and C_{10} alcohol, b.p. 112–115°/14, 75.0 g. (71.2%). Acidic products: valeric acid, b.p. 90–92°/14, 60.0 g. (88.2%) and C_{10} acid b.p. 145°/14, 2.0 g. Assuming that the general mechanism indicated above is correct, the C_{10} alcohol would be 2-propylheptanol; the C_{10} acid 2-propylheptanoic acid.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF E. BILHUBER, INC.]

THE SYNTHESIS OF ALKYLATED PENTAMETHYLENETETRAZOLE DERIVATIVES

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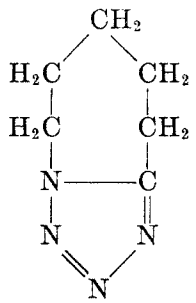
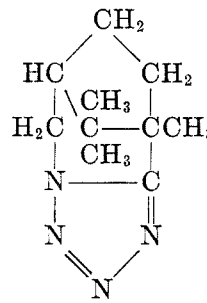
Certain tetrazole derivatives have attained notable success as medicinal agents. Perhaps the best known member of this group is Metrazol (1), pentamethylenetetrazole (I), which has found application as an analeptic agent because of its stimulatory action on the central nervous system. Several other tetrazoles, likewise bicyclic structures which can be formed from cyclohexanone derivatives, have received favorable comment in the pharmacologic literature as analeptic agents. Notable among these are the "camphor tetrazole" (II) and the tetrazoles derived from α-thujone and mixtures of α- and β-thujone (2, 3). More recently several methyl substituted pentamethylenetetrazoles (III) have been described (4, 5, 6, 7) and a number of other bicyclic tetrazoles have been studied in which the tetrazole ring is fused to either a larger (8) or a smaller (9, 10) ring system than the seven membered heterocycle of pentamethylenetetrazole.



(I)



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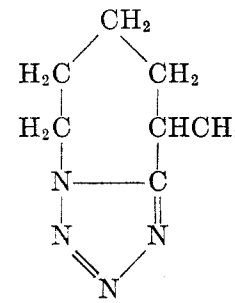

(III)

In view of the interest attaching to pentamethylenetetrazole, it seemed desirable to initiate a systematic investigation of derivatives both of the fused bicyclic type and of the monocyclic type and to attempt to correlate the changes in structure with changes in pharmacologic action. The tetrazole ring system (IVa and b) is an unusual cyclic structure in that the possibility of position isomerism is limited by the presence of only two replaceable hydrogen atoms. The tautomeric shift of the hydrogen attached to nitrogen permits the existence of three monosubstituted isomers and two series of disubstituted derivatives. Examples of all types are known. The addition of fused ring systems usually in

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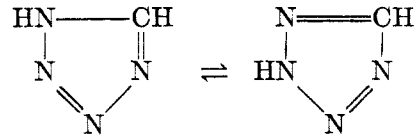
the 1,5 positions greatly increases the number of isomeric substitution products that may be prepared.

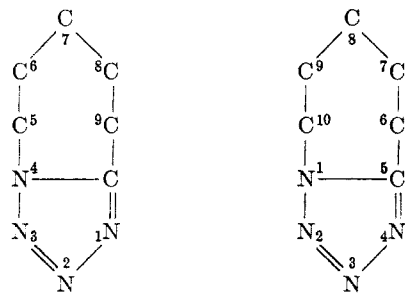


IVa IVb

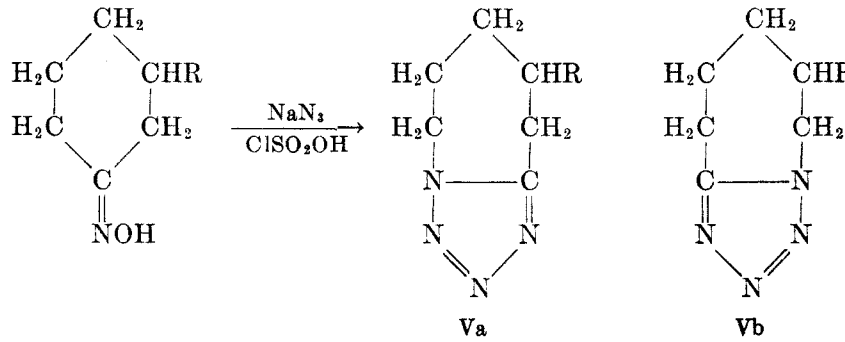
The present report is concerned only with the preparation of mono- and polyalkylpentamethylenetetrazole derivatives. These can be prepared readily by methods essentially similar to those applied to the synthesis of pentamethylenetetrazole itself. The method chosen involves treatment of the oxime of a suitably substituted cyclohexanone with sodium azide and chlorosulfonic acid in an inert organic solvent (4). During the reaction a carbon-carbon bond adjacent to the carboximino group is ruptured to permit introduction of the nitrogen and formation of the seven-membered heterocyclic entity. Either the 1,2- or the 1,6-bond of the cyclohexanone oxime will be broken. Except in the case of symmetrically substituted oximes, isomeric compounds of structures Va and b will result in varying proportions, depending on the extent to which the reaction involves the 1,6- or the 1,2-bond, respectively.[4]

No attempt has been made to establish the form represented by the compounds described in Table II; however, it is probable that each compound represents a single molecular species of structure Va or b in view of the sharpness of the melting points, which did not change on crystallization from different solvents and which were always easily reproducible in different preparations. For purposes of uniformity it has been assumed that the 1,6-bond is broken and structures have been assigned arbitrarily so that the position of methyl groups is always indicated by the lowest number. Only a single alkylpentamethylenetetrazole can be formed from the 4-alkylcyclohexanone oximes and from 3,5-

[4] Although the pentamethylenetetrazole structure is classified as 6,7,8,9-tetrahydro-5-azepotetrazole (VIa) in Chemical Abstracts, we would prefer to consider the new compounds as alkylpentamethylenetetrazole derivatives numbered as in (VIb). The accepted numbering of the tetrazole ring is retained in VIb and the names bear a more obvious relationship to that commonly used for the parent bicyclic system.



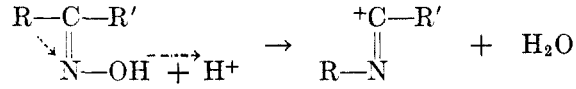
VIa VIb



dimethylcyclohexanone oxime. The product formed from 2-methylcyclohexanone oxime probably has the structure corresponding to a 10-methylpentamethylene-tetrazole (analogous to Vb) since Ungnade and McLaren (11) have shown that the Beckmann rearrangement product of this oxime is almost exclusively the cyclic amide formed by breaking the 1,2-bond of the cyclohexanone ring.

In their initial phases the reactions leading to tetrazole formation appear to be closely akin to the Beckmann rearrangement. Since the two processes take place under similar conditions, it is probable that an intermediate is formed at some stage which may be converted either into an amide by the addition of water or some group which may eventually be replaced by a hydroxyl group, or to a tetrazole by the additon of hydrazoic acid. Newman and Gildenhorn (12) have recently discussed the mechanism of the Schmidt reaction for the conversion of acids to amines by interaction with hydrazoic acid, and Smith (13) has suggested a mechanism for another aspect of the same reaction, the conversion of ketones to amides by interaction with hydrazoic acid. These reactions bear a close relationship to the Curtius and the Beckmann rearrangements, respectively, and similarity in the mechanism of these reactions has been implied by both authors. Smith has postulated the formation of an imino carbonium ion, $R—N{=}C^{+}—R$, as an intermediate in the Schmidt reaction with ketones, an intermediate also postulated by Waters (14) for the Beckmann rearrangement. In the mechanism suggested by Waters an intermediate of the type, $R_2{=}C{=}N^{+}$, is considered to result from the dissociation of a ketoxime ester and then rearrange to the imino carbonium ion form. Unless it is assumed that the charge on the nitrogen in the Waters intermediate retains its configuration, difficulty is experienced in accounting for the different rearrangement products of geometrically isomeric ketoximes. We would suggest that the intermediate formed by dissociation of the oxime according to Waters is not essential, and that the imino carbonium ion proposed by Smith is formed directly from the oxime or ketoxime ester. The reaction may be visualized as involving the addition of a proton to the hydroxyl oxygen of the oxime followed by elimination of water, or the proton may serve simply as an attractive force drawing the hydroxyl group away from the nitrogen as an ion and eventually uniting with it to form water. In either case it would not be unreasonable to assume that the alkyl (or aryl) group in *trans* position with respect to the hydroxyl group is pulled closer to the nitrogen as the hydroxyl group is drawn away, the rearrangement being completed by the simultaneous formation

of the imino carbonium ion and the elimination of the hydroxyl ion. In this way the effect of the configuration of the isomeric oximes on the rearrangement products may be explained without the assumption of ionic intermediates with a configurationally stable charge. A mechanism of this type has recently been discussed by Pearson and Ball (29) who indicate, however, the formation of the



sulfuric acid ester of the oxime as an intermediate. Although there are numerous reports of the rearrangement of oxime esters in the literature, it is conceivable that the reaction may take place without ester formation in the presence of such a strong proton donor as sulfuric acid.

As has already been pointed out by Smith, the imino carbonium ion may serve equally well as an intermediate for amide formation in either the Schmidt reaction or the Beckmann rearrangement, as well as for tetrazole formation. The latter process would be completed by addition of hydrazoic acid to the carbonium ion followed by cyclization and elimination of a proton.

As indicated in Table II a variety of pentamethylenetetrazole derivatives having alkyl groups variously substituted on the pentamethylene ring has been prepared from suitably substituted cyclohexanone oximes. Alkyl substitution caused very marked changes in the solubility of the homologs as compared with the parent structure. Pentamethylenetetrazole is extremely soluble in water, aqueous solutions containing 70% by weight of the tetrazole being easily prepared. The introduction of a single methyl group into the pentamethylene ring caused the solubility to decrease to barely 5% for the most soluble isomer. Introduction of a second methyl group caused almost complete disappearance of water solubility at room temperature. Similarly, water solubility disappeared almost completely upon substitution of a single alkyl group of three or more carbon atoms on the pentamethylene ring. Excepting the three isomeric monomethylpentamethylenetetrazoles, the water solubility of all the compounds listed in Table II is less than 1% by weight at room temperature and in most instances the compounds are insoluble in water for all practical purposes.

The results of investigations of the pharmacologic actions of the alkylpentamethylenetetrazoles listed in Table II have been reported in detail by Gross and Featherstone (15). Their results indicated that the compounds were generally stimulants of the central nervous system although interesting exceptions were noted. Contrary to the conclusion expressed by Issekutz and co-workers (5) based on investigations with tetramethylenetetrazole derivatives, the activity of pentamethylenetetrazoles was not increased by polysubstitution with alkyl groups. The substitution of a single methyl group on the pentamethylene ring increased the central nervous stimulating action and the effect was enhanced by moving the substituent away from the linkage common to both members of the fused ring system, 8-methylpentamethylenetetrazole exhibiting the highest potency. Introduction of a second alkyl group caused a profound drop in activity to levels much lower than that of the unalkylated system. Of particular interest were

the results of modification of the methyl group in position 8 by replacing its hydrogens with methyl and ethyl groups. The stimulatory potency increased markedly as the group in position 8 became successively isopropyl and *tert*-butyl. On the other hand, when the group was modified to become *sec*-butyl or *tert*-amyl, a profound loss of activity resulted. Further modification of the group as in 8-cyclohexylpentamethylenetetrazole resulted in a compound having mildly sedative action.

During the course of these investigations it was observed that pentamethylenetetrazole would form a crystalline quaternary salt with both methyl benzenesulfonate and methyl iodide. In this connection it might be emphasized that the pentamethylenetetrazoles fail to form salts with either acids or bases, that their water solutions are generally neutral in reaction toward litmus and that they fail to exhibit most of the characteristic reactions of nitrogen bases. Nevertheless, an exothermic reaction was observed to take place between methyl benzenesulfonate and pentamethylenetetrazoles, resulting in the formation of a quaternary salt. Which of the four nitrogen atoms is involved in quaternary salt formation has not been determined. The quaternary salts are very soluble in water. Several compounds of this type are described in Table III.

Although the analeptic activity of pentamethylenetetrazole disappeared upon quaternary salt formation, it seemed worthwhile to attempt to solubilize one of the most active alkylpentamethylenetetrazole derivatives in this manner. The quaternary salt of 8-*tert*-butylpentamethylenetetrazole with methyl benzenesulfonate was prepared and was found to retain some stimulatory action (15), but water-solubility was acquired at too great a sacrifice in activity to make the compound useful.

EXPERIMENTAL[5]

Cyclohexanones: Except for the three isomeric methylcyclohexanones which were available from commercial sources, the alkylcyclohexanones were prepared by the catalytic hydrogenation of the corresponding di- or tri-alkylcyclohexenones or by the oxidation of the appropriate alkylcyclohexanols. The dialkylcyclohexenones were prepared by the Knoevenagel technique (16) from ethyl acetoacetate and aliphatic aldehydes as modified by Horning, Denekas, and Field (17). Catalytic hydrogenations were carried out essentially as suggested by Henze, Wilson, and Townley (18). The oxidation of the cyclohexanols[6] followed the procedure outlined for the preparation of menthone from menthol (19). 3,5,5-Trimethylcyclohexanone was prepared both by catalytic hydrogenation of isophorone and by oxidation of trimethylcyclohexanol. The properties of the various cyclohexanones are given in Table I.

Cyclohexanone oximes. The cyclohexanones were converted into their oximes by treatment with an aqueous solution of hydroxylamine. The liquid oximes were purified by distillation, usually under reduced pressure, while the solid oximes were purified by crystallization from aqueous (75–80%) methanol except in the case of 4-*tert*-butylcyclohexanone oxime where propylene dichloride was a more effective solvent for crystallization. The properties of the oximes are summarized in Table I.

Pentamethylenetetrazoles. The cyclohexanone oximes were converted into tetrazoles by procedures essentially analogous to those recorded in the patent literature (4). As a typical

[5] Microanalyses on all compounds were carried out by Mr. William Saschek.

[6] We are indebted to the Dow Chemical Company for the preparation of generous samples of 4-isopropylcyclohexanol, 4-*sec*-butylcyclohexanol, and 4-*tert*-butylcyclohexanol.

TABLE I

ALKYL SUBSTITUTED CYCLOHEXANONES AND THEIR OXIMES

ALKYLCYCLOHEXANONE	YIELD, %	B.P., °C./MM.	REF.	OXIMES						
				YIELD, %	B.P., °C./MM.	M.P., °C.	MOLECULAR FORMULA	N		REF.
								Calc'd	Found	
2-Methyl	—	—	(20)	53	117–118/22	—	$C_7H_{13}NO$	—	—	(20)
3-Methyl	—	—	(21)	60	121–122/25 108/12	—	$C_7H_{13}NO$	—	—	(21)
4-Methyl	—	—	(22)	81	115/20 120/26	—	$C_7H_{13}NO$	—	—	(22)
4-Isopropyl	91	212.5–213	(23)	92	117/6	—	$C_9H_{17}NO$	9.0	9.0	
4-*tert*-Butyl	84	83–84.5/6	(24)	85	—	137.5–138.5	$C_{10}H_{19}NO$	8.4	8.3	
4-*tert*-Amyl	61	109–111/11	[b]	92[a]	—	98–99	$C_{11}H_{21}NO$	7.6	8.0	
4-Cyclohexyl	94	125–127/6	(25)	96	—	103.5–104.5	$C_{12}H_{21}NO$	7.2	7.8	
3,5-Dimethyl	89	181–182	(16)	87	—	63–64	$C_8H_{15}NO$	—	—	(16)
3-Methyl-5-ethyl	86	200–201.5	(18)	73	127–128/11	—	$C_9H_{17}NO$	9.0	9.0	
3-Methyl-5-*n*-propyl	83	217.5–219	[c]	68	139–140/11	—	$C_{10}H_{19}NO$	8.3	8.2	
3-Methyl-5-isopropyl	73	216–217	(16)	90	134–136/11	—	$C_{10}H_{19}NO$	8.3	8.1	
3-Methyl-6-isopropyl	85	204–207	(26)	83	—	79–80	$C_{10}H_{19}NO$	—	—	(26)
3,5,5-Trimethyl	85	187–188	(16, 27)	92	—	79–81	$C_9H_{17}NO$	—	—	(16, 28)

[a] Allowing for recovered ketone.

[b] Calc'd for $C_{11}H_{20}O$: C, 78.5; H, 12.0. Found: C, 78.5; H, 12.1.

[c] Calc'd for $C_{10}H_{18}O$: C, 77.9; H, 11.8. Found: C, 78.0; H, 11.6.

example the preparation of 8-isopropylpentamethylenetetrazole may be described. Powdered sodium azide (58.5 g.) was suspended in 1 l. of ethylene dichloride in a 5-l. three-necked flask equipped with an efficient mechanical stirrer, a dropping-funnel with the tip immersed in the liquid reaction mixture,[7] an exit tube, and a long-stemmed alcohol thermometer with the bulb immersed in the reaction mixture. The apparatus was set up in an efficient hood. To the vigorously stirred suspension 478 g. of chlorosulfonic acid was added through the dropping-funnel at such a rate that the temperature of the reaction mixture did not rise above 35°. After complete addition of the chlorosulfonic acid a solution of 70 g. of 4-isopropylcyclohexanone oxime in 500 cc. of ethylene dichloride was added drop-wise with continuous, vigorous stirring at such a rate that the temperature of the reaction mixture remained between 35–45°. Occasionally, external cooling was required. Upon complete addition of the oxime, stirring was continued until the reaction mixture had cooled to room temperature, when water was added slowly, with vigorous stirring and external cooling, in sufficient quantity to decompose the excess chlorosulfonic acid. The aqueous acid layer was then separated from the ethylene dichloride solution, the acid neutralized with aqueous sodium hydroxide, and the neutral solution extracted with four 300-cc. portions of ethylene dichloride. The extracts were combined with the ethylene dichloride solution, dried over sodium sulfate, and the solvent removed by distillation. The residue was boiled with 300 cc. of 10% aqueous hydrochloric acid for three hours and the product was extracted from the acid mixture with several portions of ethylene dichloride. After washing the combined extracts with water and drying over sodium sulfate, the solvent was removed by distillation and the residue was fractionated under reduced pressure; b.p. 159–160° at 6 mm. On standing the distillate crystallized, after which the product could be purified by recrystallization from ether-petroleum ether, from which it separated as fine needles, m.p. 48–49°.

In other cases the crude tetrazoles frequently crystallized readily so that distillation under reduced pressure could be omitted, since satisfactory purification could be achieved more easily by crystallization. In some instances it was also possible to omit the treatment with hydrochloric acid. This step was designed to hydrolyze the cyclic amides formed as by-products through Beckmann rearrangement of the oximes and could be omitted when the quantity of by-product was very small or did not interfere with the crystallization of the tetrazole.

The alkylpentamethylenetetrazoles were generally moderately or easily soluble in solvents such as ethyl ether, methyl or isopropyl alcohol, benzene and the chlorinated hydrocarbons such as ethylene or propylene dichloride. They were practically insoluble in water or petroleum ether except in the case of the isomeric monomethylpentamethylenetetrazoles which showed moderate water-solubility. The properties and analyses of the tetrazoles prepared by the above procedure are recorded in Table II.

Quaternary salts. The quaternary salts of the pentamethylenetetrazoles were formed by heating an equimolar mixture of the tetrazole and methyl benzenesulfonate on a boiling-water bath until the exothermic reaction was complete. In a typical preparation a mixture of 69 g. (0.5 mole) of pentamethylenetetrazole and 86 g. (0.5 mole) of methyl benzenesulfonate was heated on a boiling-water bath. A homogeneous solution resulted; the temperature rose gradually to about 90° when an exothermic reaction set in causing a rapid further rise to about 170°. Heating was continued for about a half-hour while the mass cooled to the bath temperature. On standing for several days at room temperature the thick, gummy product crystallized; then purification was easily effected by recrystallization from ethylene dichloride, from which the product separated as glistening plates, m.p. 145–146°.

The quaternary salt of 8-*tert*-butylpentamethylenetetrazole was prepared in the same way, while the methiodide of pentamethylenetetrazole was prepared by prolonged boiling of a solution of the tetrazole in absolute isopropyl alcohol with an excess of methyl iodide.

The quaternary salts are very soluble in water. The benzenesulfonates exhibit moderate

[7] Unconfirmed reports that serious explosions had resulted when concentrated sulfuric acid and similar reagents were dropped through vapors containing hydrazoic acid made this precautionary technique seem desirable. We have not attempted to confirm the observations.

TABLE II

Alkyl Substituted Pentamethylenetetrazoles

Alkylpentamethylenetetrazole[a]	Yield, %	M.P., °C.	Crystals	Solvent	Molecular Formula	Analysis					
						Calc'd			Found		
						C	H	N	C	H	N
10-Methyl (5)	61	31–32 b.p. 185–186/15	Ref. (4, 6)	—	$C_7H_{12}N_4$	55.2	7.9	36.8	55.0	7.5	36.7
7-Methyl (8)	63	53–54	Ref. (7)	Ether-pet. ether	$C_7H_{12}N_4$	55.2	7.9	36.8	55.1	7.6	36.8
8-Methyl (7)	57	43–44	Ref. (4)	Ether-pet. ether	$C_7H_{12}N_4$	55.2	7.9	36.8	55.3	8.1	36.7
8-Isopropyl (7)	67	48–49	Small needles	Ether-pet. ether	$C_9H_{16}N_4$	60.0	8.9	31.1	60.2	8.6	31.2
8-*sec*-Butyl (7)	50	70–71	Prisms	Heptane-propylenedichloride	$C_{10}H_{18}N_4$	61.9	9.3	28.9	62.0	9.1	29.3
8-*tert*-Butyl (7)	68	132.5–133	Needles	Isopropyl alcohol	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.5	9.1	28.9
8-*tert*-Amyl (7)	57	73–74	Needles	Methanol	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.6	9.7	26.9
8-Cyclohexyl (7)	51	92–93	Leaflets	Heptane	$C_{12}H_{20}N_4$	65.5	9.1	25.5	65.6	9.3	25.3
7,9-Dimethyl (6,8)	58	156	Leaflets	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.8	8.4	33.4
7-Methyl-9-ethyl (8,6)	32	88.5–89.5	Small needles	Isopropyl alcohol	$C_9H_{16}N_4$	60.0	8.9	31.1	59.6	8.8	31.4
7-Methyl-9-*n*-propyl (8,6)	37	64.5–65.5	Prisms	Isopropyl alcohol	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.9	9.2	29.0
7-Methyl-9-isopropyl (8,6)	50	135	Small needles	Ether-pet. ether	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.7	9.0	29.0
7-Methyl-10-isopropyl (8,5)	27	49–49.5	Prisms	Ether-pet. ether	$C_{10}H_{18}N_4$	61.9	9.3	28.9	62.0	9.4	29.0
7,9,9-Trimethyl (8,6,6)	72	115–117	Needles	Water	$C_9H_{16}N_4$	60.0	8.9	31.1	60.2	8.9	30.9

[a] The numbers in parentheses indicate the corresponding positions of the respective groups as substituents on the 6,7,8,9-tetrahydro-5-azepotetrazole nucleus.

TABLE III

QUATERNARY SALTS OF PENTAMETHYLENETETRAZOLES

COMPOUND	YIELD, %	M.P., °C.	CRYSTALS	SOLVENT	ANALYSIS N		
					FORMULA	Calc'd	Found
Pentamethylenetetrazole methyl benzenesulfonate	63	145–146	Glistening plates	Ethylene dichloride	$C_{13}H_{18}N_4O_3S$	18.1	18.3
Pentamethylenetetrazole methiodide	40	175–180	Needles	Abs. isopropyl alcohol	$C_7H_3IN_4$	20.0	20.0
8-*tert*-Butylpentamethylenetetrazole methyl benzenesulfonate	71	171.5–172.5	Needles	Propylene dichloride	$C_{17}H_{26}N_4O_3S$	15.3	15.1

solubility in cold methanol and cold isopropyl alcohol, while both the iodide and the benzenesulfonates are rather easily soluble in hot ethylene or propylene dichloride but only sparingly soluble in the cold solvents. The methiodide is rather easily soluble in hot absolute isopropyl alcohol but difficultly soluble in the cold solvent. The properties and analyses of the quaternary salts are summarized in Table III.

SUMMARY

1. The preparation and properties of a series of alkyl substituted pentamethylenetetrazole derivatives have been described.

2. The formation of quaternary salts of pentamethylenetetrazoles with methyl iodide and methyl benzenesulfonate has been observed and their preparation described.

3. Relationships between the structure and pharmacologic properties of the alkylpentamethylenetetrazoles are discussed.

4. The relationship between the mechanism of tetrazole formation from cyclohexanone oximes and the Beckmann rearrangement is discussed and intermediates are suggested for the reactions which will account for the simultaneous occurrence of both reactions.

ORANGE, NEW JERSEY

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

THE SYNTHESIS OF 2,3-PIPERAZINEDIONES FROM 1,2-DIAMINES AND OXALIC ESTERS

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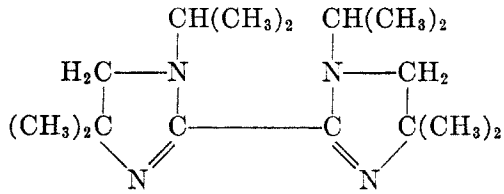
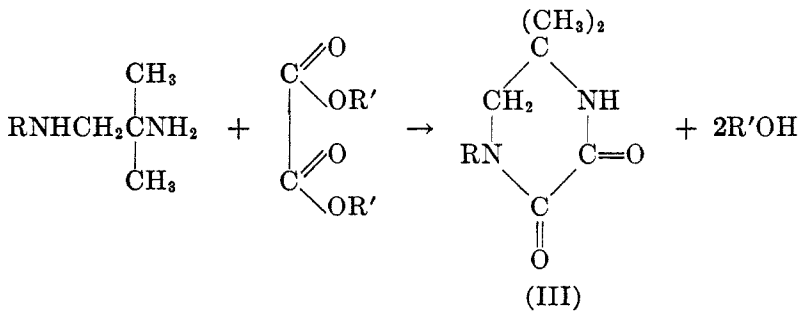
It has been shown previously (1) that the common dibasic acids with four or more carbon atoms per molecule react with 1,2-diamines to produce *bis*-imidazolines. These reactions were effected under substantially the same conditions as for another series of imidazolines prepared from monobasic acids and 1,2-diamines (2). But when oxalic acid was heated with N-(2-aminoisobutyl)isopropylamine the possible *bis*-imidazoline (I) did not form, but instead there was



(I)

obtained a low yield of 1-isopropyl-4,4-dimethyl-2-imidazoline (II). This result suggested that one of the two carboxyl groups of the oxalic acid reacted in the usual manner to form an imidazoline and that the second carboxyl group lost carbon dioxide, thus forming (II).

In view of the relative instability of oxalic acid, it appeared that (I) might possibly be synthesized by interacting methyl oxalate with N-(2-aminoisobutyl)-isopropylamine, and splitting out methanol and water instead of water alone as in the previous imidazoline synthesis. This procedure failed to produce (I) but did give a fair yield (63%) of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione. The by-product was a viscous liquid of undetermined nature. It may have been a polyamide which one might reasonably expect. This same type of reaction was tried with other 1,2-diamines and seems to be reasonably satisfactory when the diamine contains one primary and one secondary amino group. The general reaction may be formulated as follows:

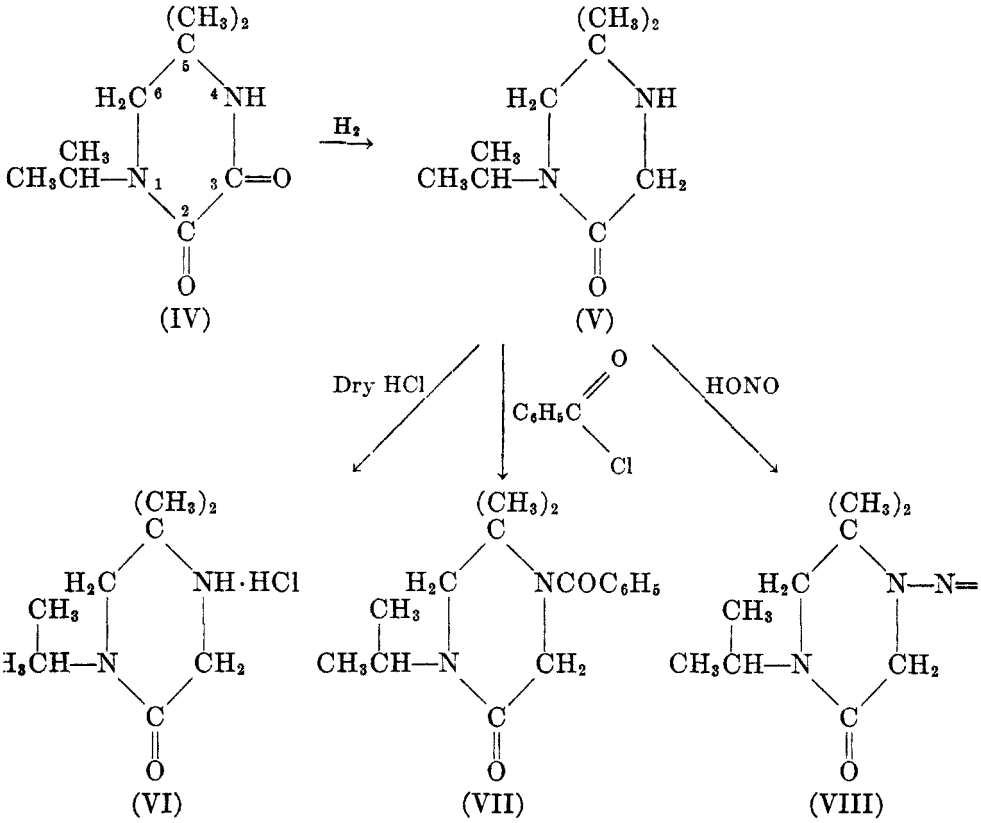


(III)

in which R may be alkyl or aryl and R′ may be methyl or ethyl.

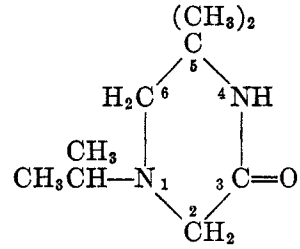
The piperazinediones of type (III) were all colorless solids with relatively high melting points. They were insoluble in ether and usually soluble in water, giving substantially neutral solutions. These facts would be expected of materials of this structure.

The proof of structure of compounds of type (III) is based upon the method of synthesis and upon the products formed by their reduction (either catalytically or by use of the Clemmensen method) and by a study of the reduced products. The structure determination can be described using (IV) as an example.



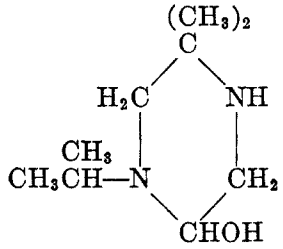
Compound (IV) reduced smoothly to (V) which was a colorless liquid, b.p. 151–153°/20, with a distinct amine odor. It titrated as a monoacid base; formed a monobenzoyl derivative which was neutral to bromophenol blue; and formed a monohydrochloride and the nitroso derivative (VIII) which it should do as a secondary amine. The possibility that (IV) had reduced to the isomeric compound (Va) was considered, but the evidence seems clearly against it. Compound (Va) might boil at about the same temperature as (V). It should give the same neutral equivalent and form a monohydrochloride. But since N^4 (formula Va) is essentially like that in an amide, one would not expect it to form a benzoyl or

nitroso derivative. Even if it did, these derivatives should be basic in character because of the tertiary amino-nitrogen, N^1. Since the monobenzoyl derivative was neutral in character and for the other reasons indicated, (Va) cannot be considered a possibility.



(Va)

Some of the analytical data for (V) could be explained on the assumption that it was (Vb) since it differs in composition from (V) by only two atoms of



(Vb)

hydrogen. If this were the correct structure, it should form a dibenzoyl derivative, a dihydrochloride and titrate as a diacid base which, as indicated above, did not prove to be the case.

EXPERIMENTAL

The 2,3-*piperazinediones* were all prepared using substantially the same procedure. One example will be given in detail.

Preparation of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione (IV). A mixture of 65 g. (0.5 mole) of N-(2-aminoisobutyl)isopropylamine and 59 g. (0.5 mole) of dimethyl oxalate was heated under conditions to distill the methanol produced from the reaction through a 4′-packed column. The temperature of the reaction flask was slowly increased during a period of 4 hours to a maximum of 180°. A total of 30 g. (0.94 mole) of methanol was thus removed. Upon cooling, the product solidified and upon crystallization from acetone melted at 203°. Yield 58 g. (63%). The solvent was removed from the filtrate and the residue found to be a viscous oil. The nature of this residue was not determined.

Table I gives a summary of the 2,3-piperazinediones prepared by this method.

Reduction of 5,5-dimethyl-1-isopropyl-2,3-piperazinedione (IV) to *5,5-dimethyl-1-isopropyl-2-keto-1,4-hexahydrodiazine* (V). This reduction was carried out by two methods. A. *Catalytic reduction.* To a solution containing 89 g. of (IV) in 800 ml. of methanol was added 10 g. of Raney nickel and hydrogenation was carried out for 19 hours at 200° and at 2000 p.s.i. The product was filtered, 0.9 g. of platinum black was added and hydrogenation was continued 7 more hours at 200° and 2000 p.s.i. The platinum black was removed and the

TABLE I

2,3-PIPERAZINEDIONES

AMINE USED	PRODUCT	FORMULA	M.P., °C.	YIELD, %	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
N-(2-Aminoisobutyl)isopropylamine	5,5-Dimethyl-1-isopropyl-2,3-piperazinedione	$C_9H_{16}N_2O_2$	203	63	58.65	8.76	15.26	58.35	8.64	15.00
N-(2-Aminoisobutyl)-*n*-butylamine	1-*n*-Butyl-5,5-dimethyl-2,3-piperazinedione	$C_{10}H_{18}N_2O_2$	118	50	60.55	9.15	—	59.76	9.20	—
N-(2-Aminoisobutyl)-*sec*-butylamine	1-*sec*-Butyl-5,5-dimethyl-2,3-piperazinedione	$C_{10}H_{18}N_2O_2$	210–212	34	—	—	14.26	—	—	14.14
N-(2-Aminoisobutyl)aniline	5,5-Dimethyl-1-phenyl-2,3-piperazinedione	$C_{12}H_{14}N_2O_2$	194–196	53	66.00	6.44	—	65.70	6.36	—
N-(2-Aminoisobutyl)-*p*-toluidine	5,5-Dimethyl-1-*p*-tolyl-2,3-piperazinedione	$C_{13}H_{16}N_2O_2$	246–247	26	—	—	12.07	—	—	12.04

methanol was evaporated, leaving a residue with an amine odor. Upon distillation, the only distinct fraction boiled at 152–153°/20; yield 18.6 g. (23%).

Anal. Calc'd for (V) $C_9H_{18}N_2O$: C, 63.48; H, 10.66.
Found: C, 63.84; H, 10.79.

B. *Clemmensen reduction.* A mixture of 100 g. of mossy zinc, 8 g. of mercuric chloride, 5 ml. of conc'd hydrochloric acid, and 125 ml. of water was stirred 5 minutes. The aqueous solution was decanted and to the amalgamated zinc was added 75 ml. of water, 100 ml. of conc'd hydrochloric acid, and 36.8 g. (0.2 moles) of (IV). This mixture was refluxed 9 hours. The solution was decanted from the unused zinc and potassium hydroxide was added in excess. This alkaline solution was extracted with ether, the ether extract was dried over solid potassium hydroxide, and distilled; b.p. 130–131°/4, yield 17 g. (50%).

Anal. Calc'd for (V) $C_9H_{18}N_2O$: N, 16.45; neut. equiv., 170.14.
Found: N, 16.32; neut. equiv., 172.79.

Preparation of the hydrochloride of (V). The hydrochloride was prepared from samples of (V) obtained by each of the reduction methods. The properties were identical for both preparations. Two g. of (V) was dissolved in dry ether and treated with dry hydrogen chloride. A white solid formed and the ether was decanted. The solid was crystallized from ethanol; yield 1.5 g., m.p. 192°.

Anal. Calc'd for $C_9H_{19}ClN_2O$: N, 13.55; Cl, 17.18.
Found: N, 13.46; Cl, 17.32.

Preparation of the benzoyl derivative of (V). To 2 g. of (V) was added 5 ml. of water and 4 g. of benzoyl chloride. The mixture was agitated while 20 ml. of 20% aqueous sodium hydroxide was added portionwise. A white solid formed which, upon crystallization from 90% ethanol, melted at 152–153°; yield 1.6 g.

Anal. Calc'd for $C_{16}H_{22}N_2O_2$: N, 10.21. Found: N, 10.15.

This benzoyl derivative was neutral in character.

Preparation of 5,5-dimethyl-1-isopropyl-2-keto-4-nitroso-1,4-hexahydrodiazine. To 4.5 g. (0.0265 mole) of (V) was added 4.4 ml. (0.053 mole) of conc'd hydrochloric acid in 5 ml. of water. This mixture was cooled to 0° and an aqueous solution of sodium nitrite was added slowly with stirring. The temperature was maintained at 0–5°. An oil separated which crystallized upon standing, and was purified by recrystallization from ethanol; m.p. 115°, yield 3.9 g. (75%).

Anal. Calc'd for $C_9H_{17}N_3O_2$: N, 21.09. Found: N, 21.00.

Reduction of 1-n-butyl-5,5-dimethyl-2,3-piperazinedione (IX) to *1-n-butyl-5,5-dimethyl-2-keto-1,4-hexahydrodiazine* (X). The Clemmensen reduction of 0.2 mole of (IX) was carried out as described for (IV) above. The product (X) boiled at 155–157°/6; yield 11.4 g. (31%).

Anal. Calc'd for (X) $C_{10}H_{20}N_2O$: N, 15,20; neut. equiv., 184.16.
Found: N, 15.07; neut. equiv., 185.53.

The *hydrochloride* of (X) was prepared by the usual method; m.p. 127–129°.

Anal. Calc'd for $C_{10}H_{21}ClN_2O$: N, 12.58; Cl, 15.93.
Found: N, 12.46; Cl, 16.17.

Reduction of 1-sec-butyl-5,5-dimethyl-2,3-piperazinedione (XI) to *5,5-dimethyl-2-keto-1-sec-butyl-1,4-hexahydrodiazine* (XII). The Clemmensen reduction of 0.2 mole of (XI) was carried out as described for (IV) above. The product (XII) boiled at 140–141°/6, yield 8.5 g. (23%).

Anal. Calc'd for (XII) $C_{10}H_{20}N_2O$: N, 15.20; neut. equiv., 184.16.
Found: N, 14.87; neut. equiv., 187.75.

The *hydrochloride* of (XII) was prepared by the usual method; m.p. 175–176°.

Anal. Calc'd for $C_{10}H_{21}ClN_2O$: N, 12.58; Cl, 15.93.
Found: N, 12.64; Cl, 16.16.

Attempts were made to reduce 5,5-dimethyl-1-phenyl-2,3-piperazinedione and 5,5-dimethyl-1-*p*-tolyl-2,3-piperazinedione by the Clemmensen method, but none of the expected products were obtained. The reduced material possessed an amine odor, but the yields were low and attempts at purification failed.

Acknowledgment. The author is pleased to express his appreciation to Commercial Solvents Corporation for generous support of this study.

SUMMARY

1. Oxalic esters react with 1,2-diamines to produce 2,3-piperazinediones. Five examples have been described.

2. These piperazinediones can be reduced to 2-keto-1,4-hexahydrodiazines.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

CYCLOPROPANES III.[1] CYCLOPROPYLMALONIC ESTER AND RELATED COMPOUNDS

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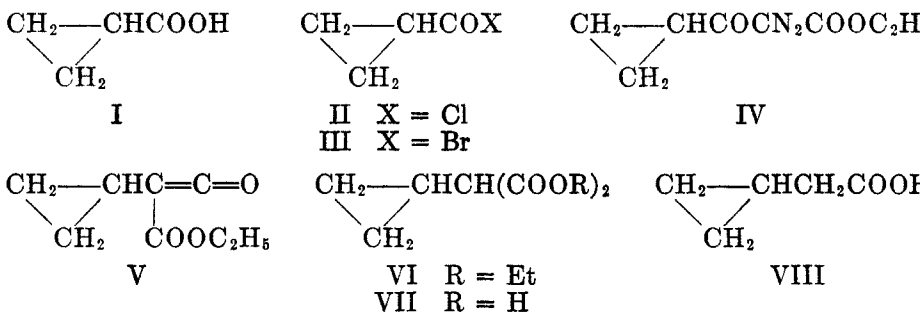
Reactions involving ring closure to form small rings usually cannot be employed for synthesis of compounds containing one or more carbon atoms between the ring and the functional group. This is so because the ring closure itself involves withdrawal of an atom which must be sufficiently activated to react preferentially; this activation is most commonly produced by locating the atom to be withdrawn in the α-position to some functional group such as carbonyl, carbethoxy, etc. Rearrangements involving expansion or contraction of the small ring occur frequently in replacement reactions of a halogen or other group attached either directly to the ring or to an α-carbon atom; this makes difficult the extension of a one-carbon side chain attached to a small ring.

Cyclopropanecarboxylic acid has been converted into cyclopropylacetic acid by a sequence of reactions involving no attack upon the carbon atom joined directly to the ring. The acid (I) was converted into the acid halide (II, III), and the latter was converted, by action of ethyl diazoacetate, into the acyldiazoester (IV) (1). The diazoester (IV), when refluxed in toluene in the presence of silver oxide, lost nitrogen and rearranged into the ketene (V), and the ketene, by action of ethanol, was converted into ethyl cyclopropylmalonate (VI). Basic hydrolysis of VI gave the malonic acid (VII), which, on decarboxylation, gave cyclopropylacetic acid (VIII).



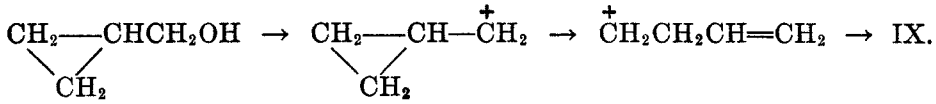
Demjanov and Dojarenko (2) reported the preparation of VIII from cyclopropylcarbinol, but no derivative of VIII was prepared and the substance was characterized only by the boiling point and refractive index. These properties of VIII prepared *via* the ketene (V) agreed well with those given by Demjanov and Dojarenko, but it was decided to prepare VIII from cyclopropylcarbinol for comparison.

Ethyl cyclopropanecarboxylate was reduced to cyclopropylcarbinol by actio

[1] Paper II, *J. Am. Chem. Soc.*, **71**, 2676 (1949).

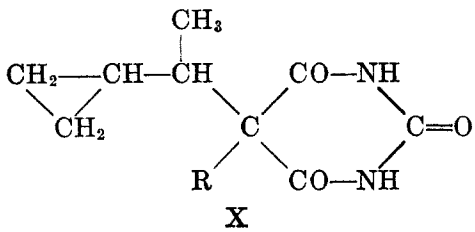
[2] General Mills post-doctorate fellow.

of lithium aluminum hydride;[3] the properties of the carbinol agreed well with those given by Demjanov (3) who reduced the ester by the Bouveault-Blanc procedure. The carbinol was converted into the bromide by action of phosphorus tribromide at 0°; the properties of the bromide agreed with those given by Demjanov (3). However, carbonation of the Grignard reagent from this bromide gave an unsaturated acid (IX) isomeric with VIII. The unsaturated acid reduced permanganate, and gave a *p*-bromophenacyl ester melting at 57–58°; VIII did not reduce permanganate, and gave a *p*-bromophenacyl ester melting at 83°. The most likely structure for IX appeared to be that of allylacetic acid; this acid was accordingly prepared from allylmalonic acid (4) and converted into its *p*-bromophenacyl ester. The ester so prepared melted at 57–58°, alone or when mixed with the *p*-bromophenacyl ester of IX. It followed, therefore, that at some stage in the conversion of cyclopropyl carbinol into IX a rearrangement occurred; this most likely occurred in the first step, when the carbinol was converted into the bromide.

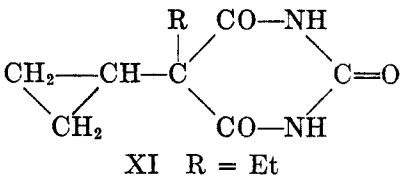


Braker, Pribyl, and Lott (5) have recently prepared bromides from cyclopropyl carbinol and ethylcyclopropyl carbinol, and have used these bromides for alkylation of malonic esters; no evidence, other than the method of synthesis, was given to show that the resulting malonic esters actually contained a cyclopropyl group. An attempt was made to degrade the methyl ester of VIII to I by the method of Barbier-Wieland (6) but no I could be obtained; nor could VIII be obtained from methyl cyclopropyl ketone by a Willgerodt reaction.

These reactions show that the product obtained from cyclopropyl carbinol by extension of the side chain is definitely not VIII. Although the structure of VIII has not been confirmed by conversion into a known cyclopropane derivative, the method of synthesis and the lack of reaction with permanganate indicate that VIII is really cyclopropylacetic acid.



X



XI R = Et

Many compounds containing the cyclopropyl group are physiologically active. Having in hand cyclopropylmalonic ester (VI), it was of interest to convert it into a barbiturate, and to test the barbiturate for physiological activity. Opie, Seifter, Bruce, and Mueller (7) have prepared a barbiturate of type X; the barbiturate from VI would be one of type XI in which the cyclopropyl group is joined directly

[3] The authors desire to thank Mr. E. Rogier for performing this reduction.

TABLE I

BARBITAL HYPNOTICS IN WHITE MICE

DRUG	DOSE, MG./KG.						
	10	30	50	100	200	300	400
Pentobarbital Sodium Salt	5/10* showed slight depression, others hyperactive	3/5 asleep for 40 min.	10/10 asleep for 45–80 min.	5/5 asleep for 100 min.	10/10 dead		
5-Ethyl-5-cyclopropyl Barbituric Acid Sodium Salt	5/5 showed slight hyperactivity	3/5 asleep for 50 min., others drowsy for 100 min.	5/10 asleep for 120 min., others drowsy for 180 min.	4/5 asleep for 3 hrs.	10/10 asleep for 4 hrs. (marked hypnosis)	5/5 asleep for 24 hrs. 1 dead	4/5 dead
Phenobarbital Sodium Salt		5/5 asleep 120 min.		4/5 sleepy and drowsy at 18 hrs.	1/5 dead		
Phanodorn	at 350 mg. per kg., 4/5 dead.						

* 5/10 is to be read, 5 out of 10 mice showed slight depression, etc.

to the barbituric acid group in the 5-position. Accordingly, VI was ethylated by action of ethyl iodide and alkali, and the resulting ethylcyclopropylmalonic ester was subjected to the action of urea. The barbiturate XI was obtained as colorless needles melting at 173–174°.[4]

EXPERIMENTAL PART

Ethyl diazoacetate. A solution of glycine ethyl ester hydrochloride (500 g.)[5] and sodium acetate (2.5 g.) in water (1000 cc.) was placed in a 3-l. separatory funnel. At room temperature, sodium nitrite (10 g.) in a small amount of water was carefully added; the solution was extracted at once with ether (200 cc.). The ether was removed; sodium nitrite (10 g.), followed by sulfuric acid (2 *N*, 25 cc.) was added to the aqueous layer, which was again extracted with ether (200 cc.). This procedure was repeated until a total of 375 g. of sodium nitrite and 2200 cc. of ether were used. The combined ethereal extracts were washed with saturated aqueous sodium carbonate and dried (magnesium sulfate). Ether was removed and the residue was distilled under reduced pressure (25–35 mm.). The product weighed 300 g. (73%). This procedure is a modification of that of Womack and Nelson (10).

Cyclopropanecarboxylic acid (I) *A.* The acid was prepared *via* trimethylene chlorohydrin (11), trimethylene chlorobromide (12), and γ-chlorobutyronitrile (13) as described by McCloskey and Coleman (14). *B.* The acid (55 g., 64%) was prepared from methyl cyclopropyl ketone (84 g.), bromine (480 g.), and sodium hydroxide (320 g.) essentially according to the procedure described by Sandborn and Bourquet (15) for preparation of trimethylacetic acid.

Cyclopropanecarboxylyl chloride (II) (16). A mixture of the acid (I) (21.5 g.) and phosphorus trichloride (22.6 g.) was protected from moisture while it was stirred at 50° for one hour. The product was distilled directly from the reaction mixture, under sufficiently reduced pressure so that the temperature did not exceed 70°. The distillate, redistilled through a short (6″) column packed with glass helices, gave an initial fraction (discarded) boiling at 72–74°/750 mm. The remainder was distilled under reduced pressure; it formed a colorless liquid which boiled at 39°/20–30 mm. and weighed 22 g. (84%). A small portion of the chloride was converted into the anilide (81%) which, crystallized from ethanol, melted at 108.5–110.5°. The reported melting point of this anilide is 110–111° (17). A mixture of this anilide with crotonanilide [m.p. 114° (18)] melted below 90°.

Cyclopropanecarboxylyl bromide (III). The acid (I) (104.3 g.) and phosphorus tribromide (108.5 g.) gave the bromide boiling at 45–47°/20 mm.

Ethyl cyclopropanecarboxylyldiazoacetate (IV). *A. From the acid chloride.* A solution of ethyl diazoacetate (54.5 g.) in dry ether (2500 cc.) was stirred while the chloride (II) (23 g.) was added slowly, and the mixture was allowed to stand for one week at room temperature. Ether was removed and the residue, when distilled under reduced pressure, formed a yellow oil (17.5 g., 44%) boiling at 76°/3 mm.; n_D^{24} 1.4952. The substance must be distilled at as low a temperature as possible, and no column should be used, for prolonged heating causes the substance to decompose vigorously.

Anal. Calc'd for $C_8H_{10}N_2O_3$: C, 52.72; H, 5.53.
Found: C, 52.57; H, 6.08.

B. From the acid bromide. A solution of ethyl diazoacetate (152.4 g.) in dry ether (500 cc.) was stirred while the bromide (III) (85 g.) was added. The mixture, cooled for a few moments until the evolution of nitrogen subsided somewhat, was allowed to stand at room temperature for a day, after which it was refluxed gently for two days. The product, isolated and purified as above, weighed 75 g. (72%).

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[4] The 5-ethyl-5-cyclopropyl barbiturate as the sodium salt was tested pharmacologically by Dr. R. N. Bieter of the Department of Pharmacology, University of Minnesota, whom we wish to thank for his kindness. The results are given in Table I; for comparison, the activities of three other hypnotics are included.

[5] Prepared from methyleneaminoacetonitrile (8) by the method of Marvel (9).

Ethyl cyclopropylmalonate (VI). A mixture of the diazoester (IV) (82 g.), anhydrous toluene (80 cc.), and silver oxide (0.5 g.) was refluxed under an atmosphere of carbon dioxide until evolution of nitrogen ceased (3–4 hours). The toluene was removed (20 mm.) and the residue was distilled under reduced pressure (3 mm.) into cooled (Dry Ice–acetone) ethanol (50 cc.). Distillation was continued until the bath temperature reached 220°. Ethanol was removed from the distillate, and the product was fractionated. The colorless liquid, b.p. 76–80°/3 mm., n_D^{24} 1.4315, weighed 39 g. (43%).

Anal. Calc'd for $C_{10}H_{16}O_4$: C, 59.96; H, 8.05.
Found: C, 60.15; H, 7.88.

Variants of the above procedure included (a) substitution of xylene for the toluene; yield of product, 35.6%; (b) dry ethanol, silver oxide, and IV (10 g.) heated at 130° for four hours in a bomb, yield 4 g.; dry ethanol, IV, and polished platinum refluxed at atmospheric pressure; no VI was obtained.

Cyclopropylmalonic acid (VII). The ester (VI) (4 g.) was heated overnight on the steam-bath with aqueous sodium hydroxide (10 cc., 10%). The cooled mixture was extracted with ether; the aqueous layer was acidified with hydrochloric acid and extracted continuously with ether in an extractor for three days. The ether extract was dried (magnesium sulfate), ether was removed, and the residue was crystallized from nitromethane. The colorless needles (2.4 g., 83%) melted at 174–175° (dec.) (block). The substance did not decolorize aqueous potassium permanganate.

Anal. Calc'd for $C_6H_8O_4$: C, 50.00; H, 5.55.
Found: C, 49.69; H, 5.69.

Cyclopropylacetic acid (VIII). The acid (VII) (4 g.) was decomposed and distilled by heating it in a 20-cc. Claisen flask with a flame until evolution of carbon dioxide ceased. The distillate was a colorless liquid, yield 2.5 g. (90%); b.p. 189–191°/750 mm., n_D^{23} 1.4330, n_D^{25} 1.4320. Demjanov and Dojarenko (2) reported for their acid b.p., 189–190°/740 mm., n_D^{21} 1.4343. The *p-bromophenacyl ester*, prepared in the usual way and crystallized from ethanol, melted at 83°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.52; H, 4.38.
Found: C, 52.36; H, 4.57.

The *methyl ester* (4.5 g., 79%) prepared from the acid (5 g.) by action of ethereal diazomethane, had b.p. 132°/745 mm., n_D^{23} 1.4175.

Anal. Calc'd for $C_6H_{10}O_2$: C, 63.16; H, 8.77.
Found: C, 63.32; H, 9.22.

A mixture of methyl cyclopropyl ketone (8.4 g.), sulfur (16 g.), ammonium hydroxide (25 cc.), and pyridine (15 cc.) was heated in a sealed tube at 165° for four hours (19). No acidic material was obtained when the product was processed in the usual manner. Methyl cyclopropyl ketone (8.4 g.) and sulfur (5 g.) were heated at 200° for four hours in a sealed tube with ammonium hydroxide (50 cc.) which had been saturated with hydrogen sulfide. No cyclopropylacetic acid could be isolated from the product. Methylcyclopropyl ketone (42 g.) in carbon tetrachloride (50 cc.) containing sulfuryl chloride (75 g.) was stirred and heated to 45° for one hour (20). The solution was washed with water and dried (calcium chloride). Solvent was removed, and the residue, when distilled, formed a colorless, lachrymatory liquid, b.p. 60–62°/20 mm., n_D^{16} 1.4840. The product was a mixture of chloro compounds which could not be separated; the composition approximated that of the dichloro ketone.

Anal. Calc'd for C_5H_7ClO: C, 50.63; H, 5.97.
Calc'd for $C_5H_6Cl_2O$: C, 39.3; H, 3.93.
Calc'd for $C_5H_5Cl_2O$: C, 38.71, H, 4.84.
Found: C, 41.08; H, 4.84.

Attempted degradation of methyl cyclopropylacetate. The ester (4 g.) in dry ether (50 cc.) was added, with stirring, to a solution of phenylmagnesium bromide (from bromobenzene, 23.6 g., magnesium, 3.65 g., and ether, 100 cc.). The product, isolated in the usual way and

distilled, gave a small fore-run (0.5 g.) boiling at 75°/7–8 mm., followed by the main product (6 g.), an oil boiling at 125°/7–8 mm. The oil could not be purified further.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.73; H, 7.27.
Calc'd for $C_{17}H_{18}O$: C, 85.71; H, 7.56.
Found: C, 90.87; H, 7.44.

A solution of potassium permanganate (1.92 g.) in water (60 cc.) containing pyridine (80 cc.) was added to a solution of the above oil (1 g.) in pyridine (80 cc.) and the solution was allowed to stand for three days, with occasional shaking. Sodium sulfite (solid) was added until the color was discharged; then the manganese dioxide was removed and washed with water. The combined filtrates and washings were evaporated under reduced pressure to a volume of 150 cc., then cooled and extracted several times with ether. The aqueous layer was concentrated to a volume of 20 cc., acidified with hydrochloric acid, and extracted with ether. No acidic material was found in the ether extract. Action of permanganate in acetone upon the oil likewise led to no acidic material.

Cyclopropyl carbinol[3]. Ethyl cyclopropanecarboxylate (22.4 g.), reduced by the action of lithium aluminum hydride (2.2 g.) according to the procedure of Nystrom and Brown (21) gave the carbinol (8.3 g., 58%); b.p. 122–123°, n_D^{20} 1.426. The carbinol did not react with a solution of bromine in chloroform, nor with permanganate. The *phenylurethane*, prepared in the usual way and crystallized from benzene-petroleum ether or from aqueous ethanol had m.p. 75.5–76°.

Anal. Calc'd for $C_{11}H_{13}NO_2$: C, 69.10; H, 6.85.
Found: C, 69.31; H, 6.81.

Bromide from cyclopropyl carbinol. The carbinol (5.5 g.) was added dropwise, with stirring and cooling (0°) to phosphorus tribromide (6.3 g.). The mixture was stirred for thirty minutes; the product was washed twice with cold water, dried (calcium chloride) and distilled. The distillate (7.3 g., 66%) had b.p. 105–108°, n_D^{25} 1.4700. Demjanov (3) reported that his bromide, obtained from cyclopropyl carbinol, boiled at 105–106° and had $n_D^{19.5}$ 1.475.

Carbonation of the Grignard reagent from the above bromide. A solution of the bromide (6 g.) in ether (50 cc.) was added dropwise and with stirring to magnesium (1.22 g.) and ether (40 cc.). The reaction mixture was poured over solid carbon dioxide (20 g., small pieces) and then processed in the usual way. The product (2 g., 50%) was a colorless liquid, b.p. 175–180°, n_D^{25} 1.4274; it readily decolorized permanganate. The *p-bromophenacyl ester*, prepared in the usual way and crystallized from aqueous ethanol, melted at 57–58°. A mixture of this ester and the *p*-bromophenacyl ester of VII (m.p. 83°) melted at 52–75°. A mixture of this ester and the *p*-bromophenacyl ester of allylacetic acid (IX) (4) melted at 57–58°.

Anal. Calc'd for $C_{13}H_{13}BrO_3$: C, 52.52; H, 4.38.
Found: C, 52.84; H, 4.68.

5-Ethyl-5-cyclopropylbarbituric acid (XI). Ethyl cyclopropylmalonate (VI) (28 g.) was added, with stirring, to a solution of sodium ethoxide [from sodium (3.26 g.) in dry ethanol (100 cc.)]. The solution was stirred for one hour, then ethyl iodide (23.5 g.) was added and the solution was stirred at 50° for two hours, after which it was allowed to stand overnight. The product was diluted with water (1000 cc.) and extracted several times with ether. The extracts were washed with aqueous sodium bisulfite, dried (magnesium sulfate), and the solvent was removed. The residual oil gave a main fraction (24 g.) boiling at 83–87°/3 mm. Analysis indicated that ethylation was not complete, but the material, ethylated again as above, was not of improved purity, nor did extraction with aqueous sodium hydroxide (10%) give a better product.

Anal. Calc'd for $C_{12}H_{20}O_4$: C, 63.16; H, 8.77.
Found: C, 62.05; H, 8.84.

The above ester (XI) (5 g.) was added to a warm solution of sodium ethoxide [from sodium (0.7 g.) in dry ethanol (50 cc.)]. Urea (3 g.) was added, and the mixture was heated on the steam-bath until the solvent was removed; the residue was heated for one hour on

the bath. Water (15 cc.) was added and the solution was extracted with ether. The aqueous layer was warmed to remove ether, then cooled and acidified with hydrochloric acid (5 cc.). The solid was removed and recrystallized three times from water, when it formed colorless needles (1.5 g., 26%) melting at 173–175° (block).

Anal. Calc'd for $C_9H_{12}N_2O_3$: C, 55.10; H, 6.12.
Found: C, 55.15; H, 6.14.

SUMMARY

1. Cyclopropylmalonic ester (VI) has been synthesized from cyclopropanecarboxylic acid (I) by a method which does not involve an attack upon the carbon atom joined to the ring. From the malonic ester (VI), the malonic acid (VII) has been obtained by hydrolysis; the malonic acid (VII) has been decarboxylated to cyclopropylacetic acid (VIII).

2. The cyclopropylacetic acid so obtained differs from the product prepared by Demjanov and Dojarenko *via* cyclopropyl carbinol, "cyclopropylmethylbromide", and the Grignard reagent from this bromide, and it is shown that the synthesis of Demjanov and Dojarenko actually leads to allylacetic acid, not cyclopropylacetic acid.

3. From the malonic ester (VI), by ethylation followed by condensation with urea, 5-ethyl-5-cyclopropylbarbituric acid (XI) has been prepared. This is a barbiturate of low toxicity.

MINNEAPOLIS 14, MINNESOTA

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[CONTRIBUTION NO. 186 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. VI. AZLACTONES AND RHODANINES PREPARED FROM 2-THENALDEHYDE AND SOME SUBSTITUTED 2-THENALDEHYDES[1]

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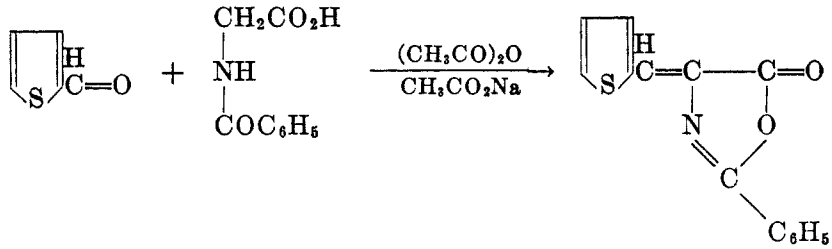
Received July 5, 1949

AZLACTONES

The Erlenmeyer azlactone synthesis involving the reaction of an aldehyde with hippuric acid in the presence of acetic anhydride and sodium acetate, has been applied in the thiophene series to 2-thenaldehyde (1) and 3-thenaldehyde (2). In view of the availability of a number of substituted 2-thenaldehydes (3) it was decided to prepare their azlactones since these compounds serve as useful derivatives and intermediates for further syntheses. This reaction may be represented as indicated in Chart I.

CHART I

AZLACTONE FORMATION



The compounds thus prepared are recorded in Table I, using the nomenclature[e] which considers azlactones as derivatives of oxazolone.

It was thought also of interest to investigate the effect of the substituents in the 5-position of the thiophene ring on the ultra-violet absorption spectra of the azlactones prepared. Two major absorption peaks were observed, the first in the region 270–272 mμ and the second in the range 393–412 mμ. Only the second peak seemed to be influenced by alkyl substituents on the thiophene ring and as shown in Figure 1 this effect is of the order $-C_3H_7 > -C_2H_5 > -CH_3$ as evidenced by a shift of this peak toward longer wave lengths and an increase in the molecular extinction coefficients. For a comparison with members of the benzene series 2-phenyl-4-benzal-5-oxazolone was also prepared and its ultra-violet absorption curve is recorded in Figure 1.

RHODANINES

Gränacher has shown the applicability of rhodanine to organic syntheses (4). Its active methylene group permits reactions with aldehydes yielding stable

[1] For paper V of this series see *J. Org. Chem.*, **14**, 638 (1949). This investigation was carried out under the auspices of the Office of Naval Research. For a preliminary communication see *Nature*, **163**, 876 (1949).

TABLE I

COMPOUNDS PREPARED BY ERLENMEYER AZLACTONE SYNTHESIS

PRODUCT	YIELD, %	M.P., °C.	ANALYSES	
			Calc'd	Found
2-Phenyl-4-(2-thenal)-5-oxazolone	68	174.5–175.5	C—65.88	C—66.10
			H— 3.53	H— 3.66
			N— 5.49	N— 5.69
2-Phenyl-4-(2-thenal-3-methyl)-5-oxazolone	60	151–152	C—66.91	C—66.87
			H— 4.09	H— 4.07
			N— 5.20	N— 5.51
2-Phenyl-4-(2-thenal-5-methyl)-5-oxazolone	58	152–153	C—66.91	C—67.00
			H— 4.09	H— 3.94
			N— 5.20	N— 5.40
2-Phenyl-4-(2-thenal-5-ethyl)-5-oxazolone	60	107.5–109	C—67.84	C—68.02
			H— 4.59	H— 4.48
			N— 4.94	N— 4.94
2-Phenyl-4-(2-thenal-5-propyl)-5-oxazolone	60	97–98.5	C—68.69	C—68.80
			H— 5.05	H— 5.28
			N— 4.71	N— 4.90
2-Phenyl-4-(2-thenal-5-chloro)-5-oxazolone	61	182.5–183.5	C—58.03	C—58.40
			H— 2.76	H— 2.74
			N— 4.83	N— 5.19
2-Phenyl-4-(2-thenal-5-bromo)-5-oxazolone	64	186–187	C—50.29	C—50.10
			H— 2.39	H— 2.25
			N— 4.19	N— 4.33

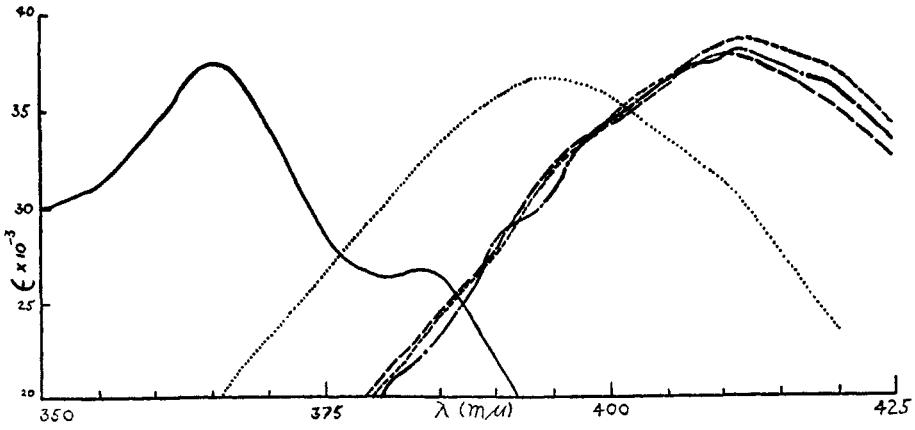


FIG. 1. ULTRA-VIOLET ABSORPTION CURVES OF AZLACTONES

——— 2-Phenyl-4-(benzal)-5-oxazolone
. . . . . 2-Phenyl-4-(2-thenal)-5-oxazolone
— — — 2-Phenyl-4-(2-thenal-5-methyl)-5-oxazolone
·———· 2-Phenyl-4-(2-thenal-5-ethyl)-5-oxazolone
- - - - - 2-Phenyl-4-(2-thenal-5-propyl)-5-oxazolone

condensation products. These are easily cleaved with alkali to thioketo acids which are believed to exist in equilibrium with the tautomeric sulfhydryl forms since they give a deep green color with ferric chloride. Oximino acids, produced by the action of hydroxylamine on the thioketo acids, are readily converted with sodium amalgam to amino acids and with acetic anhydride to nitriles which in turn may be hydrolyzed to acetic acid derivatives.

TABLE II

ABSORPTION MAXIMA AND MOLECULAR EXTINCTION COEFFICIENTS OF COMPOUNDS PREPARED BY ERLENMEYER AZLACTONE SYNTHESIS

COMPOUND	MAXIMA	
	Millimicrons	$\epsilon \times 10^{-3}$
2-Phenyl-4-benzal-5-oxazolone	262	15.9
	365	37.5
2-Phenyl-4-(2-thenal)-5-oxazolone	270	15.1
	393–395	36.6
2-Phenyl-4-(2-thenal-3-methyl)-5-oxazolone	271	15.5
	406–408	36.0
2-Phenyl-4-(2-thenal-5-methyl)-5-oxazolone	272	13.0
	410	37.7
2-Phenyl-4-(2-thenal-5-ethyl)-5-oxazolone	272	13.1
	411	38.1
2-Phenyl-4-(2-thenal-5-propyl)-5-oxazolone	272	15.1
	412	38.5
2-Phenyl-4-(2-thenal-5-chloro)5-oxazolone	274	14.0
	406	37.9

The rhodanine synthesis has been applied to veratraldehyde (5) and to furfural (6) for the preparation of 2-furanacetic acid, while 3-thenalrhodanine (2) has been used as a derivative for the identification of 3-thenaldehyde.

In Chart II is presented the series of reactions applied to the 2-thenaldehydes under consideration. Only 2-thenaldehyde itself has been carried through the complete series of reactions. The others have been converted as far as their thioketo acids.

The reduction of 2-thienylacetonitrile to the corresponding amine was effected with lithium aluminum hydride[2] in 34% yield. It is possible that improvements of this procedure may increase that figure. This is true also for the yield of 2-thienylacetamide formed with alcoholic hydrogen peroxide.

It was found impossible to obtain accurate melting points for the thienylthioketo acids after recrystallization from acetic acid. These attempts applying a 12-power lens demonstrated that part of the sample melted first while the rest remained solid and finally melted at a higher temperature. This could be understood on the basis of the presence of the two tautomeric forms which of course would give the same results when analyzed for carbon and hydrogen content.

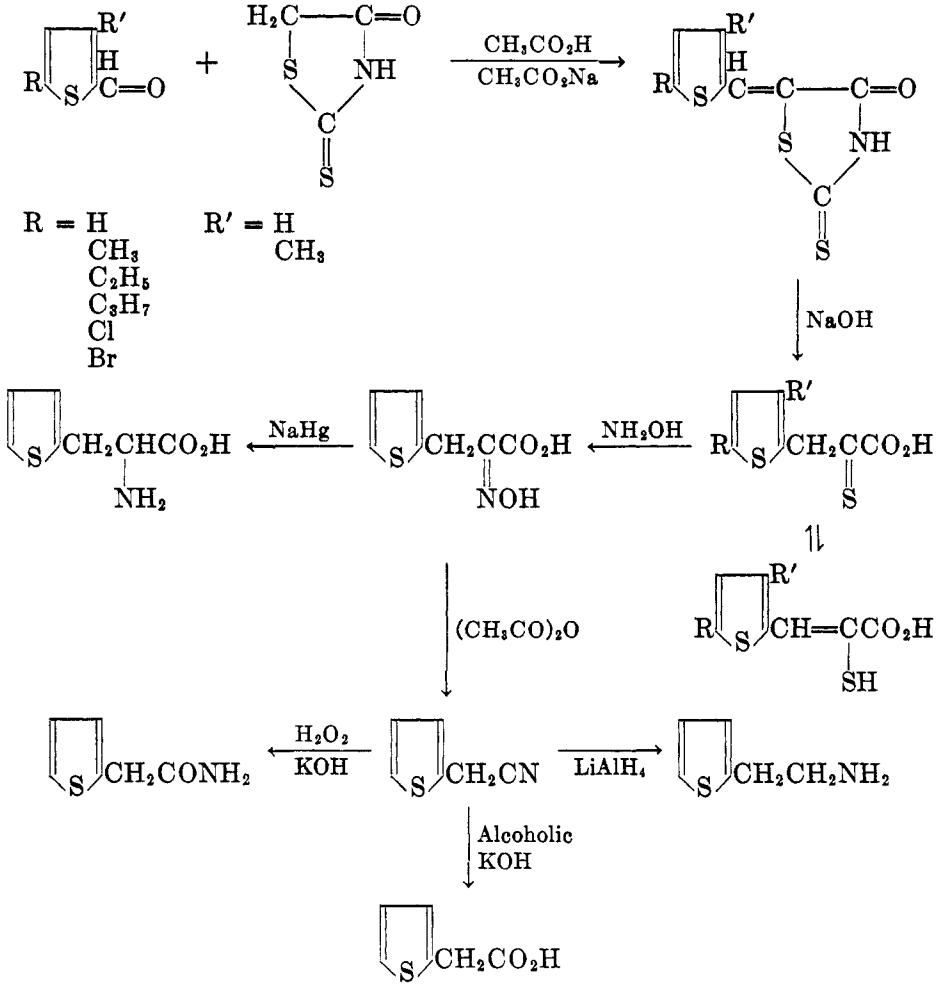
The oximino acid from 2-thenalrhodanine gave evidence of the presence of two

[2] The applicability of lithium aluminum hydride for reductions in the thiophene series has been previously demonstrated by Gilsdorf and Nord (unpublished data).

isomeric forms. The fraction obtained from the ether solution after neutralization of the sodium salt was much more soluble in toluene than that collected from the water solution. This phenomenon was noted in the furan series (6) and the *syn*-furyl configuration was tentatively assigned to the lower-melting, more soluble form in conformity with the theory of Hantzsch (7).

CHART II

SCHEME OF RHODANINE SYNTHESES



EXPERIMENTAL[3]

Azlactones. The modified procedure (8) of Kropp and Decker (9) was employed for the synthesis of all the azlactones recorded in Table 1 as exemplified by the first member of the series.

[3] The rhodanine used in this work was obtained through the courtesy of the B. F. Goodrich Chemical Company, Cleveland, Ohio. The analyses were carried out by M. Bier and Dr. F. Bühler of this Department.

2-Phenyl-4-(2-thenal)-5-oxazolone. 2-Thenaldehyde (10.14 g., 0.09 mole), 7.42 g. (0.09 mole) of freshly fused sodium acetate, 16.2 g. (0.09 mole) of hippuric acid, and 27.7 g. (0.27 mole) of acetic anhydride were heated on the steam-bath for a few minutes with manual stirring. The yellow paste which formed was left on the steam-bath for two hours. Then 30 cc. of alcohol was added and the product placed in the ice-box overnight. The crude azlactone was filtered and washed with hot water. After recrystallization from aqueous ethanol 15.85 g. (68%) of the azlactone were obtained in the form of yellow needles, (m.p. 174.5–175.5°). Barger and Easson reported 175° (1).

TABLE III

RHODANINE CONDENSATION PRODUCTS

COMPOUND	YIELD, %	M.P., °C.	ANALYSES	
			Calc'd	Found
2-Thenalrhodanine	95	231–232	C—42.29	C—42.40
			H— 2.20	H— 2.41
			N— 6.17	N— 6.39
3-Methyl-2-thenalrhodanine	94	226–227.5	C—44.81	C—44.65
			H— 2.90	H— 2.78
			N— 5.81	N— 5.81
5-Methyl-2-thenalrhodanine	94	221.5–222.5	C—44.81	C—44.60
			H— 2.90	H— 2.98
			N— 5.81	N— 5.99
5-Ethyl-2-thenalrhodanine	94	176–177	C—47.05	C—46.90
			H— 3.53	H— 3.57
			N— 5.49	N— 5.60
5-Propyl-2-thenalrhodanine	90	134–135.5	C—49.09	C—49.10
			H— 4.09	H— 3.74
			N— 5.20	N— 5.44
5-Chloro-2-thenalrhodanine	92	237–237.5	C—36.71	C—36.95
			H— 1.53	H— 1.88
			N— 5.36	N— 5.59
5-Bromo-2-thenalrhodanine	92	245.5–246.5	C—31.37	C—31.45
			H— 1.30	H— 1.42
			N— 4.57	N— 4.68

Ultra-violet absorption spectra. These measurements were taken with a Beckman quartz spectrophotometer, Model DU, using chloroform as the solvent.

Rhodanines. The rhodanines and thioketo acids listed in Tables III and IV were prepared according to the method of Julian and Sturgis (5). The yields of the thioketo acids were 97–99%.

2-Thenalrhodanine. To a warm solution of 77.6 g. (0.693 mole) of 2-thenaldehyde and 92 g. (0.693 mole) of rhodanine in 476 g. (7.93 mole) of glacial acetic acid, was added 170.3 g. (2.08 mole) of freshly fused sodium acetate. A thick orange mass resulted which was refluxed for a half-hour with occasional shaking, and then poured into 3 liters of water. The product after filtration was washed first with water and then with alcohol and ether. After drying *in vacuo* over KOH the yield was 149.6 g. (95%). Orange crystals, m.p. 231–232°, were obtained from an acetone-water mixture.

2-Thienylthiopyruvic acid. 2-Thenalrhodanine (35.6 g., 0.157 mole) was suspended in 200 cc. of 15% NaOH and heated on the water-bath with occasional stirring for a half-hour. The dark red solution which formed was cooled and 200 cc. of 10% HCl added which precipitated the thioketo acid as an amorphous yellow mass. This was filtered, washed with

water, and air dried; yield 28.6 g. (98%). Recrystallization from acetic acid gave a fine yellow powder.

3-(2-Thienyl)-2-oximinopropionic acid. Hydroxylamine hydrochloride (67.5 g.) was added to a solution of 22.5 g. of sodium in 650 cc. of ethanol. This solution was filtered and added to 57.7 g. (0.31 mole) of 2-thienylthiopyruvic acid and heated on a steam-bath for a half-hour. The alcohol was removed under vacuum and the residue dissolved in 175 cc. of 5% sodium hydroxide solution and filtered. The cooled filtrate was carefully acidified under ether with 165 cc. of 10% HCl and the precipitated acid filtered off and dried *in vacuo* over KOH. The water layer was removed in a separatory funnel and extracted with three 50-cc. portions of ether. The combined ether extracts were dried (Drierite) and evaporated

TABLE IV

RHODANINE CLEAVAGE PRODUCTS

COMPOUND	ANALYSES	
	Calc'd	Found
2-Thienylthiopyruvic acid	C—45.16 H— 3.23	C—45.25 H— 3.48
3-Methyl-2-thienylthiopyruvic acid	C—48.00 H— 4.00	C—48.05 H— 3.98
5-Methyl-2-thienylthiopyruvic acid	C—48.00 H— 4.00	C—48.15 H— 3.76
5-Ethyl-2-thienylthiopyruvic acid	C—50.46 H— 4.67	C—50.25 H— 4.57
5-Propyl-2-thienylthiopyruvic acid	C—52.63 H— 5.26	C—52.45 H— 5.41
5-Chloro-2-thienylthiopyruvic acid	C—38.09 H— 2.26	C—37.90 H— 2.12
5-Bromo-2-thienylthiopyruvic acid	C—31.69 H— 1.88	C—31.95 H— 1.74

to dryness; total yield, 51.7 g. (90%). Recrystallization from toluene gave white needles m.p. 136–137° (when the oil-bath was rapidly heated to 126°).

Anal. Calc'd for $C_7H_7NO_3S$: C, 45.41; H, 3.78.
Found: C, 45.60; H, 3.90.

2-Thienylacetonitrile. A mixture of 27 g. (0.146 mole) of 3-(2-thienyl)-2-oximinopropionic acid and 119 g. of acetic anhydride was warmed until effervescence occurred. When the reaction subsided, the nitrile was steam-distilled, and the distillate extracted with 150 cc. of ether in portions. The ether extract was neutralized with sodium carbonate solution, dried over sodium sulfate, and the ether evaporated. Distillation yielded 15.7 g. (87%), b.p. 87–90°/3, n_D^{30} 1.5041.

Anal. Calc'd for C_6H_5NS: C, 58.53; H, 4.07.
Found: C, 58.80; H, 4.18.

2-Thienylacetic acid. Hydrolysis of 5 g. (0.041 mole) of the above nitrile with alcoholic KOH [as previously described (10) for the same nitrile obtained from 2-thenyl chloride (11)] gave 3.9 g. (77%) of 2-thienylacetic acid, m.p. 63–64°. [Lit. m.p. 75° (10)]. However a sample of this acid prepared through the thenyl chloride procedure gave a m.p. of 62.5–63°. A mixture of samples of this acid prepared by both methods showed no depression of our observed m.p.

Anal. Calc'd for $C_6H_6O_2S$: C, 50.69; H, 4.22.
Found: C, 50.90; H, 4.48.

2-Thienylacetamide. A mixture of 10 g. (0.081 mole) of 2-thienylacetonitrile, 460 g. of 3% hydrogen peroxide, and 25.4 g. of 25% KOH was warmed with stirring to 50°. The heat was withdrawn and stirring continued for an hour. The mixture was placed in an ice-bath for two hours and then filtered giving 2 g. of the amide. When the filtrate was reduced to 1/3 of its volume and chilled, a further yield of 2.1 g. was obtained. The combined yield amounted to 4.1 g. (35%). Recrystallization from hot water (Norit) gave white plates, m.p. 147–148°.

Anal. Calc'd for C_6H_7NOS: C, 51.06; H, 4.96; N, 9.92.
Found: C, 50.95; H, 4.84; N, 9.81.

β-2-Thienylethylamine. In order to reduce the nitrile a solution of 22.4 g. (0.182 mole) of 2-thienylacetonitrile in 200 cc. of absolute ether was added dropwise to a solution of 7.6 g. (0.2 mole) of $LiAlH_4$ in 300 cc. of absolute ether contained in a 1-liter, 3-necked flask equipped with mechanical stirrer, dropping-funnel, and reflux condenser (12). The reaction mixture turned pink and then pale yellow. Water was added carefully to decompose excess hydride after reaction was complete. Then 500 cc. of 20% sodium potassium tartrate was added, the ether layer was removed in a separatory funnel and the water layer extracted with two 100-cc. portions of ether. The combined ether extracts were dried (Drierite), the ether removed, and the amine distilled under nitrogen. Yield, 7.86 g. (34%) of amine, b.p. 72–74°/3. A considerable amount of viscous, ether-soluble, dark red liquid remained in the flask and resisted further distillation. Since the free amine forms a carbonate rapidly when exposed to air (1), the hydrochloride was prepared for analysis by the addition of alcoholic HCl to an ether solution of the amine. Recrystallization of the *amine hydrochloride* from absolute alcohol gave white needles, m.p. 202–203.8°). Barger and Easson reported 200–202°.

Anal. Calc'd for $C_6H_{10}ClNS$: C, 44.03; H, 6.12; N, 8.56.
Found: C, 44.05; H, 6.14; N, 8.72.

The *phenylthiourea* prepared according to the usual method (13) gave m.p. 109.5–110°.

Anal. Calc'd for $C_{13}H_{14}N_2S_2$: C, 59.54; H, 5.34.
Found: C, 59.15; H, 5.07.

β-2-Thienylalanine. 3-(2-thienyl)-2-oximinopropionic acid (3.8 g., 0.021 mole) was dissolved in 77 cc. of absolute alcohol and 150 g. of 2% sodium amalgam was added in small portions with heating on the steam-bath. The solution was kept acidic with small additions of lactic acid. After all the amalgam had been added, the alcoholic solution was decanted and left in the ice-box overnight. Upon filtration 2.29 g. of the amino acid was obtained. The filtrate was evaporated to a brown syrup which was dissolved in a small amount of absolute alcohol and chilled. This gave an additional 0.1 g. of amino acid; total yield, 2.39. g (68%). Recrystallization from 68% alcohol (Norit) gave white crystals which showed a positive ninhydrin reaction; m.p. 273–275° (when the oil bath was preheated to 270°) [Lit. m.p. 274–275° (1); 243–245° (14)].

Anal. Calc'd for $C_7H_9NO_2S$: C, 49.12; H, 5.26; N, 8.18.
Found: C, 49.20; H, 5.14; N, 8.27.

The *ureide* was prepared by dissolving 1 g. of the amino acid in 10 cc. of 3% NaOH and shaking this solution with 0.9 g. of phenyl isocyanate. The diphenylurea was filtered off and the ureide precipitated with dilute HCl. White crystals were formed from dilute alcohol, m.p. 175–176° (when the oil bath was preheated to 165°). With no preheating the m.p. 164–164.5° was obtained. [Lit. m.p. 165–166° (capillary); 182° (Dennis melting-point bar) (15)].

Anal. Calc'd for $C_{14}H_{14}N_2O_3S$: C, 57.93; H, 4.82.
Found: C, 57.70; H, 4.82.

SUMMARY

1. The azlactones and rhodanines of 2-thenaldehyde, 3-methyl-2-thenaldehyde, 5-methyl-2-thenaldehyde, 5-ethyl-2-thenaldehyde, 5-propyl-2-thenaldehyde, 5-

chloro-2-thenaldehyde, and 5-bromo-2-thenaldehyde were prepared. All but the azlactone of 2-thenaldehyde are new compounds.

2. The ultra-violet absorption spectra of some of these azlactones were compared.

3. The application of rhodanine to syntheses in the thiophene series has been demonstrated by a series of reactions from 2-thenalrhodanine and by alkali cleavage of all seven rhodanines to their corresponding thiopyruvic acids which are not listed in the literature.

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[CONTRIBUTION NO. 187 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES IN THE THIOPHENE SERIES. VII.[1] THE APPLICATION OF THE REFORMATSKY REACTION TO THIOPHENE ALDEHYDES AND KETONES

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Although the use of the Reformatsky reaction has been widespread in the aliphatic and aromatic series, only few attempts have been recorded with heterocyclic aldehydes or ketones (1, 2, 3). Since recent work in this laboratory (4) led to the development of a direct, one-step procedure for the preparation of various substituted thenaldehydes, it was desired to test the applicability of the Reformatsky reaction with these compounds.

The Reformatsky reaction involves the interaction of a carbonyl compound, such as an aldehyde, a ketone, or an ester with an α-haloester in the presence of zinc. With aldehydes or ketones, a β-hydroxyester is produced, although simultaneous dehydration during the reaction may produce an unsaturated ester. These syntheses involve the formation of an organozinc halide as an intermediate (5), which then adds to the carbonyl compound to form an addition complex analogous to those involving the Grignard reagent and carbonyl compounds. The intermediate complex is decomposed with dilute acid to yield the final product:

$$XCH_2COOR + Zn \rightarrow XZnCH_2COOR \xrightarrow{R'CHO}$$

$$R'CHCH_2COOR \xrightarrow[H^+]{H_2O} R'CHCH_2COOR$$
$$\quad\;\; | \qquad\qquad\qquad\quad |$$
$$\quad OZnX \qquad\qquad\quad OH$$

The Reformatsky reaction not only offers a convenient method for producing β-hydroxy esters and the corresponding unsaturated esters and acids, but also constitutes a method for lengthening the carbon chain. By the proper choice of reactants it is possible to branch the chain on the α-, β-, or α- and β-carbon atoms. It is one of the most suitable synthetic methods for obtaining an unsaturated acid with branching on the β-carbon atom. It also offers a direct method for branching the chain on both the α- and β-carbon atoms.

First, the reaction of the carbonyl compounds with ethyl α-chloroacetate was attempted. 2-Acetothienone reacted with this ester slowly and gave only low yields of the desired product. This was not unexpected since the reactivity of the α-haloacetates is of the order $ICH_2COOC_2H_5 > BrCH_2COOC_2H_5 > ClCH_2COOC_2H_5$. The side reaction, the coupling of the haloester by the zinc, to form diethyl succinate did not occur even when the reaction time was increased. The modification described by Nieuwland and Daly (6), in which copper powder is added to the reaction mixture containing the chloroester was also applied, but without avail. This observation corroborates the findings of Kon and Nargund

[1] For paper No. VI of this series see *J. Org. Chem.*, preceding paper.

TABLE I

THIOPHENE ESTERS PREPARED BY THE REFORMATSKY REACTION

CARBONYL COMPOUND	BROMOESTER	PRODUCT	ESTERS							ACRYLIC ACIDS				
			B.P., °C./MM.	$n_D^{30°}$	YIELD,[b] %	ANALYSIS				M.P., °C.[c]	ANALYSIS			
						Calc'd		Found			Calc'd		Found	
						C	H	C	H		C	H	C	H
2-Acetothienone	Ethyl bromoacetate	Ethyl β-methyl-β-(2-thienyl)acrylate	116–119/4	1.5575	61–63	61.21	6.16	60.75	6.27	112.5–113	57.12	4.79	57.14	4.74
” ”	Ethyl α-bromopropionate	Ethyl α,β-dimethyl-β-hydroxy-β-(2-thienyl)propionate	113–117/3	1.5168	58–60	57.86	7.06	57.85	6.97	not isolated				
” ”	Ethyl α-bromoisovalerate	Ethyl α-isopropyl-β-methyl-β-(2-thienyl)acrylate	156–160/1.5	1.5079	16–20	65.56	7.61	65.56	7.84	not isolated				
” ”	Ethyl bromomalonate	Ethyl α-carbethoxy-β-methyl-β-(2-thienyl)acrylate	155–155/1.5	solid at 30°	10–12	58.19	6.01	58.45	5.73	112.5–113	57.12	4.79	57.07	4.74
2-Thenaldehyde	Ethyl bromoacetate	Ethyl β-(2-thienyl) acrylate	118–120/3[a]	1.5573	50–55	59.30	5.53	59.55	5.65	142.5–143[e,f]	54.55	3.89	54.53	3.92
” ”	Ethyl α-bromopropionate	Ethyl α-methyl-β-hydroxy-β-(2-thienyl) propionate	119–122/4	1.5151	50–55	56.05	6.58	56.18	6.68	139.5–140	57.12	4.79	56.84	4.69
” ”	Ethyl α-bromo-*n*-butyrate	Ethyl α-ethyl-β-hydroxy-β-(2-thienyl) propionate	133–136/3	1.5071	58–60	57.86	7.06	57.78	6.87	not isolated				
3-Methyl-2-thenaldehyde	Ethyl bromoacetate	Ethyl β-(3-methyl-2-thienyl)acrylate	122–126/4[b]	solid[g] at 30°	40–45	61.21	6.16	60.86	6.35	171.5–172[d,f]	57.12	4.79	57.00	4.69
3-Methyl-2-thenaldehyde	Ethyl α-bromopropionate	Ethyl α-methyl-β-hydroxy-β-(3-methyl-2-thienyl)propionate	136–139/4	1.5170	47–50	57.86	7.06	58.14	7.15	152 –153	59.31	5.53	59.40	5.54
3-Methyl-2-thenaldehyde	Ethyl α-bromoisovalerate	Ethyl α-isopropyl-β-(3-methyl-2-thienyl) acrylate	118–120/1.5	1.5338	54–56	65.51	7.65	64.75	7.64	not isolated				
5-Chloro-2-thenaldehyde	Ethyl bromoacetate	Ethyl β-hydroxy-β-(5-chloro-2-thienyl) propionate	119–122/3	1.5561	60–65	46.06	4.73	46.25	4.94	198.5–199.5[e,f]	44.57	2.67	44.55	2.80

5-Chloro-2-thenaldehyde	Ethyl α-bromopropionate	Ethyl α-methyl-β-hydroxy-β-(5-chloro-2-thienyl)propionate	144–147/4	1.5595	60–65	48.29	5.26	48.05	5.11	197	–197.5	47.42	3.48	47.55	3.56
5-Bromo-2-thenaldehyde	Ethyl bromoacetate	Ethyl β-(5-bromo-2-thienyl)acrylate	141–144/3	1.5988	53–55	41.38	3.47	41.60	3.63	209	–210	36.07	2.16	35.75	2.15
5-Bromo-2-thenaldehyde	Ethyl α-bromopropionate	Ethyl α-methyl-β-hydroxy-β-(5-chloro-2-thienyl)propionate	143–145/3	1.5396	54–56	43.65	4.03	43.55	4.38	204	–205	38.88	2.85	38.75	2.75
3-Acetothianaphthone	Ethyl bromoacetate	Ethyl β-methyl-β-(3-thianaphthyl)acrylate	137–140/1	1.6002	40–43	68.26	5.73	68.25	5.67	149	–150	66.03	4.62	65.95	4.58

[a] Ref. (19) gives 110–116°/3.5.
[b] Ref. (19) gives 121–126°/3.
[c] Ref. (20) gives 138°; Ref. (19, 21) each give 143–144°.
[d] Ref. (19) gives 172–173°.
[e] Ref. (19) gives 201–203°.
[f] These acrylic acids were confirmed by a mixed melting point with acids prepared according to Ref. (19).
[g] M.p. 37.5–38°.
[h] Yields based on the amount of the aldehyde or ketone used.
[i] All melting points taken on a Fisher-Johns apparatus.

(7), who were unable to duplicate the results of Nieuwland and Daly, and who failed to observe a condensation between acetophenone and chloroacetic ester.

However, by utilizing various α-bromoesters, the reaction was successfully carried out with four thenaldehydes, 2-acetothienone, and 3-acetothianaphthone. The yields of the Reformatsky ester obtained in these cases ranged from 45–63%. In two instances, where the bromoester consisted of a highly branched chain, namely ethyl α-bromoisovalerate and ethyl bromomalonate, the yields amounted to 10–20%. The collected data on the Reformatsky esters prepared are recorded in Table I.

The optimum temperature for the reaction was found to be 90–95°, which can best be maintained through the use of a solvent consisting of a mixture of equal amounts of anhydrous benzene and toluene (8). Raising the temperature to 105–110° did not improve the yields.

Ethyl β-bromopropionate did not yield a Reformatsky ester (9) when reacted with 2-acetothienone even after prolonged heating (10 hours) at a higher temperature (110–115°). The addition of copper powder was also without effect.

The nature of the product seems to depend on the degree of branching of the α-bromoester. In only one case where ethyl bromoacetate was used, was a hydroxy ester obtained. However, when the carbon atom adjacent to the carbethoxy group was substituted, the product usually contained a β-hydroxyl group. That the compounds obtained with ethyl α-bromoisovalerate and ethyl bromomalonate do not appear to follow this generalization can be easily accounted for by the high temperatures required for distillation, which cause a mole of water to split out.

The fact that β-hydroxy esters and their derivatives tend to lose water during distillation or saponification often makes it difficult to isolate the pure compounds. As a matter of fact, every saponification of a β-hydroxy ester resulted in the formation of the unsaturated acid. This proved useful in the isolation of a product from the reaction of 3-acetothianaphthone with ethyl α-bromopropionate. The expected ester, ethyl α,β-dimethyl-β-hydroxy-β-(3-thianaphthyl)propionate, did not give a correct analysis after repeated distillations. The product was therefore saponified and the crystalline unsaturated acid, α,β-dimethyl-β-(3-thianaphthyl)acrylic acid, so obtained analyzed correctly.

In the following, the effect of a dehydrating agent which could be applied to the hydroxy esters without attacking the sensitive thiophene nucleus was investigated. Reagents of a strongly acidic nature, especially on heating, caused the formation of tarry by-products when attempts were made to dehydrate various hydroxy esters with thionyl chloride and pyridine (7, 10, 11) or phosphorus oxychloride (7, 12, 13). The use of aqueous oxalic acid (14, 15, 16) however, resulted in a nearly quantitative conversion to the unsaturated ester. These data are recorded in Table II.

3-Acetothianaphthone did not react with the α-bromoesters under the conditions previously employed. The reaction was effected, however, by employing the method of Newman (17), with modifications; the compound was hydrolyzed and distilled in the usual manner.

TABLE II

DEHYDRATIONS WITH OXALIC ACID

ESTER	REACTION	REAGENT	PRODUCT	B.P. OR M.P., °C.	$n_D^{30°}$	ANALYSIS			
						Calc'd		Found	
						C	H	C	H
Ethyl α,β-dimethyl-β-hydroxy-β-(2-thienyl)propionate	Dehydration	6% aqueous Oxalic Acid	Ethyl α,β-dimethyl-β-(2-thienyl)acrylate	104–105/2	1.5246	62.83	6.71	62.70	6.85
Ethyl α-methyl-β-hydroxy-β-(2-thienyl)propionate	"	6% aqueous Oxalic Acid	Ethyl α-methyl-β-(2-thienyl)acrylate	111–113/2	1.5779	61.23	6.16	60.96	6.03
Ethyl α-methyl-β-hydroxy-β-(3-methyl-2-thienyl)-propionate	"	6% aqueous Oxalic Acid	Ethyl α-methyl-β-(3-methyl-2-thienyl)acrylate	108–110/1	1.5738	62.82	6.71	63.09	6.96
Ethyl β-methyl-β-(2-thienyl)acrylate	Reduction	Sodium Amalgam	Ethyl β-methyl-β-(2-thienyl)propionate	106–107/3	1.4993	60.60	7.12	60.49	6.88
* Ethyl α,β-dimethyl-β-hydroxy-β-(3-thianaphthyl)propionate	Saponification	6% aq. Potassium Hydroxide	α,β-Dimethyl-β-(3-thianaphthyl)acrylic acid	52–53[a]	—	67.24	5.21	67.05	5.20

* This was the expected product; it did not analyze correctly after repeated distillations, however.

[a] The low melting point may be an indication that this is the *cis* isomer.

EXPERIMENTAL[2]

Materials. 2-Acetothienone and 3-acetothianaphthone were obtained through the courtesy of Dr. N. B. Sommer of the Jefferson Chemical Company.

Reformatsky reactions. The general procedure for all thenaldehydes and 2-acetothienone was as follows: In a clean, dry 250-cc. three-necked flask fitted with a mechanical stirrer, a 250-cc. separatory funnel, and a reflux condenser protected from moisture was placed 20 gm. (0.31 mole) of 20-mesh zinc granules. A solution of approximately 0.25 mole of the ethyl α-bromoester and 0.31 mole of the aldehyde or ketone in 40 cc. of dry benzene and 40 cc. of dry toluene was placed in the separatory funnel. A few cc. of this solution was added to the zinc and a crystal of iodine was introduced. The flask was warmed until a vigorous reaction set in. The mixture was stirred and the rest of the solution introduced at such a rate that gentle refluxing occurred. This required one-half to three-quarters of an hour. As the mixture was refluxed, the iodine color faded and the solution became cloudy. Refluxing and stirring were continued for one hour after addition was complete. Not all the zinc was used up. The flask was then cooled, and the contents poured into 200 cc. of ice-cold 10% hydrochloric acid with vigorous stirring. The acid layer was drawn off and the benzene layer was washed twice with 100-cc. portions of water, then neutralized with 20% aqueous sodium carbonate solution, and again washed with 25-cc. portions of water. The acid extracts were washed with ether and the combined benzene and ether extracts were dried over Drierite. After filtration, the solvent was removed on a steam-bath and the residue fractionated *in vacuo*.

The following modification was applied to 3-acetothianaphthone reactions. The ketone (20 g.), zinc (20 g.), and 30 g. of the α-bromoester were added to 100-cc. of dry benzene in a flask. A crystal of iodine was introduced and the mixture was heated to boiling. The reaction commenced and the heat of reaction was sufficient to reflux the solvent for a short time. When the reaction moderated, the mixture was stirred and refluxed over a free flame for ten hours. The product was hydrolyzed and distilled in the usual manner.

Dehydration of the hydroxyesters. The ester (10 cc.) was refluxed with 100 cc. of 6% aqueous oxalic acid for 3–6 hours. The aqueous layer was drawn off and the acrylic ester was washed thoroughly with two 25-cc. portions of water, dried (Drierite) and distilled.

Reduction of double bonds (18). The ester (10 cc.) was dissolved in 100 cc. of ethyl alcohol and freshly prepared sodium amalgam (5%) was added with continual shaking. To complete the reaction, the mixture was warmed on a steam-bath until all the mercury had collected in liquid form. When the solution had cooled the metal was separated, the solvent removed, and the ester distilled.

Saponification of the esters was accomplished by refluxing 10 cc. of the ester with 120 cc. of 20% aqueous potassium hydroxide for 2–3 hours, or until the ester layer had disappeared. The solution was cooled and then acidified with ice-cold dilute hydrochloric acid. The acid was recrystallized from ethyl alcohol.

SUMMARY

1. The Reformatsky reaction was shown to be applicable to four thenaldehydes, 2-acetothienone, and 3-acetothianaphthone.

2. Seven β-hydroxy esters, eight acrylic esters, α,β-dimethyl-β-(3-thianaphthyl)acrylic acid, and ethyl β-methyl-β-(2-thienyl)propionate heretofore not listed in the literature, were prepared. The acids of both types of esters were unsaturated.

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[2] The analyses recorded in this paper were carried out by Dr. F. Bühler of this Department. This investigation was carried out under the auspices of the Office of Naval Research.

3. Aqueous oxalic acid was found to be an excellent dehydrating agent for thiophenehydracrylic acids.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, THE BINGHAM OCEANOGRAPHIC LABORATORY, AND THE BERMUDA BIOLOGICAL STATION FOR RESEARCH]

CONTRIBUTIONS TO THE STUDY OF MARINE PRODUCTS. XXVI.[1] STEROLS FROM SPONGES OF THE FAMILY SUBERITIDAE[2]

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During the past decade the sterols of numerous animals, belonging to many phyla, have been investigated in this laboratory. These studies have revealed the interesting fact that the greatest diversity of sterols is to be found among the most primitive animals such as sponges and coelenterates. As has been pointed out in another communication of this series[1], it now appears that the process of evolution in animals has been accompanied by a discontinuation of the use of a variety of sterols in favor of the practically exclusive use of cholesterol.

TABLE I

ORDERS AND FAMILIES OF SPONGES[4]

Order: HALICHONDRINA (Vosmaer)
Family: Hymeniacidonidae (de Laubenfels)
Order: HADROMERINA (Topsent)
Family: Choanitidae (de Laubenfels)
Family: Suberitidae (Schmidt)
Family: Clionidae (Gray)

Best known among the sterols of lower invertebrates are those of the sponges of which more than fifty species have been studied in this laboratory. At present eight sponge sterols have been well characterized, and the occurrence in sponges of several other sterols has been indicated. Numerous as they are, the available data do not yet suffice to establish well defined relationships between the sterol content of sponges and the taxonomy of Porifera in general. Within certain families, however, such relationships have already been observed, particularly in regard to the families listed in Table I.

It has been shown in a previous communication (2) that the sterols of *Sphe-ciospongia vesparia*, of the family Choanitidae, are a mixture of the *levorotatory* poriferasterol and clionasterol. A similar mixture has been isolated from *Cliona*

[1] Communication XXV of this series will appear in the Journal of Marine Research, Sears Foundation.

[2] The authors are greatly indebted to Dr. M. W. de Laubenfels, University of Hawaii, for the identification of the majority of the sponges.

[3] The authors express their gratitude to the Emergency Science Research Fund of the Sheffield Scientific School, Yale University, for a grant which has made possible the collection of the sponges.

[4] This classification is based on that proposed by de Laubenfels (1).

celata, a species belonging to the Clionidae. In contrast, two species of Suberitidae, *Suberites compacta* and *S. domuncula*, have afforded mixtures of the *dextrorotatory* cholestanol and neospongosterol (3). These preliminary observations at once pointed to a significant and readily detectable biochemical difference between the families of Choanitidae and Clionidae and the family of Suberitidae. Since then several other species belonging to the respective families have been investigated, and the nature of their sterols has been found in accord with the earlier observations. The lipoid contents of these sponges are listed in Table II.

TABLE II

COMPOSITION OF DRIED SPONGES

SPECIES	% OF TOTAL		% OF ORGANIC	% OF FAT	% OF UNSAP.
	Spicules	Organic	Fat	Unsapon.	Sterol
Spheciospongia	22	78	4.5	46	50
Anthosigmella	59	41	6	48	58
Cliona	16	84	9	27	58
Terpios fugax	11	89	13.5	23	82
Terpios zeteki	46	54	8.5	41	64
Aaptos	17	83	5	33	69
Radiella	73	27	11	37	55
Weberella	30	70	11	64	55
Polymastia	51	49	11	35	66

FAMILY: CHOANITIDAE

Spheciospongia sp.[5] This sponge is one of the most common, and because of its large size, one of the most conspicuous sponges of the Bermuda Archipelago. Its crude sterol is strongly levorotatory. Bromination of the steryl acetate afforded a high-melting tetrabromide which upon debromination gave poriferasteryl acetate, m.p. 145–146°; $[\alpha]_D - 51°$. Debromination of the more soluble dibromide led to the isolation of clionasteryl acetate, m.p. 136°; $[\alpha]_D - 45°$. It is estimated that the original sterol mixture contained about forty % of poriferasterol and more than fifty % of clionasterol.

Anthosigmella varians (Topsent). This sponge is exceedingly common in the waters near Virginia Key, Florida, where it was collected in 1945.[6] Perbenzoic acid titration of the crude, levorotatory, sterol mixture indicated the presence of about thirty % of a diunsaturated sterol. By separation over the acetate bromides, the former was identified as poriferasterol, m.p. 156°; $[\alpha]_D - 49°$, and the latter as clionasterol, m.p. 140°; $[\alpha]_D - 39°$.

[5] A description of this new species will be given by de Laubenfels in his forthcoming paper on the sponges of Bermuda.

[6] The authors express their gratitude to Dr. W. F. Smith, University of Miami, for his generous assistance in the collection of this sponge.

FAMILY: CLIONIDAE

Cliona carriboea Carter. The first lot of this sponge was obtained from the coast of Florida in 1943. The sponges were of a tubular shape with an average height of about twenty cm. and a diameter of about five cm. The mixture of sterols obtained from this sponge consisted of approximately forty % of poriferasterol, m.p. 156°; $[\alpha]_D$ −49.5°, and more than fifty % of clionasterol, m.p. 139°; $[\alpha]_D$ −40°.

A second lot of this sponge had been collected in the coastal waters of Bermuda. Unlike the tall species from Florida, the Bermuda variety was of a flat and irregular shape. Its sterol mixture also consisted of clionasterol and poriferasterol, but the latter represented less than ten % of the total.

FAMILY: SUBERITIDAE

Suberites suberea Montague. A few dried specimens of this sponge were obtained through the courtesy of the U. S. National Museum. They had been collected off the coast of Alaska prior to 1900. The sponge afforded a dextrorotatory sterol mixture. Bromination of the steryl acetate, m.p. 124°; $[\alpha]_D$ +14.5°, gave the characteristic "spongosteryl acetate bromide" of m.p. 150°, which has previously been shown to be an adduct of cholestanyl acetate and neospongosteryl acetate dibromide (3). It may therefore be assumed that the sterol mixture from this sponge is essentially of the same composition as that present in *Suberites compacta* and *S. domuncula.*

Terpios fugax (Duchassaing and Michelotti). Substantial quantities of this sponge were collected in 1946 and 1947 in Harington Sound and Walsingham Pond, Bermuda. Upon continuous extraction of the dried sponge with acetone, there separated from the boiling solvent considerable amounts of a white, powdery material, which will be discussed in a future publication. The properties of the crude sterol obtained from this sponge, $[\alpha]_D$ +14°, 0.2 double bonds, at first suggested the presence of "spongosterol", *i.e.* a mixture of cholestanol and neospongosterol (3). Repeated brominations of the steryl acetate, however, failed to yield the characteristic "spongosteryl acetate bromide". No difficulties were encountered in identifying cholestanol as the principal saturated component of the sterol mixture. The isolation of the unsaturated component in a reasonable state of purity has so far met with little success. An acetate fraction, enriched with unsaturated material, melted at 136.5°; $[\alpha]_D$ +8°. It appears at present that the unidentified, unsaturated sterol is slightly dextrorotatory, and that, like neospongosterol, it is unsaturated in the side chain only.

Terpios zeteki de Laubenfels. This sponge was received from the Hawaiian Islands through the courtesy of Dr. de Laubenfels. Upon extraction with acetone it yielded products identical with those described under *Terpios fugax.*

Aaptos sp.[5] A collection of this sponge was made in Harington Sound, Bermuda in 1947. Titration of the crude steryl acetate, m.p. 121–125°; $[\alpha]_D$ +13°, with perbenzoic acid showed the presence of about ten % of unsaturated material, which was at once removed according to the procedure of Anderson and Nabenhauer (4). The relatively high melting point, 122–124°, of the product thus ob-

tained indicated the presence of a saturated compound other than cholestanyl acetate. Repeated recrystallizations of the acetate mixture eventually gave a fraction melting constantly at 133.5°; $[\alpha]_D$ +14°. Hydrolysis of the acetate gave the stanol, m.p. 135°; $[\alpha]_D$ +22.2°. Analysis of the stanyl-*m*-dinitrobenzoate, m.p. 209–212°; $[\alpha]_D$ +15.6°, indicated an empirical formula of $C_{28}H_{50}O$ for the stanol. It is proposed to refer to this compound as aptostanol until its relation to known sterols has been established.

Concentration of the mother liquors from the recrystallization of the original acetate gave lower-melting fractions. These were combined, saponified, and the resulting stanol was benzoylated. Recrystallization of the benzoate eventually gave cholestanyl benzoate.

Radiella sol Schmidt. This sponge which is rather common in the deep waters of the Atlantic Ocean was collected by the research ship "Atlantis" during the summer of 1948. The high dextro-rotation of the crude sterol, $[\alpha]_D$ +20°, indicated that it consisted essentially of saturated material. The acetate, freed

TABLE III

COMPARISON OF APTOSTANOL AND HALICLONASTANOL

ORIGIN	STANOL M.P., °C. $[\alpha]^\circ_D$	ACETATE M.P., °C. $[\alpha]^\circ_D$	BENZOATE M.P., °C. $[\alpha]^\circ_D$	*m*-DINITROBENZOATE M.P., °C. $[\alpha]^\circ_D$
Aaptos	135.5 +22	133.5 +14		212 +16
Radiella	134.5 +22	134 +15	133.5 +19	— –
Weberella	135.5 +20	134.5 +12		208 +18
Haliclonasterol	137.5 +18	136.5 +11	133.5	218

from unsaturated material (4), melted at 131°; $[\alpha]_D$ +14.5°, and after a few recrystallizations at 133–134°; $[\alpha]_D$ +15°. It was converted to the stanol, m.p. 134.5°; $[\alpha]_D$ +22°, and the stanyl benzoate, m.p. 133.5°; $[\alpha]_D$ +19°. A comparison of the physical data of this stanol with those of aptostanol (Table III) suggests the identity of the two sterols.

The mother liquors from the original acetate did not yield any low-melting fractions indicative of the presence of cholestanyl acetate, and systematic recrystallization of the benzoate failed to give cholestanyl benzoate. It appears therefore that the sterol of *Radiella sol* consists essentially of aptostanol.

Weberella bursa (Müller). This sponge[7] was obtained from the Atlantic Ocean near Newfoundland. Recrystallization of the steryl acetate, freed from unsaturated material, eventually afforded a fraction, m.p. 134°; $[\alpha]_D$ +12°, which appeared to be identical with aptostanyl acetate (Table III). Saponification of the lower-melting acetate fraction, benzoylation of the resulting stanol, and recrystallization of the benzoate gave cholestanyl benzoate.

Polymastia infrapilosa Topsent. This sponge[7] was collected in the same localities as the one discussed above. The saturated fraction of the steryl ace-

[7] Identified by Mr. W. Hartman, Yale University.

tates melted at 111–117°; $[\alpha]_D$ +11°. Lack of material has so far prevented a satisfactory separation of the mixture. The isolation of a fraction of m.p. 125°; $[\alpha]_D$ +11.2°, indicated the presence of aptostanyl acetate. In addition the presence of cholestanol in the original mixture was clearly demonstrated.

DISCUSSION

The investigations described above prove convincingly the existence of relations between the sterol content of sponges and their conventional taxonomic features. Within the order of Hadromerina species belonging to the family of Suberitidae have all been found to contain saturated compounds as the principal constituents of their sterol mixtures. In contrast members of the families of Choanitidae and Clionidae have been shown to contain as their principal sterols the Δ^5-unsaturated clionasterol and poriferasterol. Since the saturated sterols are distinctly dextrorotatory, and since the Δ^5-unsaturated sterols are strongly levorotatory, the optical rotation of the sterol mixture from a sponge of the order Hadromerina may be used as an aid in its classification. The usefulness of sterol analysis in the identification and classification of sponges has already been demonstrated in several instances, one of which is of particular interest in the present connection.

The sponge *Anthosigmella varians*, which has been discussed above, had originally been identified as *Suberites distortus*. Serious doubts concerning the correctness of this identification were raised when it was found that the sterols from this sponge, unlike those from other Suberitidae, were strongly levorotatory. When a more detailed analysis revealed the presence in the mixture of clionasterol and poriferasterol the authors concluded that the sponge in question belonged to the families of Choanitidae or Clionidae rather than to the Suberitidae. The correctness of this conclusion was eventually established by de Laubenfels. In the course of a careful study of the freshly caught sponge, this investigator detected certain features, easily overlooked, which proved this sponge to be indeed a species of Choanitidae.

With the exception of *Radiella sol*, all sponges of the Suberitidae which have so far been investigated contain cholestanol as a substantial component of their sterol mixture. In sponges of the genus *Suberites* and possibly also of the genus *Terpios* this stanol is accompanied by feebly dextrorotatory, unsaturated sterols, devoid of cyclic unsaturation, such as neospongosterol (3). The sterol mixtures from other Suberitidae, such as *Aaptos*, *Weberella*, *Polymastia*, and *Radiella*, contain in addition to, or to the practical exclusion of, cholestanol a stanol of the order $C_{28}H_{50}O$, which has tentatively been named aptostanol. This compound is the second saturated sterol which has so far been found to occur in animals. At present it does not appear that aptostanol is identical with any one of the well-characterized stanols. As shown in Table III, its physical properties are reminiscent of those of the recently described haliclonastanol (5) and hence indicate the possible identity of the two stanols.

In a future revision of the families of the order of Hadromerina, cognizance should be taken of the fact that the sterols of Suberitidae are quite distinct

from those of Choanitidae and Clionidae. The saturated nature of the principal sterols of Suberitidae implies a sterol metabolism in these sponges which is different from that taking place in the sponges from the two other families in which unsaturated sterols predominate. This difference appears at least as significant as the more conventional taxonomic evidence. It suggests that in a regrouping of the species of Hadromerina those belonging to the Suberitidae should be set distinctly apart from those assigned to the other families.

Another sponge which is of interest in this connection is *Hymeniacidon heliophila*. This species had first been described as *Stylotella heliophila*, but had been referred by de Laubenfels (1) to *Hymeniacidon* because of its close resemblance to various European species of this genus. If this sponge were indeed a species of the genus *Stylotella* it would belong to the Suberitidae of the order Hadromerina (Table I), and one should expect it to contain a saturated sterol as the principal component of its sterol mixture. Otherwise it would belong to the family of Hymeniacodinidae of the order Halichondrina. It has been shown in a previous communication (6) that the principal sterol of this sponge is cholestanol. On the basis of this evidence it might therefore be argued that the sponge under consideration is indeed a species of Suberitidae and that it should be reassigned to this family. Such a transfer, however, will remain premature until more is known about the sterol content of other species of Hymeniacidon and also of the closely related Halichondria. It appears at present, however, that there exist closer biochemical relationships between *Hymeniacidon heliophila* and the Suberitidae, than between the latter and Choanitidae and Clionidae.

EXPERIMENTAL

All melting points are corrected. Unless stated otherwise, all optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3.06 cc. of chloroform. In all but one case the sterols were obtained by the following method. The air-dried sponges were ground and then thoroughly extracted with acetone in a Soxhlet apparatus. After evaporation of the solvent, the residue was dissolved in benzene, and the water removed by codistillation. In all instances, varying amounts of smeary, brown, water-soluble material remained undissolved in the benzene. The benzene extract was then evaporated to dryness, and the residue dried to constant weight at 80°. This acetone–benzene soluble fraction is referred to as fat in Table II. The data in this table are all based on weights of crude sponge material from which the non-spicular ash has been subtracted as described in a previous communication (7). The saponification of the fat and the isolation of the sterol was carried out as previously described. The sterol content of an aliquot part of the non-saponifiable fraction was determined by precipitation with digitonin.

Spheciospongia sp. The crude steryl acetate, m.p. 133°; $[\alpha]_D$ −45°, upon titration with perbenzoic acid showed unsaturation corresponding to 1.4 double bonds. The acetate mixture was separated into *poriferasteryl acetate*, m.p. 145–146°; $[\alpha]_D^{23°}$ −51°, and *clionasteryl acetate*, m.p. 136°; $[\alpha]_D^{23}$ −45° by way of the bromides as described previously in connection with the separation of the sterols from *Spheciospongia vesparia* (2).

Anthosigmella varians. The crude steryl acetate melted at 132–133°; $[\alpha]_D^{20°}$ −45.5. Titration with perbenzoic acid showed unsaturation corresponding to 1.3 double bonds. Bromination of the acetate mixture in the manner described previously gave the difficultly soluble poriferasteryl acetate tetrabromide, m.p. 190–192°. Its identity was demonstrated by its conversion to *poriferasteryl acetate*, m.p. 146°; $[\alpha]_D^{24°}$ −52.6° (20.4 mg., α −0.35°), to poriferasterol, m.p. 154°; $[\alpha]_D^{24°}$ −49.1° (24.3 mg., α −0.39°) and poriferasteryl-*m*-dinitrobenzoate,

m.p. 227°; $[\alpha]_D^{25°}$ −22.2° (31.7 mg., α −0.23°). None of these compounds showed a depression of the melting point when mixed with authentic material.

Debromination of the soluble bromides afforded an acetate which after frequent recrystallization gave *clionasteryl acetate*, m.p. 139.5–140°; $[\alpha]_D^{26°}$ −42°. It was converted to clionasterol, m.p. 139.5–140°; $[\alpha]_D^{26°}$ −39.3° (26.5 mg., α −0.34°), and clionasteryl benzoate, m.p. 135–136°, $[\alpha]_D^{28°}$ −18.4° (28.3 mg., α −0.17°).

Cliona carriboea. A total of 17.8 g. of sterol was obtained from the Bermuda species. The sterol mixture was separated in the usual manner by way of the acetate bromides. The difficultly soluble bromide was identified as poriferasteryl acetate tetrabromide, m.p. 187° by its conversion to *poriferasteryl acetate*, m.p. 146–147°; $[\alpha]_D^{26°}$ −54.5° (30.2 mg., α −0.54°), poriferasterol, m.p. 153–154°; $[\alpha]_D^{26°}$ −50.5° (30.3 mg., α −0.50°), and poriferasteryl propionate, m.p. 125–126°; $[\alpha]_D^{26°}$ −51.5° (29.8 mg., α −0.50°).

Debromination of the soluble bromides gave *clionasteryl acetate*, m.p. 137.5°; $[\alpha]_D^{26°}$ −42.5° (30.8 mg., α −0.44°), which was converted to clionasterol, m.p. 137.5°; $[\alpha]_D^{26°}$ −38° (30.6 mg., α −0.38°), clionasteryl propionate, m.p. 118–119°; $[\alpha]_D^{25°}$ −42.4° (29.5 mg., α −0.41°), and clionasteryl benzoate, m.p. 139–140°; $[\alpha]_D^{26°}$ −38° (30.6 mg., α −0.38°).

The acetate obtained from 25 g. of sterol isolated from the Florida species showed unsaturation equivalent to 1.35 double bonds when titrated according to Rosenmund's (8) method. Upon separation of the acetates by way of the bromides results analogous to those described above were obtained with the exception that the yield of poriferasteryl acetate was substantially higher.

Suberites suberea. A total of 63.5 g. of the dried sponge was ground and exhaustively extracted first with ether and then with acetone. The residue from the combined extracts, (0.6 g.), was dissolved in 50 cc. of hot 80% ethanol, and the solution mixed with 80 cc. of a hot 1% solution of digitonin in 80% ethanol. The mixture was then refluxed until the digitonide began to separate. After twenty-four hours it was collected and washed with ethanol and ether; 560 mg., equivalent to 140 mg. of sterol.

The digitonide was refluxed with 15 cc. of acetic anhydride for two hours. The solution was then diluted with water, and the precipitated acetate filtered, washed with water and methanol, and recrystallized twice from methanol; m.p. 122–124°, $[\alpha]_D^{27°}$ +14.4° (20.1 mg., α +0.095°). To a solution of 0.1 g. of acetate in 0.5 cc. of anhydrous ether was added 1.1 cc. of a 5% solution of bromine in acetic acid. After standing in the refrigerator overnight, the mixture was filtered, and the solid washed with acetic acid and methanol, and dried; m.p. 140–145°. After recrystallization from ethyl acetate–methanol, the bromide melted at 155°. It gave no depression of melting point when mixed with an authentic sample of *"spongosteryl acetate monobromide"* (3).

Anal. Calc'd for $C_{29}H_{50}O_2 + C_{30}H_{50}Br_2O_2$: Br, 15.5. Found: Br, 14.8.

Terpios fugax. During the acetone extraction of the dried, ground sponge a white, powdery material separated from the boiling solvent. After twenty-four hours of extraction, the suspension was cooled and filtered. The insoluble material represented approximately 1.5% of the dry sponge. The solvent was then evaporated and the sterol, m.p. 131°; $[\alpha]_D$ +14°, isolated as described previously. Titration of the crude steryl acetate, m.p. 120–122°, with perbenzoic acid showed unsaturation corresponding to 0.2 double bonds. Bromination of the acetate under a variety of conditions failed to yield a difficultly soluble bromide.

Numerous recrystallizations of the crude steryl benzoate from dioxane, absolute ethanol, and chloroform–methanol gave *cholestanyl benzoate*, m.p. 135.2° (turbid liquid), 155° (clear); $[\alpha]_D^{24°}$ +23.6°. The benzoate was converted to cholestanol, m.p. 142–142.5°; $[\alpha]_D^{24°}$ +13.5° (38.6 mg., 1.32 cc., α +0.395). None of these compounds gave melting point depressions when mixed with authentic material.

Terpios zeteki. Extraction of this sponge with acetone gave results analogous to those described above. Repeated recrystallization of the crude steryl benzoate, m.p. 130–135°, 0.25 double bonds, from dioxane, chloroform–methanol, acetone, and ether afforded *cholestanyl benzoate*, m.p. 135° (turbid liquid), 155° (clear); $[\alpha]_D^{23°}$ +22.1.° (31 mg., α +0.22°). It was converted to cholestanol, m.p. 142–142.5°; $[\alpha]_D^{23°}$ +23.1° (26.5 mg., α +0.20°) and to cholestanyl acetate, m.p. 111–112°; $[\alpha]_D^{23°}$ +12.9° (29.0 mg., α +0.12°).

Aaptos sp. The crude sterol, 3.1 g., melted at 118–125°; $[\alpha]_D$ +19°. Upon acetylation a dark-red solution was obtained, and the precipitated acetate was also colored. The acetate was then dissolved in chloroform and the solution treated with Norit. After filtration and concentration, methanol was added to the solution. A reddish oil precipitated. It was immediately separated from the supernatant liquid, which upon concentration gave 1.75 g. of acetate, m.p. 121–125°; $[\alpha]_D$ +13°; 0.15 double bonds.

Aptostanyl acetate. To a solution of 1.7 g. of the above acetate in 35 cc. of carbon tetrachloride and 18 cc. of acetic anhydride was added dropwise and with constant stirring and cooling, about 1 cc. of conc'd sulfuric acid. After twenty minutes, water and more carbon tetrachloride were gradually added until a clear separation of layers had taken place. The carbon tetrachloride layer was then washed once with a sodium chloride solution and twice with a solution of sodium bicarbonate, dried, and evaporated to dryness. The residue was recrystallized once from acetic anhydride; 1.25 g., m.p. 122–124°. After six recrystallizations from ethanol, ether, and ether–methanol, the *acetate*, 250 mg., melted constantly at 132.5–133.5°; $[\alpha]_D^{28°}$ +14.0° (30.6 mg., α +0.14°).

Anal. Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.
Found: C, 80.94; H, 11.86.

Aptostanol. Saponification of the above acetate gave the *stanol* which was recrystallized from ether–methanol; m.p. 134.5–135.5°; $[\alpha]_D^{27°}$ +22.2° (28.9 mg., α +0.21°).

Aptostanyl-m-dinitrobenzoate. A mixture of 65 mg. of the above stanol and 85 mg. of freshly prepared *m*-dinitrobenzoyl chloride was dissolved in a small volume of anhydrous benzene and two drops of pyridine. The mixture was refluxed for 90 minutes and then evaporated to dryness under reduced pressure. Recrystallization of the residue from chloroform–methanol, absolute ethanol, and ether–ethanol gave 60 mg. of the *m-dinitrobenzoate*, m.p. 210–212°; $[\alpha]_D^{28°}$ +15.6° (27.5 mg., α +0.14°).

Anal. Calc'd for $C_{35}H_{52}N_2O_6$: C, 70.44; H, 8.78.
Found: C, 70.36; H, 8.69.

Cholestanol. Concentration of the first mother liquors from the series of recrystallizations which led to aptostanyl acetate gave 470 mg. of an acetate of m.p. 116–118°. It was saponified, and the free sterol at once benzoylated. Five recrystallizations of the benzoate from chloroform–methanol, benzene–ethanol, ether–methanol, and ether led to 85 mg. of cholestanyl benzoate, m.p. 135° (turbid liquid), 154° clear; $[\alpha]_D^{22°}$ +22.0° (26.9 mg., α +0.19°). Saponification of the benzoate and acetylation of the resulting stanol gave cholestanyl acetate, m.p. 111.5–113°; $[\alpha]_D^{21°}$ +14.4° (29.7 mg., α +0.14°).

Radiella sol. The total amount of sterol obtained from less than 200 g. of the dry sponge was 0.65 g; m.p. 120–124°, $[\alpha]_D$ +20°. The sterol was benzoylated and the benzoate recrystallized several times from chloroform–methanol; m.p. 128–131°; $[\alpha]_D$ +14°. The benzoate gave a very faintly positive Liebermann-Burchard reaction.

The total benzoate was then saponified and the sterol, 0.5 g., converted to the acetate, m.p. 125–128°. It was then treated with carbon tetrachloride, acetic anhydride, and sulfuric acid as described above to eliminate unsaturated impurities. After three recrystallizations from ethanol and ethyl acetate, the purified *acetate* melted at 133–134°; $[\alpha]_D^{23°}$ +15.0° (28.6 mg., α + 0.14°). It gave no depression of the melting point when mixed with *aptostanyl acetate* described above.

Anal. Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.
Found: C, 80.89; H, 11.95.

Saponification of the actate gave the *stanol*, m.p. 133.5–134.5°; $[\alpha]_D^{25°}$ +22.0° (24.0 mg., 3.09 cc., α +0.17°).

Benzoylation of the stanol with benzoyl chloride gave a *benzoate* of m.p. 132–133.5°; $[\alpha]_D^{25°}$ +19.0° (24.2 mg., α +0.15°).

Anal. Calc'd for $C_{35}H_{54}O_2$: C, 82.95; H, 10.73.
Found: C, 82.82; H, 10.92.

Fractionation of the residues obtained from the mother liquors of the recrystallizations of the acetate and benzoate failed to yield derivatives of cholestanol.

Weberella bursa. The acetate obtained from the crude sterol, 4.9 g., was freed from unsaturated material by the method described above, and the resulting product was recrystallized from ethanol, ether–methanol, and chloroform–methanol until the m.p. remained constant at 133–134.5°; $[\alpha]_D^{28°}$ +12.0° (24.5 mg., α +0.10°). The *acetate* did not give a depression of the melting point when mixed with *aptostanyl acetate*.

Anal. Calc'd for $C_{30}H_{52}O_2$: C, 81.02; H, 11.79.
Found: C, 80.85; H, 12.0.

The *stanol* obtained from the purified acetate melted at 134.5–135.5°; $[\alpha]_D^{24°}$ +19.6° (25.0 mg., α +0.16°).

The *m-dinitrobenzoate* of the stanol was prepared as described above; m.p. 208°; $[\alpha]_D^{25°}$ +18.0° (22.2 mg., α +0.13°).

Anal. Calc'd for $C_{35}H_{52}N_2O_6$: C, 70.44; H, 8.78.
Found: C, 70.32; H, 8.84.

Residues from the first mother liquors of the recrystallization of the acetate were saponified and the resulting stanol was benzoylated. Systematic recrystallization of the bezonate eventually yielded *cholestanyl benzoate*, m.p. 134° (turbid liquid), 154° (clear); $[\alpha]_D^{24°}$ +22.2° (27.6 mg., α +0.20°).

It was converted to cholestanol, m.p. 141–142°, and cholestanyl acetate, m.p. 113.5–115°; $[\alpha]_D^{24°}$ +14.5° (21.3 mg., 3.09 cc., α +0.10°).

Polymastia infrapilosa. A total of 85 g. of dry sponge gave 0.8 g. of a very crude sterol, m.p. 110–112°; $[\alpha]_D$ +6°. The acetate, m.p. 108–116°; $[\alpha]_D$ −1°, was freed from unsaturated material by the method described above. After several recrystallizations, an *acetate* of m.p. 125°, $[\alpha]_D^{21°}$ +11.2° was obtained. Lack of material prevented further purification of this product.

The residues from the acetate mother liquors were saponified and the resulting stanol was benzoylated. Repeated recrystallizations of the benzoate eventually yielded *cholestanyl benzoate*, m.p. 135° (turbid liquid), 149° (clear).

SUMMARY

1. The sterols of ten species of sponges of the order Hadromerina have been isolated and investigated.

2. It has been shown that the principal sterols from species of the families Choanitidae and Clionidae are levorotatory, and that those from species of the family Suberitidae are dextrorotatory.

3. Poriferasterol and clionasterol have been found to be the principal sterols of the sponges *Spheciospongia sp.* and *Anthosigmella varians* of the family Choanitidae, and of *Cliona carriboea* of the family Clionidae.

4. Cholestanol has been shown to occur in the following species of the family Suberitidae: *Terpios fugax*, *T. zeteki*, *Aaptos sp.*, *Weberella bursa*, and *Polymastia infrapilosa*.

5. A new saturated sterol, $C_{28}H_{50}O$, tentatively named aptostanol, has been isolated from *Aaptos sp.* The occurrence of this stanol in *Radiella sol*, *Weberella bursa*, and *Polymastia infrapilosa* has been indicated.

6. Attention has been called to the possible identity of haliclonastanol and aptostanol.

7. The significance of these observations in relation to the classification of sponges has been discussed.

NEW HAVEN, CONNECTICUT

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[CONTRIBUTION FROM THE RESEARCH LABORATORY, GENERAL ELECTRIC CO.]

II. THE REACTION OF CHLOROSILANES WITH 2-METHOXYETHANOL

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The reaction of organochlorosilanes with 2-methoxyethanol has been shown to give good yields of 2-methoxyethoxyorganosilanes. The formation of silyl ethers by reaction of an organochlorosilane with alcohols has been described (2); however, the ethers which have been reported in previous publications have been insoluble in water, or at most have shown only slight solubility. In contrast, the introduction of the 2-methoxyethoxy radical very greatly increases the water solubility of the resulting silyl ether as compared to the corresponding *n*-butoxy ether, or even the ethoxy ether. The extent to which increased solubility is effected is dependent upon the size and number of hydrocarbon radicals that are directly attached to the silicon atom. The silyl ethers that contain the 2-methoxyethoxy radical are of interest in those cases where a homogeneous aqueous system of silanes is desired.

TABLE I

2-ALKOXYETHOXY ETHERS OF ORGANOSILANES

COMPOUND	B.P., °C. (MM)	n_D^{20}	d_4^{20}	MR_D[a]		ANALYSIS				SOLUBILITY IN WATER
						Calc'd		Found		
				Calc'd	Found	C	H	C	H	
Methyl*tris*-2-methoxyethoxysilane	145 (16)	1.4200	1.0454	65.1	65.0	44.75	9.02	43.8 43.4	8.9 8.9	∞
Dimethyl*bis*-2-methoxyethoxysilane	203–204	1.4114	0.9663	53.5	53.6	46.13	9.68	45.8 46.3	9.5 9.6	∞
Trimethyl-2-methoxyethoxysilane	128	1.3952	.8492	41.9	41.9	48.61	10.88	49.0	11.0	*ca.* 5%
Azeotrope[b]	118	1.3988	.8936							
Methylbenzyl*bis*-2-methoxyethoxysilane	181–185 (15)	1.4795	1.0141	77.5	79.6	59.12	8.51	59.1	8.7	*ca.* 5%
Methyl-2-pentyl*bis*-2-methoxyethoxysilane	146–152 (15)	1.4298	0.9454	71.1	72.2	54.50	10.67	53.4	10.0	*ca.* 5%
Phenyl*tris*-2-methoxyethoxysilane	204 (15)	1.4727	1.0818	84.1	85.6	54.52	7.93	54.0	8.1	*ca.* 25%
Dimethyl*bis*-2-ethoxyethoxysilane	136 (30)	1.4131	0.9368	62.0	62.9	50.81	10.24	51.7	10.6	*ca.* 50%

[a] Sauer, *J. Am. Chem. Soc.*, **69**, 701 (1947).

[b] This is an azeotrope of trimethyl-2-methoxyethoxysilane and 2-methoxyethanol (approx. 50–50).

The preparation of *tetrakis*-2-methoxyethoxysilane and *tris*-2-methoxyethoxychlorosilane from 2-methoxyethanol and silicon tetrachloride was described in a previous publication (1). Both of these compounds are miscible with water in all proportions.

These new silyl ethers appear to possess reasonable hydrolytic stability. Aqueous solutions of dimethyl*bis*-2-methoxyethoxysilane remain clear for approximately fifteen to thirty minutes before clouding is observed. The extent of clouding increases slowly as the solution is allowed to stand. After 24 hours only very little dimethylsilicone oil separates from the solution. If a small amount of dilute acid or base is added to the clear aqueous solution of dimethyl*bis*-2-methoxyethoxysilane an oil layer separates almost immediately.

The 2-ethoxyethoxy radical also promotes water solubility of the silyl ethers but to a somewhat lesser extent than the 2-methoxyethoxy radical.

The 2-methoxyethoxy ethers of the following organochlorosilanes have been prepared: methyltrichloro-, dichlorodimethyl-, chlorotrimethyl-, benzylmethyldichloro-[1], methyl-2-pentyldichloro-, and phenyltrichloro-silane. The 2-ethoxyethoxy ether of dichlorodimethylsilane was also prepared. The physical properties and analyses of these compounds are tabulated in Table I.

Trimethyl-2-methoxyethoxysilane and 2-methoxyethanol form an azeotrope whose composition is approximately 50% 2-methoxyethanol.

EXPERIMENTAL

The following procedure was used in the preparation of the ethers.

The organochlorosilane is placed in a three-necked flask, which is fitted with a dropping-funnel, thermometer, and condenser. A tube filled with Drierite is attached at the end of the condenser. A slight excess of the 2-alkoxyethanol is added dropwise while the mixture is heated at reflux with an electric mantle. The heating is continued after complete addition of the alcohol until hydrogen chloride evolution ceases. The products are then distilled.

The author wishes to acknowledge the aid given by Mr. L. B. Bronk and Mrs. M. Lennig for the analytical data, and Mr. E. J. Baldwin for his aid in preparing several of these compounds.

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[1] Dr. B. A. Bluestein supplied the sample of benzylmethyldichlorosilane. He will describe this compound in a future publication.

[CONTRIBUTION FROM THE WILLIAM H. NICHOLS LABORATORY, NEW YORK UNIVERSITY]

THE EFFECT OF ALKALI AND ACID UPON THE ROTATORY POWER OF CERTAIN DIPEPTIDES[1]

MELVIN A. NYMAN[2] AND ROBERT M. HERBST[3]

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It is well known that the salt of an optically-active substance may exhibit a rotation different from that of the parent substance. The alkali salts of optically-active α-bromo acids, for instance, show different rotations from those of the free acids, frequently with reversal of sign (1). Similarly the salts of optically-active amines show large changes in rotation as compared with the bases. The curves for the changes in rotation of optically-active acids and bases with the basicity or acidity of the medium bear a close relationship to the titration curves of the respective compounds in that they reflect the proportion of undissociated acid or base and ion in the solution. Attempts have been made to use such curves for the calculation of acidic and basic dissociation constants (2). Usually the curves are of relatively simple form; however, amino acids and proteins, which include both acidic and basic functional groups as structural elements, would be expected to exhibit a more complex behavior. About eighteen years ago Lutz and Jirgensons (3) determined the effect of different degrees of acidity and basicity upon the rotation of a number of amino acids. They were the first to plot as a continuous curve the changes in rotation accompanying the stepwise shift from strongly acidic to strongly basic solutions. Earlier work has been reviewed in a previous paper (4). They observed that all the naturally-occurring amino acids had curves of the same general shape and exhibited a minimum positive or maximum negative rotation in the isoelectric region which led them to conclude that the amino acids commonly found in proteins were configurationally related. Since several of the simpler natural amino acids had been shown to be configurationally related to L-lactic acid, it was proposed that all the natural amino acids belonged to the L-series. Although the natural occurrence of enantiomorphs of several amino acids has been recognized, no exceptions to the rule that members of the L-series have a minimum rotation in the isoelectric region have been encountered.

More recently attempts have been made to extend the relationship between configuration and rotational changes evoked by acids or bases to compounds having two or more asymmetric carbon atoms in their structure. Akasi (5) attempted to establish the configuration of octopine in this manner. Attention has been called to certain errors in his results and the conclusions have been critically reviewed (6). The complexity of the rotation curves of octopine and

[1] Abstracted from a thesis presented by Melvin A. Nyman to the faculty of New York University in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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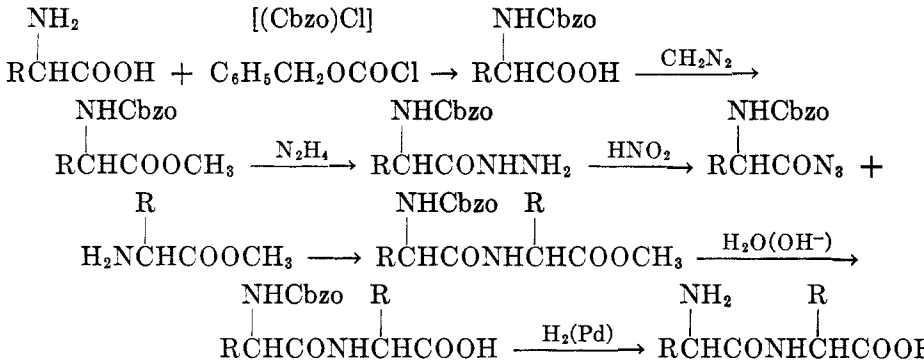
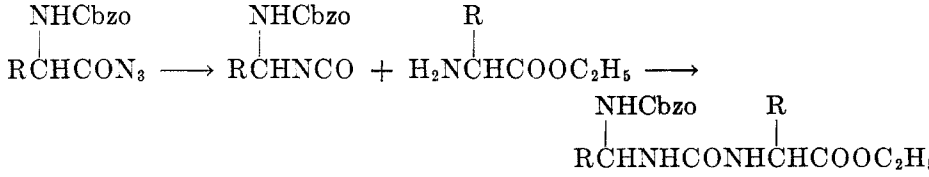
some closely related analogs emphasized the need for a study of the rotatory properties of simpler compounds in which the results would not be complicated by a multipicity of functional groups. For this purpose the rotation curves of dipeptides seemed well suited since such factors as the number of asymmetric carbon atoms, the number and variety of functional groups, and the effects of chemical changes such as acylation could be studied systematically. With this in mind a number of simple dipeptides having one or two asymmetric carbon atoms and only a single free amino and carboxyl group in their structure have been prepared and their rotation curves determined.

In order to synthesize dipeptides whose configurational relationship to the constituent amino acids is known unequivocally, the elegant techniques devised by Bergmann and his co-workers (7) involving the N-carbobenzoxy derivatives of the amino acids were the procedures of choice. An attempt was made to prepare L-valyl-L-valine[4] from N-carbobenzoxy-L-valine but difficulties were encountered in the preparation of the acid chloride. To circumvent the preparation of the acid chloride the Curtius technique (8) which had been adapted to their procedures by Bergmann, Zervas, and Greenstein (9) was employed.



R = $(CH_3)_2CH$—, $(CH_3)_2CHCH_2$—

No difficulty was encountered in the preparation of carbobenzoxy-L-valylhydrazide and this appeared to be converted into the azide by interaction with nitrous acid. However, attempts to couple the azide with D- or L-valine ethyl ester did not proceed smoothly. Although a very small amount of the desired carbobenzoxyvalylvaline was isolated in each case, the main product of the reaction was invariably the substituted urea formed by interaction of the Curtius rearrangement product of the azide and the amino acid ester.



[4] The compounds designated as *d*- and *l*-valine by Fischer (14) are now assigned the L and D configurations, respectively. The convention of indicating configurational relationship by the symbols L and D as suggested by Vickery (21) has been used throughout this discussion.

Since the valylvalines could not be prepared readily in sufficiently large amounts for rotation studies, attention was turned to the preparation of leucine peptides. Adequate amounts of both L-leucyl-L-leucine and L-leucyl-D-leucine were prepared in the manner indicated above. The L-leucyl-L-leucine could be obtained in anhydrous form by drying at 78° over phosphorus pentoxide in a vacuum but was so hygroscopic in this form that it was impractical to weigh the material. On the other hand, when placed in a moist atmosphere, it attained a

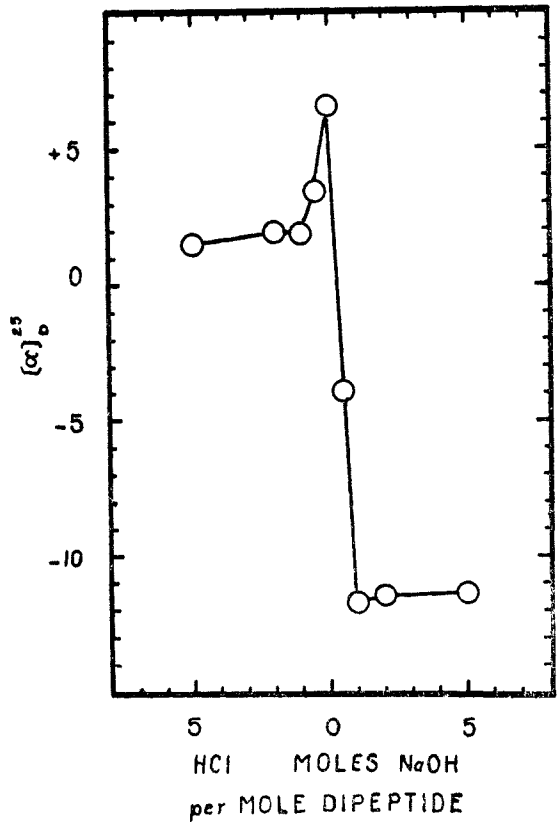


FIGURE 1. The effect of hydrochloric acid and sodium hydroxide on the specific rotation of L-leucyl-L-leucine.

constant weight after about two and a quarter moles of water had been absorbed and in this form it could be handled without difficulty. By application of the same technique to carbobenzoxy-β-alanine it was possible to prepare adequate quantities of β-alanyl-L-leucine. Carbobenzoxy-L-leucylglycine was prepared similarly, but the L-leucylglycine formed on hydrogenolysis of the former could not be obtained in solid form even by means of the expedients suggested by Fischer (10). Glycyl-L-leucine was prepared easily by the interaction of carbobenzoxyglycyl chloride and L-leucine ethyl ester followed by hydrolysis of the ester linkage and hydrogenolysis of the carbobenzoxy group.

The rotation of each of the solid dipeptides was determined in the presence of varying amounts of acid and base. From the results it appears that both L-leucyl-L-leucine (Figure 1) and L-leucyl-D-leucine (Figure 2) exhibit a maximum value in water in the isoelectric region, the rotation falling to less positive or more negative values upon the addition of either base or acid. After addition of one equivalent the further addition of acid or base caused only slight changes in the rotation such as would result on changing the solvent medium. These

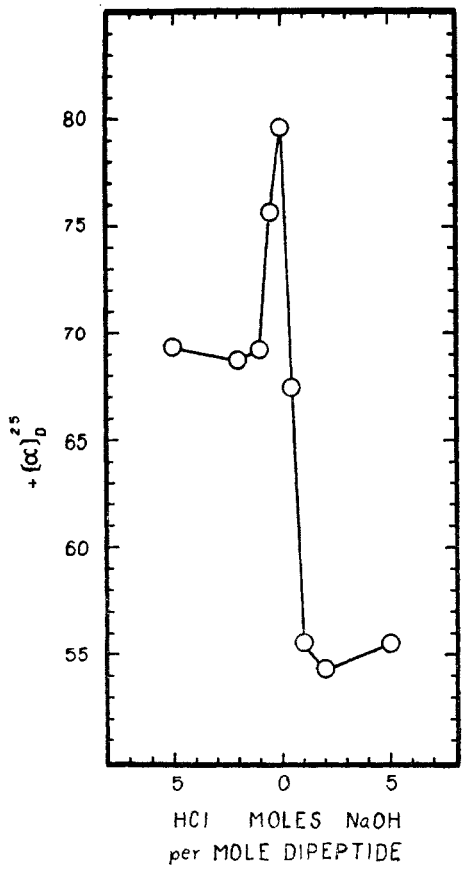


FIGURE 2. The effect of hydrochloric acid and sodium hydroxide on the specific rotation of L-leucyl-D-leucine.

curves are of the same type as those observed by Lutz and Jirgensons for simple monoaminomonocarboxylic acids except that they are the mirror images of the latter exhibiting a maximum rather than a minimum rotation in the isoelectric region. The similarity of the curves for the two leucylleucines suggests that when the two residues are similar the configuration of the amino acid entity carrying the free amino group determines the shape of the curve; however, further evidence would be required to establish this hypothesis.

The curves for glycyl-L-leucine and β-alanyl-L-leucine (Figure 3) appear to

be difficult to interpret at first glance. The latter is of the same general form as those for the leucylleucines and has a maximum in the isoelectric region, while the former is essentially the mirror image and exhibits a minimum rotation in the same region. The discrepancy between the curves for the leucylleucines and glycylleucine is, however, only apparent as becomes clear from an analysis of the contributions of the individual asymmetric carbon atoms according to the van't Hoff principle of optical superposition. For the leucylleucines, if A repre-

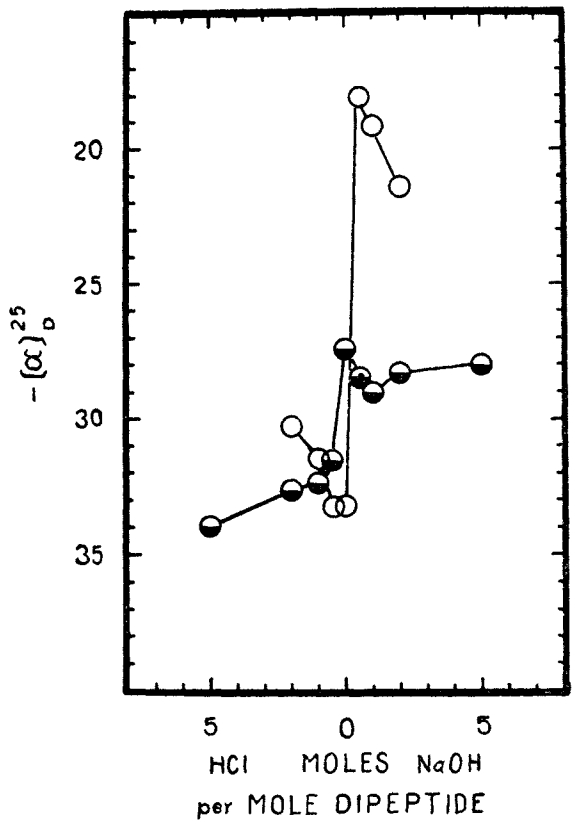


FIGURE 3. The effect of hydrochloric acid and sodium hydroxide on the specific rotations of glycyl-L-leucine (unshaded circles) and β-alanyl-L-leucine (half-shaded circles).

sents the contribution of the leucyl moiety and B represents the contribution of the leucine portion to the molecular rotation of the compound, the molecular rotation of L-leucyl-L-leucine may be expressed as the sum of A and B and that of L-leucyl-D-leucine as the difference between A and B. From the sum of these expressions the value of A may be calculated and from their difference the value of B is obtained. In Table I the values for the contribution of each asymmetric carbon atom for the various combinations of ionic forms are given together with the values for analogous L-leucine portions of glycyl-L-leucine and β-alanyl-L-leucine.

It is reasonable to assume, as appears from the values in Table I, that the contribution of the L-leucyl portion is the same in both leucylleucines. Similarly the contributions of the L- and D-leucine portions should be numerically the same but of opposite sign. It will be noted that the contribution calculated for the L-leucine moiety exhibits a minimum value in the isoelectric region and that acylation of the amino group has endowed the residue with a much greater *levo* rotation as compared with the free amino acid (3). An approximate value for the rotation of formyl-D-leucine in alkaline aqueous solution given by Fischer and Warburg (11) is included in the table since it supports the sign attributed to the rotation of the leucine portion of the peptide. Amide formation with the

TABLE I

CONTRIBUTION OF INDIVIDUAL ASYMMETRIC CARBON ATOMS TO THE MOLECULAR ROTATION[a] OF LEUCINE PEPTIDES

	$\overset{NH_2}{RCHCO}$ —— $\overset{R}{NHCHCOOH}$				
	L		L		D
Leucylleucines	(NH_3^+)	+86.9	(COOH)	−82	+82
	(NH_3^+)	+104.9	(COO^-)	−89.1	+89.1
	(NH_2)	+53.7	(COO^-)	−82.7	+82.7
Formyl-D-leucine (11)			(COO^-)		+74 appr.
Glycyl-L-leucine	(NH_3^+)	—	(COOH)	−59	
	(NH_3^+)	—	(COO^-)	−62	
	(NH_2)	—	(COO^-)	−35.7	
β-Alanyl-L-leucine	(NH_3^+)	—	(COOH)	−65.2	
	(NH_3^+)	—	(COO^-)	−55.5	
	(NH_2)	—	(COO^-)	−58.6	

[a] Molecular rotation $= [\alpha]_D \times \frac{\text{Mol. Wt.}}{100}$

carboxyl group, as exemplified by the L-leucyl portion of the peptide, has reversed not only the sign of the rotation for this configuration but has also reversed the direction of change of the rotation so that a maximum value is reached in the isoelectric region in going from acidic to basic solutions. Consequently, the rotational changes which the two asymmetric carbon atoms undergo are opposed in the L-leucyl-L-leucine, while in the diastereoisomer they are in the same direction and enhance each other, effects which are reflected in the larger over-all changes in rotation of the L-D-isomer as compared with the L-L-isomer. Another interesting point is the markedly greater effect produced upon the rotation by the ionization of the amino group as compared with the ionization of the carboxyl group.

Considering now the rotation curve of glycyl-L-leucine, it will be noted that the changes in rotation are those due to the L-leucine residue and that these are qualitatively in complete agreement with the results for the comparable portion of the leucylleucines. The greater effect of ionization of the amino group is noteworthy. It is perhaps surprising that β-alanyl-L-leucine should show a maximum

rotation in the isoelectric region since, here too, the asymmetry is in the leucine residue. However, the discrepancy may be due to the shift of the amino group to the *beta* position of the alanyl residue and thus may be related to other differences in properties associated with the β-amino acids. Further investigation of this point is desirable.

EXPERIMENTAL

DL-*Valine.* (a). Valine was prepared from isobutyraldehyde by interaction with a mixture of ammonium chloride and sodium cyanide suspended in methanol, followed by hydrolysis of the aminonitrile with conc'd hydrochloric acid. The yield of recrystallized amino acid was 36%. (b). A second preparation of DL-valine was carried out from isovaleric acid which was brominated according to the procedure of Marvel (12) and then aminated by the method of Cheronis and Spitzmueller (13). Yield, based on isovaleric acid, 47%.

*Formyl-*DL-*valine.* A solution of 100 g. of DL-valine in 500 ml. of 98–100% formic acid was heated to 50° and 300 g. of acetic anhydride was added. The temperature of the reaction mixture first dropped to 45° and then rose to 75° where it was maintained for twenty minutes. The solution was then evaporated under reduced pressure to a syrupy consistency, cooled and treated with 500 ml. of ice-water. The resulting aqueous solution was evaporated under reduced pressure until crystallization began, when, after chilling and filtering, 61.4 g of formyl-DL-valine was obtained. Concentration of the mother liquor gave an additional 36 g. After recrystallization from five times its weight of water, 89 g. of the formyl derivative was isolated as colorless plates, m.p. 142–142.5° after sintering at 136°. Fischer (14) reported a less sharp melting point in the same range.

*Resolution of formyl-*DL-*valine.* The resolution into the optically-active forms followed closely the procedure employed by Fischer (14). From 80 g. of the inactive formylvaline 20 g. of formyl-D-valine, m.p. 148–149°, $[\alpha]_D^{25}$ −13.3° in ethanol, and 19.8 g. of formyl-L-valine, m.p. 148–149°, $[\alpha]_D^{25}$ +13° in ethanol, were obtained.

The free amino acids were obtained on hydrolysis of the formyl derivatives by boiling with 20% hydrochloric acid for two hours. After isolation in the usual manner (14), 9.4 g. of L-valine, $[\alpha]_D^{25}$ +27.2° in 20% hydrochloric acid, was obtained from 14.4 g. of formyl-L-valine and a comparable amount of D-valine, $[\alpha]_D^{25}$ −27.6° in 20% hydrochloric acid, was obtained from formyl-D-valine.

Benzyl chlorocarbonate. This reagent was prepared by the method of Bergmann and Zervas (9) from phosgene and benzyl alcohol in toluene solution.

*Carbobenzoxy-*L-*valine methyl ester.* A solution of 5 g. of L-valine in 40 ml. of 1 *N* sodium hydroxide was treated with 13.6 g. of benzyl chlorocarbonate and 80 ml. of 1 *N* sodium hydroxide was added alternately in small portions during thirty minutes while the mixture was thoroughly shaken and kept at about 0°. Shaking was continued for an additional thirty minutes after addition of the reagents was complete or until the odor of benzyl chlorocarbonate had disappeared. After extraction of the alkaline solution with ether and acidification to Congo Red with hydrochloric acid the carbobenzoxy-L-valine separated as an oil which was taken up in ether and dried over sodium sulfate. Since the product could not be crystallized, it was converted into the methyl ester by treatment with diazomethane in ethereal solution. The methyl ester crystallized on evaporation of the solvent and was isolated in the form of colorless needles, m.p. 55–55.5°, $[\alpha]_D^{30}$ +16.4° in ethanol, yield, 6.6 g. (58%).

Anal. Calc'd for $C_{14}H_{19}NO_4$: N, 5.3. Found: N, 5.3.

*Carbobenzoxy-*L-*valylhydrazide.* A solution of 6.3 g. of carbobenzoxy-L-valine methyl ester in 50 ml. of absolute ethanol was treated with 3.2 g. of anhydrous hydrazine. After three days at room temperature the hydrazide had crystallized; the mixture was diluted with 10 ml. of water and the product filtered. A small amount of insoluble material remained when the hydrazide was dissolved in cold normal hydrochloric acid. After filtration of the acid solution, the hydrazide was precipitated by the addition of sodium acetate and re-

crystallized from ethanol from which it separated as silky needles, m.p. 178°, $[\alpha]_D^{22}$ −22.1° (*c*, 2.3 in 1 *N* HCl), $[\alpha]_D^{27}$ −22.8° (*c*, 2.5 in 1 *N* HCl).

Anal. Calc'd for $C_{13}H_{19}N_3O_4$: N, 15.8. Found: N, 15.9 (microDumas).

L-*Valyl*-D-*valine*. To a solution of 1 g. of carbobenzoxy-L-valylhydrazide in 6 ml. of glacial acetic acid and 30 ml. of dilute hydrochloric acid (1:10) cooled to 0–5° a solution of 0.4 g. of sodium nitrite in 4 ml. of water was added dropwise during five minutes. The oily product which separated was taken up in ether and the ethereal solution washed repeatedly with ice-water before drying over magnesium sulfate at refrigerator temperature for thirty minutes. The azide solution was then added to a solution of 1.57 g. of D-valine ethyl ester in 50 ml. of dry ether. After two days the ethereal reaction mixture was washed successively with dilute hydrochloric acid and 5% potassium carbonate solution, again dried over magnesium sulfate and evaporated to dryness under reduced pressure. Recrystallization of the partially crystalline residue from ether-hexane mixtures gave 0.89 g. of a product which separated as colorless needles, m.p. 176–177°, $[\alpha]_D^{27}$ +8.1° (*c*, 3.58 in ethanol) and appeared to be *N*-*α*-L-*carbobenzoxyaminoisobutyl*-*N'*-*α*-D-*carbethoxyisobutyl urea*, formed by interaction of the Curtius rearrangement product of the azide and the amino acid ester.

Anal. Calc'd for $C_{20}H_{31}N_3O_5$: N, 10.7. Found: N, 10.8.

Evaporation of the mother liquors from the crystallization of the urea derivative left an oily product which was saponified with ethanolic potassium hydroxide solution at room temperature. From the saponification mixture after dilution with water and evaporation of the ethanol under reduced pressure, a solid product separated upon acidification with hydrochloric acid. Recrystallization from ethanol gave 52 mg. of *carbobenzoxy*-L-*valyl*-D-*valine*, needles, m.p. 184–185° with sublimation, $[\alpha]_D^{25}$ −21.3° (*c*, 1.5 in aqueous 1 *N* KOH).

Anal. Calc'd for $C_{18}H_{26}N_2O_5$: N, 8.0. Found: N, 8.1.

Hydrogenation of 33 mg. of the carbobenzoxydipeptide in aqueous ethanol with palladium on charcoal as catalyst permitted the isolation of 11 mg. of L-*valyl*-D-*valine*, needles from aqueous ethanol.

Anal. Calc'd for $C_{10}H_{20}N_2O_3$: N, 13.0. Found: N, 13.0.

The amount of product isolated did not suffice for determination of the rotation.

L-*Valyl*-L-*valine*. From 2 g. of carbobenzoxy-L-valylhydrazide and 1.24 g. of L-valine ethyl ester following closely the procedure used in the preceeding preparation, the following products were isolated in the order given: (a) *N*-*α*-L-*Carbobenzoxyaminoisobutyl*-*N'*-*α*-L-*carbethoxyisobutyl urea* (1.42 g.), needles from ether-hexane mixtures, m.p. 167–168°, $[\alpha]_D^{25}$ +1.6° (*c*, 3.15 in ethanol).

Anal. Calc'd for $C_{20}H_{31}N_3O_5$: N, 10.7. Found: N, 10.8.

(b) *Carbobenzoxy*-L-*valyl*-L-*valine* (0.30 g.), needles from aqueous ethanol, m.p. 139.5–140°, $[\alpha]_D^{20}$ −36.6° (*c*, 3.15 in aqueous 1 *N* KOH).

Anal. Calc'd for $C_{18}H_{26}N_2O_5$: N, 8.0. Found: N, 8.1.

(c) L-*Valyl*-L-*valine* (0.15 g.), needles from aqueous ethanol.

Anal. Calc'd for $C_{10}H_{20}N_2O_3$: N, 13.0. Found: N, 12.9, 13.1.

L-*Leucine*. Commercial L-leucine obtained from the Corn Products Refining Corporation was purified by the method of Dunn (15). The purified product had a specific rotation of +15.2° in 6.15 *N* HCl.

Carbobenzoxy-L-*leucylhydrazide*. This derivative was prepared by essentially the same procedure as that employed by Bergmann and coworkers (16). The melting point, 121°, agreed with that reported; $[\alpha]_D^{25}$ −20.8° (*c*, 4.1 in ethanol).

L-*Leucyl*-L-*leucine*. Carbobenzoxy-L-leucyhydrazide (8.0 g.) was converted into the azide and allowed to react with the free ester from 5.5 g. of L-leucine methyl ester hydrochloride under conditions similar to those employed for the preparation of the valylvalines. Upon evaporation of the solvent from the reaction mixture the carbobenzoxydipeptide ester remained as an oil part of which could be isolated in crystalline form through solution in ethyl acetate-petroleum ether mixtures. After several crystallizations from the same solvent mixture, 2.35 g. of *carbobenzoxy*-L-*leucyl*-L-*leucine methyl ester* was obtained as needles, m.p. 97–98°.

Anal. Calc'd for $C_{21}H_{32}N_2O_5$: N, 7.1. Found: N, 7.1.

Although the analytical result was good, there was some question concerning the ultimate purity of the compound since it could not be freed of an odor reminiscent of the azide solutions.

Saponification of the ester gave an oily carbobenzoxydipeptide which was converted directly into the free dipeptide by hydrogenation in the presence of palladium on charcoal. After two recrystallizations from aqueous ethanol, 750 mg. of L-*leucyl*-L-*leucine* was isolated as very fine crystals, m.p. 266°, $[\alpha]_D^{25}$ +6.5° (*c*, 1.7 in water), −11.3° (*c*, 3.3 in water containing 5 equivalents of sodium hydroxide).

Anal. Calc'd for $C_{12}H_{24}N_2O_3$: total N, 11.5; amino-N, 5.7.
Found: N (Kjeldahl), 11.4; N (van Slyke), 5.8.

Fischer (14) reported m.p. 270°, and $[\alpha]_D^{20}$ +7° in water and −13.36° in 1 *N* sodium hydroxide.

L-*Leucyl*-D-*leucine*. Carbobenzoxy-L-leucylhydrazide (7 g.) was converted into the azide and allowed to react with the free ester from 4.5 g. of D-leucine methyl ester hydrochloride as previously described. Upon evaporation of the solvent the carbobenzoxy-L-leucyl-D-leucine methyl ester remained as a syrupy residue. Attempts to purify it by means of an adsorption column failed to give a crystalline product. Saponification of the crude ester with ethanolic potassium hydroxide solution gave an oily, acidic material and a small amount of apparently neutral material which was not further investigated. The acidic material had approximately the correct neutralization equivalent and nitrogen content for carbobenzoxy-L-leucyl-D-leucine but was not characterized further. After hydrogenation of the acidic material in 50% aqueous ethanol, L-*leucyl*-D-*leucine* could be isolated as a solid separating from aqueous ethanol as colorless needles in a yield of 0.7 g. Upon drying over phosphorus pentoxide at 78° and 0.01 mm. pressure the dipeptide was anhydrous but exceedingly hygroscopic. On exposure to moisture 701 mg. of the dipeptide reached a constant weight after absorbing 117 mg. of water, corresponding to 14.3% in the hydrated material or 2.27 moles of water per mole of peptide. The hydrated material was used for all analytical procedures, results being corrected for the water content of the product; $[\alpha]_D^{25}$ +69.3° (*c*, 2.76 in water containing 5 equivalents of hydrochloric acid). Fischer and Steingröver (17) reported the specific rotation as +68.95° in 1 *N* hydrochloric acid at 20°.

Anal. Calc'd for $C_{12}H_{24}N_2O_3$: total N, 11.5; amino-N, 5.7.
Found: N (Kjeldahl), 11.5; N (van Slyke), 5.8.

L-*Leucylglycine*. By interaction of the azide prepared from 1 g. of carbobenzoxy-L-leucylhydrazide with glycine ethyl ester in ether solution, essentially as described previously, 0.85 g. of *carbobenzoxy*-L-*leucylglycine ethyl ester* was obtained as colorless needles, m.p. 99°, after several crystallizations from ether-petroleum ether, $[\alpha]_D^{25}$ −26.8° (*c*, 2.6 in ethanol).

Anal. Calc'd for $C_{18}H_{26}N_2O_5$: N, 8.0. Found: N, 8.2.

Since the carbobenzoxydipeptide obtained by saponification of the ester failed to crystallize, it was hydrogenated in the usual manner. The dipeptide was isolated as a syrupy material, readily soluble in ethanol and in water, which could not be induced to crystallize even upon repeated treatment with absolute ethanol as suggested by Fischer (10).

L-*Leucine methyl ester hydrochloride*. Using the Fischer (18) technique 47 g. of L-leucine was esterified with methanolic hydrogen chloride. The methyl ester hydrochloride was isolated in 85% yield after crystallization from methanol and dry ether, m.p. 146–147°. Smith and Brown (19) give m.p. 149–150° for the D-isomer.

Glycyl-L-*leucine*. L-Leucine methyl ester, from 4.5 g. of hydrochloride, and the chloride from 2.5 g. of carbobenzoxyglycine were allowed to react in ether solution (9). Neither the ester nor the carbobenzoxydipeptide formed by saponification thereof could be crystallized, so the *glycyl*-L-*leucine* was liberated by hydrogenation and isolated in a yield of 264 mg. as colorless crystals after several recrystallizations from aqueous ethanol, $[\alpha]_D^{25}$ −33.2° (*c* 2.7 in water).

Anal. Calc'd for $C_8H_{16}N_2O_3$: total N, 14.9; amino-N, 7.4.
Found: N (Kjeldahl), 14.8, 15.0; N (van Slyke), 7.5.

Fischer and Steingröver (17) give the rotation as −35.1° in water at 20°.

Carbobenzoxy-β-alanylhydrazide. The crude ethyl ester hydrochloride prepared from 20 g. of β-alanine by esterification with absolute ethanolic hydrogen chloride, was converted into the carbobenzoxy derivative by treatment with 45 g. of benzyl chlorocarbonate and 12 g. of magnesia suspended in 100 ml. of water and 200 ml. of chloroform. Upon evaporation of the chloroform layer after washing with dilute hydrochloric acid and potassium bicarbonate solution, the carbobenzoxy ester remained as a syrup (40 g.) which was converted into the hydrazide by dissolving in 150 ml. of ethanol and boiling under reflux for two hours with 25 g. of 85% hydrazine hydrate. The hydrazide crystallized upon cooling the reaction mixture. A total of 39 g. of crude hydrazide was obtained after concentration of the mother liquors which gave after recrystallization from water, 35 g. (66%) of pure carbobenzoxy-β-alanylhydrazide, platelets, m.p. 144–145°. Using a different sequence of reactions Sifferd and du Vigneaud (20) obtained the same product, m.p. 143°.

TABLE II

CONCENTRATION, OBSERVED ROTATION, AND *p*H OF DIPEPTIDE SOLUTIONS CONTAINING VARYING AMOUNTS OF ACID AND BASE

EQUIV.	L-Leucyl-L-leucine			L-Leucyl-D-leucine			Glycyl-L-leucine			β-Alanyl-L-leucine		
	MG./CC.	α^b	*p*H	MG./CC.[a]	α^b	*p*H	MG./CC.	α^c	*p*H	MG./CC.	α^b	*p*H
HCl												
5	33.26	+0.10	0.55	27.57	+3.81	0.39				33.41	−2.27	0.42
2	33.37	+0.13	0.78	27.56	+3.79	0.98	27.03	−0.82	1.00	33.18	−2.17	0.92
1	33.10	+0.127	1.70	27.52	+3.81	2.08	27.03	−0.85	2.02	33.39	−2.16	1.97
¾				27.55	+3.88	2.54						
½	33.41	+0.11	3.30	10.51	+1.59	3.08	27.03	−0.90	3.24	33.45	−2.11	3.08
0	16.74	+0.22	5.65	10.17	+1.62	5.90	27.05	−0.90	5.88	33.22	−1.82	5.20
NaOH												
½	33.06	−0.26	7.90	10.16	+1.37	8.08	27.06	−0.49	8.15	33.37	−1.90	9.20
1	33.41	−0.78	11.48	27.28	+3.03	9.62	27.06	−0.52	9.90	33.41	−1.94	11.25
2	33.25	−0.76	—	27.44	+2.98	—	27.06	−0.58	—	33.43	−1.89	—
5	33.30	−0.76	—	27.56	+3.06	—	—	—	—	33.22	−1.86	—

[a] Calculated as anhydrous dipeptide. [b]Observed rotation in degrees at *t*, 25°, *l*, 2 dcm. [c]Observed rotation in degrees at *t*, 25°, *l*, 1 dcm.

β-Alanyl-L-leucine. By interaction in chloroform solution of the azide prepared from 7.2 g. of carbobenzoxy-β-alanylhydrazide and the ester from 5.0 g. of L-leucine methyl ester hydrochloride followed by saponification of the carbobenzoxydipeptide ester and hydrogenolysis of the carbobenzoxy group, 2.1 g. of pure β-alanyl-L-leucine was obtained as long, matted needles from 80% ethanol, $[\alpha]_D^{25}$ −27.4° (*c*, 3.3 in water). The intermediates were not obtained in crystalline form.

Anal. Calc'd for $C_9H_{18}N_2O_3$: N (total), 13.9; N (amino), 6.9.
Found: N (Kjeldahl), 13.8; N (van Slyke), 7.0.

Rotation curves. Solutions for the determination of rotations were prepared by weighing the samples into calibrated 2.5-ml. flasks. The requisite amounts of standard hydrochloric acid or sodium hydroxide were added and the solutions brought to volume with distilled water. Rotations were determined with a Schmidt and Haensch half-shadow polarimeter using a sodium lamp as the source of monochromatic light. The temperature was maintained at 25° by circulating water from a large thermostat around the polarimeter tube. With the exception of glycyl-L-leucine for which a one-dcm. semimicro tube was employed all determinations were made with the same two-dcm. semimicro tube. The *p*H of each solution was determined with a Beckman *p*H meter, Laboratory Model G. The observed rotation corresponding to each point is the average of a series of at least ten successive readings on the

same solution none of which deviated more than 0.03° from any other reading. In Table II are summarized the concentrations, observed rotations, and *p*H values for all solutions.

SUMMARY

A number of dipeptides of known configuration, including L-leucyl-L-leucine, its diastereoisomer, L-leucyl-D-leucine, glycyl-L-leucine, and β-alanyl-L-leucine were prepared. The changes in optical rotation which these peptides undergo on passing from neutral to alkaline or acid solution were determined. Both leucylleucines exhibited a maximum positive (*dextro*) rotation in the isoelectric region. Calculation of the contribution of each of the asymmetric carbon atoms indicated, when both components of the dipeptide are similar, that the amino acid residue having the free amino group made the greatest contribution to the total rotation of the dipeptide. It also appeared that, in the case of L-leucine, amide formation with the carboxyl group caused the leucyl residue to become more *dextro* rotatory while amide formation with the amino group caused the leucine residue to become more *levo* rotatory. The converse is to be expected with the D-isomer.

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[FROM THE UNIVERSITY OF CALIFORNIA, LOS ALAMOS SCIENTIFIC LABORATORY]

MICRO-SYNTHESES WITH TRACER ELEMENTS. II. METHYLDI-(BETA-CHLOROETHYL)AMINE HYDROCHLORIDE (NITROGEN MUSTARD) AND METHYL BROMIDE LABELED WITH C^{14} [1]

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"Nitrogen Mustard", methyldi-(*beta*-chloroethyl)amine hydrochloride, has received a great deal of attention because of its use in the treatment of Hodgkin's disease. It is now recognized that lymphatic tumors which are responsive to x-radiation will also respond to treatment with nitrogen mustard.

In addition, the physiologic effects of excessive doses of the mustard are so strikingly similar to the effects of radiation injury that the possibility of investigating the mechanism of this type of cell damage using labeled nitrogen mustard has been proposed.

The synthesis herein reported leads to nitrogen mustard labeled with C^{14} in the methyl group. Labeled methanol was converted to methyl bromide using concentrated hydrobromic acid. Methyl bromide was then condensed with diethanolamine. Methyl iodide does not work satsifactorily in this reaction, since it is decomposed by the diethanolamine. When equal mole ratios of methyl bromide and amine were used, an appreciable percentage (20–35%) of the amine was converted to the quaternary salt. Upon halogenating with thionyl chloride a mixture of products was obtained which were exceedingly difficult to separate from each other. However, a mole ratio of halide to amine of 1:5 gave no amine higher than the tertiary amine desired.

Attempts at separating the tertiary from the secondary amine using acetylation, benzoylation, and the Hinsberg reaction were unsuccessful. The isocyanates were also useless for this purpose. Fractional recrystallization and fractional sublimation gave only partial separation. Treatment with nitrous acid gave a good separation, doubtlessly accompanied, however, by some decomposition.

EXPERIMENTAL

Methyl bromide labeled with C^{14}. Flask *A* containing 5 ml. of HBr-H_2SO_4 mixture (made by the dropwise addition of 3.6 ml. of conc'd H_2SO_4 to 23.03 g. of chilled 48% HBr) and a glass-enclosed iron slug was attached to the manifold at the point indicated in Figure 1. After a brief initial period of outgassing, the flask was chilled with liquid nitrogen, the system evacuated to 10^{-4} mm, and the stopcock *G* closed. Methanol (0.8–10 *mM*) contained in "breakofsky" tubes *B* sealed to a manifold was attached to the line at *C*. The entire system was evacuated under high vacuum and closed off from the vacuum manifolds. With stopcock *D* closed, the methanol was distilled into *A* by chilling flask *A* with liquid nitrogen. Flask *A* was allowed to warm to room temperature and then stirred continuously by means of a magnetic stirrer *I*, while the temperature was gradually brought to 100° with oil-bath *H* (1.25 hours). The mixture was then cooled to room temperature and the product distilled into *E* through the purifying train *F* consisting of soda-lime and P_2O_5 on glass wool.

[1] This document is based on work performed under Contract No. 7405-eng-36 for the Atomic Energy Commission.

E was a light flask of 100-ml. capacity equipped with a micro stopcock. Quantitative transfer was attained by cooling *E* with liquid nitrogen. Any non-condensible gas present in the system was pumped off. The transfer of known amounts of methyl bromide by this method was quantitative (99.8 %). The yields of methyl bromide obtained were 94–96%; the product was checked for purity by analysis for Br.

The oil-bath heater was made by wrapping resistance wire around a crystallizing dish; voltage was controlled with a variable transformer. An HBr-H_2SO_4 reagent of mole ratio 1:1.55 gave slightly lower yields than the one used which corresponds to a 1:2.06 ratio.

Experiments using PBr_3 for the brominating agent resulted in yields of 60–70% of theory with runs on the 10-millimole level.

Methyldi-(beta-chloroethyl)amine hydrochloride. Methyl bromide, made from 3.86 *mM.* of methanol labeled with C^{14}, was transferred *in vacuo* in the vapor phase into a 25-ml. reaction flask *S*, Figure 2, attached to a vacuum line, by cooling the flask with liquid nitrogen. Inside the flask were a short glass-enclosed magnet and an outgassed solution of 2.1065 g. (20.04 *mM.*) of diethanolamine dissolved in 15 ml. of absolute ethanol. Stopcock *T* was closed and the mixture in flask *S* was melted as quickly as possible with the magnetic stirrer set for maximum stirring. Stirring was maintained continuously for 42 hours. At the end of

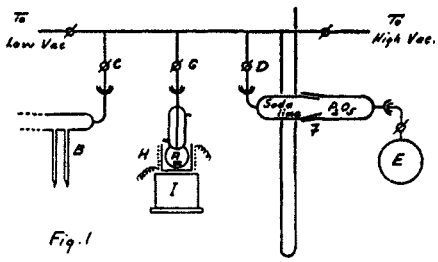

Fig. 1

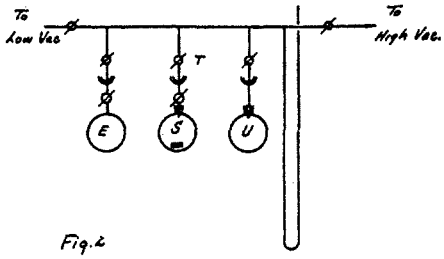

Fig. 2

this period about ¼ of the solvent was distilled into receiver *U*, containing an alcoholic solution of silver nitrate. The receiver was then stoppered and the contents of the flask were digested 48 hours at 45°. There was no trace of silver halide, indicating that the methylation reaction had been quantitative. A slight excess of potassium hydroxide over that required to free the base was dissolved in absolute alcohol and added to the cooled reaction mixture. After allowing the mixture to stir ½ hour in an ice-bath, the precipitated potassium bromide was filtered, washed several times with absolute ethanol, dried, and weighed. Yield, 0.4376 g. (95.5%) of methyl bromide from the labeled methanol. The filtrate which contained a mixture of methylated and unmethylated diethanolamine was saturated with hydrogen chloride and then concentrated to a small volume with a gentle stream of air. If too large an excess of potassium hydroxide was used, the volume of KCl at this stage was excessive and it was filtered off through a layer of diatomaceous earth. A small amount of precipitate did no harm and did not require removal. The combined filtrate and washings were transferred to a 60-ml. flask and concentrated as before. The degree of removal of ethanol was checked by weighing.

The flask was equipped with a reflux condenser and mechanical stirrer. Twenty-five ml. of benzene was added to the flask and the mixture was saturated with anhydrous hydrogen chloride. Stirring was begun and the calculated amount of purified thionyl chloride, based upon the methylated and unmethylated diethanolamine and the residual ethanol remaining in the mixture (5 ml. in all in this experiment) was added in small portions through the condenser.

At the end of the reaction, the mixture was warmed to 60° for 3.5 hours. The mixture was opalescent at the beginning of the reaction, then became successively opaque, gummy, and finally crystalline. When evolution of hydrogen chloride ceased, an additional 2 ml. of

thionyl chloride was added in 0.5-ml. portions. Stirring was maintained continuously throughout the reaction. When reaction again ceased, the excess thionyl chloride was destroyed by the dropwise addition of the calculated amount (1.4 ml.) of absolute methanol to the cooled mixture. Care was exercised to avoid any excess of methanol since this exerted some solvent action on the product. The mixture was then treated with 20 ml. of benzene, cooled in an ice-bath, filtered through a sintered-glass funnel, and washed with several 5-ml. portions of cold benzene. The crystalline mustards were roughly separated from each other by extraction with boiling chloroform in the following manner. The crystalline mass was transferred to the original flask, stirred briefly with 30 ml. of boiling chloroform, and allowed to cool for 15 minutes, while being stirred, before filtration. This was repeated four times. After the fourth extraction the residue, wt. 2.2149 g., melted at 209–212.5° (m.p. of pure $HN(C_2H_4Cl)_2 \cdot HCl$ is 214–215°) and was discarded. This quantity of unmethylated nitrogen mustard corresponded to 76.9% of the excess diethanolamine originally added to the reaction.

The chloroform was removed by evaporation at room temperature and the crude product was quantitatively transferred to a liquid-liquid extractor, dissolved in 8–10 ml. of water, and acidified with 1 ml. of conc'd. HCl. The solution was cooled in an ice bath, and 0.4 g. of sodium nitrite dissolved in the minimum amount of water was slowly added. After one hour, the nitrosoamine was removed by continuous extraction with ether for seven hours. The almost colorless raffinate was concentrated to a small volume in a gentle stream of air Final drying was accomplished by placing the residue first in a desiccator over $CaCl_2$, then over P_2O_5.

The pale yellow, powdery residue was extracted six times with boiling chloroform in order to separate the mustard from sodium chloride. The chloroform was removed by evaporation in a gentle stream of air. The crude product was dried over P_2O_5, then was dissolved in 10 ml. of pure acetone, decolorized with Norit, and filtered through a small sintered-glass funnel into a 30-ml. centrifuge cone. The cone was stoppered and the product was crystallized by cooling to −25°. After removing the mother liquor using a filter stick, the crystals were washed with several 10-ml. portions of absolute ether. The product was recrystallized by solution in 17 ml. of acetone followed by cooling to −40°. The yield from 2 runs made on this scale, using a total of 17 mc. of methanol (0.2225 g.) was 0.6995 g. (yield 52.5% based on methanol); m.p. 109–110°. None of the acetone mother liquors was reworked for a second crop of crystals.

The nitrogen mustard (cold run) yielded a chloroaurate from water solution, which, recrystallized three times from water, melted at 82–84°.

Anal. Calc'd for $CH_3N(CH_2CH_2Cl)_2 \cdot HAuCl_4$: Au, 39.80.
Found: Au, 39.50.

Methyldi-(*beta*-chloroethyl)amine hydrochloride is volatile with boiling organic solvents. When 0.0148 gram was placed in a distilling flask with dry benzene (250 ml.) and 200 ml. of benzene was distilled, the residue remaining in the flask amounted to 0.0014 g., indicating that over 90% had co-distilled with the benzene.

In neutral water solution the nitrogen mustard will undergo hydrolysis. Attempts to evaporate such solutions resulted in the loss of mustard. This hydrolysis can be totally prevented by acidifying with HCl before evaporation.

Dimethyldi-(beta-chloroethyl)ammonium bromide. When the mole ratio of methyl bromide to diethanolamine was 1:1, a mixture was obtained after treatment with thionyl chloride as described above, which left an insoluble product when extracted with acetone. After several recrystallizations from acetonitrile, colorless crystals were obtained which melted at 217–218°; yield, 20–35%. Analysis indicated the compound was the quaternary amine hydrobromide.

Anal. Calc'd for $(CH_3)_2N(C_2H_4Cl)_2 \cdot HBr$: N, 5.55. Found: N, 5.52, 5.58.

The acetone-soluble fraction was a mixture of methylated and unmethylated nitrogen mustard hydrobromide and hydrochloride.

Acknowledgment. We wish to extend our thanks to Dr. R. Macy and Dr. Benjamin Witten of Edgewood Arsenal and to Dr. Max Tishler of Merck and Company for many valuable suggestions for the synthesis and manipulation of nitrogen mustards.

SUMMARY

Methyl bromide labeled with C^{14} has been synthesized from labeled methanol. Methyldi-(*beta*-chloroethyl)amine hydrochloride, a nitrogen mustard, has been labeled at the methyl group with C^{14}. The compound obtained by this synthesis possessed an activity corresponding to 22 μc. per milligram.

LOS ALAMOS, NEW MEXICO

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. III. NEW DERIVATIVES OF N-ETHYLCARBAZOLE[1]

NG.PH. BUU-HOÏ AND RENÉ ROYER

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At the present stage of chemical cancer research, it is known that, starting from simple aromatic hydrocarbons inactive by themselves, it is possible to produce carcinogenic compounds in two different ways: firstly, by addition of supplementary aromatic rings or hydrocarbon radicals, and secondly, by introduction of certain functional groups such as $—NH_2$, $—N(CH_3)_2$, $—NHCOCH_3$, $—NO_2$, etc. The first line of research has been extensively investigated over the last two decades, and has resulted in the discovery of the largest number of carcinogens hitherto known (1). Although the second has been of more recent date, the examples so far recorded indicate that it may be no less fruitful a basis for research; thus, amination of naphthalene leads to β-naphthylamine, an agent of cancer of the bladder (2), and to 1,5-naphthylenediamine which produces lympho- and myelo-sarcomas by subcutaneous injection (3). Similarly, β-amination of the harmless tricyclic hydrocarbons fluorene and anthracene transforms them into 2-aminofluorene and 2-anthramine, two carcinogens of strikingly versatile activity (4).

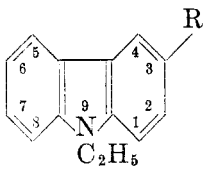
It is known that addition of benzene rings to carbazole or to N-alkylcarbazoles results in carcinogenic substances such as N-methyl-1,2-benzocarbazole (5), 1,2,5,6-, 1,2,7,8-, and 3,4,5,6-dibenzocarbazole (6) or N-ethyl-3,4,5,6-dibenzocarbazole (7). This paper deals with a study of 9-ethylcarbazole carried out mainly along the second line of research outlined above. Of the many compounds thus synthesized for biological investigation by Professor A. Lacassagne, some had already been prepared by other methods, but the rest were hitherto unknown.

3-Acetyl-9-ethylcarbazole (I) (8), best prepared by means of a Friedel-Crafts reaction from 9-ethylcarbazole, acetyl chloride, and aluminum chloride in benzene, was reduced to 3,9-diethylcarbazole (II) with amalgamated zinc and hydrochloric acid. Treatment of (II) with bromine in acetic acid resulted in 6-bromo-3,9-diethylcarbazole (XVI). Clemmensen reduction of 3,6-diacetyl-9-ethylcarbazole (XVII), a by-product in the acetylation of 9-ethylcarbazole (8), yielded 3,6,9-triethylcarbazole (XVIII). A substance isomeric with the latter is 3-isobutyl-9-ethylcarbazole (IV) obtained through similar reduction of 3-isobutyryl-9-ethylcarbazole (III), a liquid ketone prepared from 9-ethylcarbazole and isobutyryl chloride in the usual way.

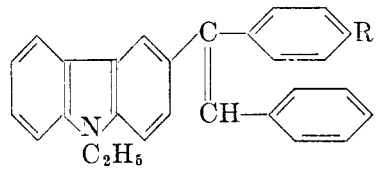
n-Butyroylation of 9-ethylcarbazole yielded a mixture of 3-*n*-butyroyl-9-ethylcarbazole (V) with but little 3,6-di-*n*-butyroyl-9-ethylcarbazole (XIX), and in the case of *n*-octanoylation, no sizable amount of a disubstituted product was

[1] For part II of this series see: Buu-Hoï, *et al.*, *J. Org. Chem.*, **14**, 802 (1949).

obtained, 3-*n*-octanoyl-9-ethylcarbazole (VI) being the sole compound isolated in a pure state. On the other hand, phenacetylation gave less 3-phenacetyl-9-



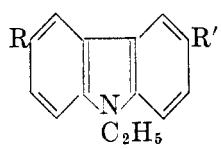
I	R = $COCH_3$	VIII	R = CO–C$_6$H$_4$–OCH_3
II	R = C_2H_5	IX	R = $COCH_2Cl$
III	R = $COCH(CH_3)_2$	X	R = $NHCOCH_3$
IV	R = $CH_2CH(CH_3)_2$	XI	R = $NHCOC_2H_5$
V	R = $CO(CH_2)_2CH_3$	XII	R = COOH
VI	R = $CO(CH_2)_6CH_3$	XIII	R = $CONH_2$
VII	R = $CO(CH_2)C_6H_5$		



XIV R = H
XV R = OCH_3

ethylcarbazole (VII) than 3,6-diphenacetyl-9-ethylcarbazole (XX). This latter substance gave 3,6-di(β-phenylethyl)-9-ethylcarbazole (XXI) on Clemmensen reduction.

Treatment of 3-benzoyl-9-ethylcarbazole (8) with benzylmagnesium chloride resulted in a tertiary carbinol which was dehydrated on vacuum-distillation into α,β-diphenyl-β-(9-ethylcarbazol-3-yl)ethylene (XIV), a substance whose interest lies in its structural connection with both the estrogenic α,β,β-triphenylethylene and the carcinogenic aminostilbenes (9). In the same series, α-phenyl-β-anisyl-β-(9-ethylcarbazol-3-yl)ethylene (XV) was prepared from benzylmagnesium chloride and 3-anisoyl-9-ethylcarbazole (VIII), a ketone which was readily obtained from anisoyl chloride, 9-ethylcarbazole, and aluminum chloride in benzene.

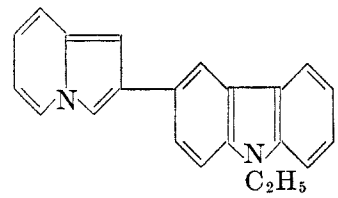


XVI	R = Br, R′ = C_2H_5
XVII	R = R′ = $COCH_3$
XVIII	R = R′ = C_2H_5
XIX	R = R′ = $CO(CH_2)_2CH_3$
XX	R = R′ = $COCH_2C_6H_5$
XXI	R = R′ = $(CH_2)_2C_6H_5$
XXII	R = Br, R′ = COOH
XXIII	R = R′ = COOH

The oxidation of 3-acetyl-9-ethylcarbazole by means of sodium hypobromite in the presence of dioxane gave a fairly good yield of 9-ethylcarbazole-3-carboxylic acid (XII), a compound which had previously been obtained with less ease by Gilman and Kirby (12) through carbonation of the lithio derivative of 9-ethylcarbazole. This acid gave on treatment with thionyl chloride a solid *chloride* which was transformed into 9-ethylcarbazole-3-carboxamide (XIII) by aqueous ammonia; with bromine in acetic acid it gave 6-bromo-9-ethylcarbazole-3-carboxylic acid (XXII). 9-Ethylcarbazole-3,6-dicarboxylic acid (XXIII) was similarly obtained in high yield by hypobromite-oxidation of 3,6-diacetyl-9-ethylcarbazole; this acid had already been prepared by Gilman and Kirby (12) by oxidation of the diketone (XVII) with potassium ferricyanide.

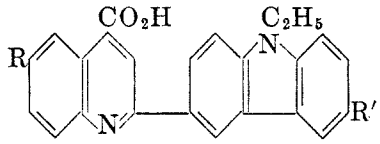
With respect to nitrogen-containing substituents, the oxime of 3-acetyl-9-

ethylcarbazole smoothly underwent a Beckmann rearrangement on treatment with phosphorus pentachloride in ether, yielding 3-acetamido-9-ethylcarbazole (X) (17), an analog of the carcinogenic 2-acetamidofluorene, and a homolog of 3-acetamidocarbazole (10). The oxime of 3-propionyl-9-ethylcarbazole (8) similarly yielded N-9-ethylcarbazol-3-ylpropionamide (XI). 3-ω-Chloroacetyl-9-ethylcarbazole (IX), prepared from 9-ethylcarbazole, chloroacetyl chloride, and aluminum chloride in the usual way, reacted with α-picoline to give a quaternary α-picolinium derivative which readily underwent the Tschitschibabin reaction (11) under the influence of sodium bicarbonate to give 2-(9′-ethylcarbazol-3′-yl)pyrrocoline (XXIV).



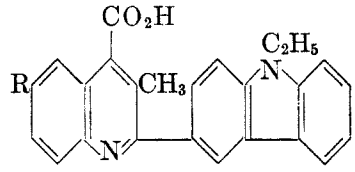
(XXIV)

The well-known ability of atophan (2-phenylcinchoninic acid) to produce under certain conditions the so-called "yellow atrophy" of the liver (13) suggests that some cinchoninic acids bearing polycyclic substituents in the 2-position might well show a similar toxicity. This has lead to the synthesis of a certain number of quinoline derivatives with a carbazole nucleus in the 2-position, some of them bearing nuclear halogen atoms, which are known to enhance the physiological properties of certain quinolines and acridines such as their antimalarial (14) or their strychnine-like activity (15). 3-Chloro-6-acetyl-9-ethylcarbazole



XXV R = H, R′ = Cl
XXVI R = Br, R′ = Cl
XXVII R = Br, R′ = H

(8) underwent a Pfitzinger reaction with isatin to give 2-(3′-chloro-9′-ethylcarbazol-3′-yl)cinchoninic acid (XXV), which could be decarboxylated by heat to 2-(3′-chloro-9′-ethylcarbazol-3′-yl)quinoline; the same ketone gave with 5-bromoisatin 6-bromo-2-(3′-chloro-9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVI); from 5-bromoisatin and 3-acetyl-9-ethylcarbazole, 6-bromo-2-(9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVII) was similarly obtained. Whereas 3-propionyl-9-ethylcarbazole readily underwent Pfitzinger reac-



XXVIII R = H
XXIX R = Br

tions with 5-bromoisatin and isatin, to give 6-bromo-3-methyl-(XXIX) and 3-methyl-2-(9′-ethylcarbazol-3′-yl)cinchoninic acid (XXVIII) respectively, no noticeable reaction occurred with 3-*n*-butyroyl-9-ethylcarbazole (V). Such inability in certain ketones to undergo the Pfitzinger reaction has already been repeatedly reported and discussed by the present authors (16).

Acknowledgment. This work has been carried out with the financial support of the U. S. Public Health Service (Federal Security Agency); the authors wish to express their thanks to the authorities concerned. Our thanks are also due to Miss Patricia F. Boshell, M.A. (Oxon.) for her assistance.

EXPERIMENTAL

Preparation of intermediates. The procedure for acetylation of 9-ethylcarbazole (8) previously described was altered as follows: to an ice-cooled solution of 40 g. of 9-ethylcarbazole and 22 g. of acetyl chloride in 300 ml. of pure dry benzene, 30 g. of finely powdered aluminum chloride was added in small portions with stirring. The mixture, which soon developed a dark green halochromic coloration, was poured on to ice after five hours at ordinary temperature. A solid precipitate was filtered off, and yielded after crystallization from benzene *3,6-diacetyl-9-ethylcarbazole* (4 g.); the benzene layer was washed with water and the solvent removed by distillation. The residue was vacuum-distilled; 26 g. of *3-acetyl-9-ethylcarbazole*, b.p. *circa* 255–260° at 18 mm., m.p. 115°, was obtained; 2 g. of 3,6-diacetyl-9-ethylcarbazole was recovered from the higher-boiling fraction.

Dry benzene was also preferred to carbon disulfide as a solvent in the preparation of *3-chloro-6-acetyl-9-ethylcarbazole* and of *3-propionyl-9-ethylcarbazole*, both of which were obtained in similar yields to the above.

3,9-Diethylcarbazole (II). A mixture of 30 g. of 3-acetyl-9-ethylcarbazole, 150 g. of granulated amalgamated zinc, 50 ml. of toluene, and 300 ml. of conc'd hydrochloric acid (*d*, 1.19) was refluxed for ten days with the daily addition of 50 ml. of hydrochloric acid. After addition of toluene, and shaking, the organic layer was decanted, washed with water, the solvent removed, and the residue vacuum-distilled. The yield was 20 g. of a rather mobile, pale yellow oil, b.p. 208–212° at 12 mm., which solidified after some standing. Recrystallization from petroleum ether (very soluble) yielded large colorless prisms, m.p. 45°, which gave with sulfuric acid a dark green coloration.

Anal. Calc'd for $C_{16}H_{17}N$: N, 6.0. Found: N, 6.2.

6-Bromo-3,9-diethylcarbazole (XVI). A solution of 9 g. of 3,9-diethylcarbazole in 100 ml. of acetic acid was treated with a solution of 6.5 g. of bromine in 20 ml. of acetic acid in small portions at room temperature. After a short heating on the water-bath, the mixture was poured into water, and the reaction product extracted with benzene. The benzene layer was worked up as usual, yielding on vacuum-distillation 6 g. of a pale yellow, viscous oil b.p. 250° at 15 mm.

Anal. Calc'd for $C_{16}H_{16}BrN$: N, 4.6. Found: N, 4.3.

3,6,9-Triethylcarbazole (XVIII). A mixture of 6 g. of 3,6-diacetyl-9-ethylcarbazole, 75 g. of amalgamated zinc, 5 ml. of xylene, and 150 ml. of conc'd hydrochloric acid was refluxed for seven days with frequent addition of further hydrochloric acid. The reaction product was worked up in the usual way, giving 4 g. of a pale yellow, mobile oil, b.p. 235° at 13 mm., which turned brown rapidly in the air.

Anal. Calc'd for $C_{18}H_{21}N$: N, 5.5. Found: N, 5.6.

This substance gave with picric acid a rather unstable *addition compound* which crystallized from ethanol in long silky brown-red needles, m.p. 158°.

3-Isobutyroyl-9-ethylcarbazole (III). To a solution of 9-ethylcarbazole (7.5 g.) and isobutyroyl chloride (5 g.) in dry benzene (100 ml.), aluminum chloride (5 g.) was added at room temperature with frequent shaking. After two days, the mixture was poured onto ice and the reaction product treated in the usual way, giving 7 g. of a thick, pale yellow oil, b.p. 270° at 13 mm., which did not solidify even after one year.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.2. Found: N, 5.2.

3-Isobutyl-9-ethylcarbazole (IV). The foregoing ketone (6.5 g.) was refluxed for seven days with 50 g. of amalgamated zinc, 10 ml. of xylene, and 100 ml. of hydrochloric acid in the usual way; the reaction product, obtained in poor yield (2 g.), was a viscous pale yellow oil, b.p. 240–245° at 15 mm., n^{27} 1.6140, giving a deep red picrate.

Anal. Calc'd for $C_{18}H_{21}N$: N, 5.4. Found: N, 5.6.

n-Butyroylation of 9-ethylcarbazole. A mixture of 7.5 g. of 9-ethylcarbazole and 4.8 g. of *n*-butyroyl chloride in 150 ml. of benzene was treated with 6 g. of aluminum chloride in small portions, then left for two days. The reaction product was worked up in the usual way and yielded 7 g. of *3-n-butyroyl-9-ethylcarbazole* (V), b.p. 285–287° at 19 mm., crystallizing from methanol in long colorless needles, m.p. 86°.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.2. Found: N, 5.1.

Repeated crystallization of the higher-boiling fraction from methanol (charcoal) gave 1.5 g. of *3,6-di-n-butyroyl-9-ethylcarbazole* (XIX) in the form of fine colorless prisms, m.p. 117–118°, giving with sulfuric acid a deep green coloration.

Anal. Calc'd for $C_{22}H_{25}NO_2$: N, 4.1. Found: N, 4.2.

n-Octanoyl-9-ethylcarbazole (VI). Prepared from 9-ethylcarbazole (10 g.) *n*-octanoyl chloride (10 g.) and aluminum chloride (10 g.) in benzene as in the previous example; it had b.p. 315–320° at 13 mm., and crystallized from ethanol or acetone in fine colorless glinting prisms, m.p. 83°.

Anal. Calc'd for $C_{22}H_{27}NO$: N, 4.3. Found: N, 4.5.

Recrystallization of the higher-boiling fraction from ethanol gave 0.5 g. of colorless needles melting over a wide range, and believed to be impure 3,6-di-*n*-octanoyl-9-ethylcarbazole.

Phenacetylation of 9-ethylcarbazole. To an ice-cooled solution of 20 g. of 9-ethylcarbazole and 20 g. of phenacetyl chloride in 200 ml. of carbon disulfide was added 20 g. of aluminum chloride; after six hours at room temperature, the mixture was poured onto ice; the solid portion was washed with water, dried, and recrystallized from benzene, giving 12.5 g. of *3,6-diphenacetyl-9-ethylcarbazole* (XX) in the form of fine colorless needles, m.p. 160°. Sulfuric acid gave a yellow-green halochromic coloration.

Anal. Calc'd for $C_{30}H_{25}NO_2$: N, 3.2. Found: N, 3.5.

The carbon disulfide layer was washed with alkaline water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 8 g. of *3-phenacetyl-9-ethylcarbazole* (VII), b.p. 335–340° at 20 mm.; after crystallization from ethanol this formed fine colorless prisms, m.p. 105°, giving with sulfuric acid a brown-yellow coloration which rapidly turned leaf-green.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.4. Found: N, 4.5.

3,6-Di-(β-phenylethyl)-9-ethylcarbazole (XXI). The ketone XX (10 g.) reduced in the usual way with amalgamated zinc and hydrochloric acid for three weeks, yielded 5 g. of compound XXI, b.p. 350–355° at 13 mm., which crystallized from ethanol in colorless, lustrous leaflets m.p. 112°, giving with sulfuric acid yellow-green coloration.

Anal. Calc'd for $C_{30}H_{29}N$: N, 3.4. Found: N, 3.1.

α,β-Diphenyl-β-(9-ethylcarbazol-3-yl)ethylene (XIV). To a solution of benzylmagnesium chloride made up from 13 g. of benzyl chloride and 2.5 g. of magnesium in anhydrous ether, 8 g. of 3-benzoyl-9-ethylcarbazole [prepared according to (8)] dissolved in several ml. of ether was added; the mixture was refluxed for 30 minutes, cooled, and decomposed with ice-cooled dilute sulfuric acid. The organic layer was washed with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 8 g. of the ethylene compound (XIV), b.p. 350–355° at 17 mm. (no decomposition), which gave with sulfuric acid a deep cherry-red coloration.

Anal. Calc'd for $C_{28}H_{23}N$: N, 3.7. Found: N, 3.6.

This substance solidified after some standing in ethanol, and crystallized from the latter solvent in the form of yellowish prisms which jellified *circa* 70°; this jelly liquefied around 100°. This behavior might be attributed to the presence of two stereoisomers.

3-Anisoyl-9-ethylcarbazole (VIII). An ice-cooled, well stirred solution of 20 g. of 9-ethylcarbazole and 19 g. of anisoyl chloride in 200 ml. of benzene was treated with 15 g. of aluminum chloride in small portions, and then kept for 16 hours at room temperature. On vacuum-distillation of the reaction product, 22 g. of ketone (VIII), b.p. *circa* 345° at 25 mm. was obtained; recrystallization from benzene gave glinting, colorless needles m.p. 154°,

sparingly soluble in ethanol, and forming an unstable orange-red addition-compound with picric acid.

Anal. Calc'd for $C_{22}H_{19}NO_2$: N, 4.2. Found: N, 4.1.

α-Phenyl-β-anisyl-β-(9-ethylcarbazol-3-yl)ethylene (XV). Prepared from the above ketone (10 g.) and benzylmagnesium chloride (made from 11 g. of benzyl chloride and 2.5 g. of magnesium) as for compound XIV; on vacuum-distillation, 12 g. of a thick, pale-yellow jelly b.p. 355–360° at 17 mm. was obtained which gave with sulfuric acid a deep lilac coloration. This substance solidified on long standing in ethanol, and crystallized from the latter solvent in fine yellowish needles which gelled at 80–85°, with total liquefication above 100°. As in the case of compound (XIV), this might be due to stereoisomerism.

Anal. Calc'd for $C_{29}H_{25}NO$: N, 3.5. Found: N, 3.3.

9-Ethylcarbazole-3-carboxylic acid (XII). A solution of 3-acetyl-9-ethylcarbazole in dioxane was stirred with an aqueous solution of sodium hypobromite made from 27 g. of sodium hydroxide (dissolved in 80 ml. of water), 14 ml. of bromine, and 100 g. of ice. After some gentle heating on a water-bath, the mixture was left overnight, the bromoform removed, and the filtered aqueous layer acidified with dilute hydrochloric acid. The precipitate was purified by solution in aqueous soda and reacidification. Recrystallization from acetic acid gave 16 g. of pale yellow, microscopic needles m.p. 225° (sublimes above 213°) which gave a greenish-blue coloration with sulfuric acid. Literature m.p. 226° Treatment with an excess of thionyl chloride yielded a solid *acid chloride* which reacted with ice-cooled conc'd ammonia to give *9-ethylcarbazole-3-carboxamide* (XIII), which from ethanol gave cream-yellow needles darkening above 192°, and melting around 222°.

Anal. Calc'd for $C_{15}H_{14}N_2O$: N, 11.7. Found: N, 11.9.

The *anilide* and the *p-toluidide*, prepared from the acid chloride and the corresponding amines in pyridine medium, both formed from ethanol cream-yellow microcrystalline powders melting over a wide range.

6-Bromo-9-ethylcarbazole-3-carboxylic acid (XXII). A suspension of 4 g. of the above acid in acetic acid was treated with a solution of 2.8 g. of bromine in acetic acid at room temperature; the mixture was left overnight, diluted with water, the precipitate collected, and recrystallized from acetic acid; an almost quantitative yield of the bromo-acid (XXII) was obtained in the form of a yellowish, microcrystalline powder m.p. 240–242° (decomp.) which gave a faint leaf-green coloration with sulfuric acid, and a solid acid chloride with thionyl chloride.

Anal. Calc'd for $C_{15}H_{12}BrNO_2$: N, 4.4. Found: N, 4.1.

9-Ethylcarbazole-3,6-dicarboxylic acid (XXIII). This acid (6.5 g.) was obtained by oxidizing 3,6-diacetyl-9-ethylcarbazole (7.5 g.) with sodium hypobromite (made from 18 g. of sodium hydroxide and 9 ml. of bromine) in the presence of dioxane in the usual way. It crystallized from a large quantity of acetic acid in microscopic cream-yellow needles m.p. > 330°, giving with sulfuric acid a jade-green coloration. Literature m.p. > 320°.

3-Acetamido-9-ethylcarbazole (X). The *oxime* of 3-acetyl-9-ethylcarbazole (20 g.), prepared by refluxing the ketone (18.5 g.) with hydroxylamine hydrochloride (16 g.) and sodium carbonate (10 g.) in aqueous ethanol, crystallized from methanol in colorless leaflets, m.p. 175–176° giving a transient green coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{16}N_2O$: N, 11.1. Found: N, 11.2.

Finely powdered phosphorus pentachloride (17 g.) was stirred into an ice-cooled suspension of the oxime (19 g.) in anhydrous ether; stirring was continued for some minutes at room temperature, and the mixture was then poured onto ice. The solid precipitate was filtered off, thoroughly washed with an aqueous solution of sodium carbonate and then with water, dried, and recrystallized twice from a mixture of ethanol and benzene. Yield, 12 g. of glinting, colorless prisms m.p. 203–204°, which reddened on exposure to air, and gave a deep greenish-blue coloration with sulfuric acid. Lindemann (17) gives m.p. 190°.

Anal. Calc'd for $C_{16}H_{16}N_2O$: N, 11.1. Found: N, 10.8.

Heating the *amide* with conc'd hydrochloric acid for three hours yielded the sparingly soluble *3-amino-9-ethylcarbazole hydrochloride* from which, on treatment with ammonia

the free *amine* was obtained; this gave with 2,3-dichloro-1,4-naphthoquinone (14) a violet-black compound which gave deep red solutions in acetic acid.

3,6-Diacetyl-9-ethylcarbazole dioxime. This compound, prepared from 3,6-diacetyl-9-ethylcarbazole and hydroxylamine in the usual way, formed a colorless microcrystalline powder, m.p. 230–232° (decomp.) from ethanol.

Anal. Calc'd for $C_{18}H_{19}N_3O_2$: N, 13.6. Found: N, 13.3.

N-9-Ethylcarbazol-3-ylpropionamide (XI). The *oxime* of 3-propionyl-9-ethylcarbazole prepared as above, crystallized from ethanol in fine colorless needles, m.p. 137–138°.

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.5. Found: N, 10.4.

The Beckman rearrangement gave *N-9-ethylcarbazol-3-ylpropionamide* in the form of long, glinting colorless needles (from ethanol) m.p. 172°, giving a deep blue coloration with sulfuric acid, and a deep red picrate.

Anal. Calc'd for $C_{17}H_{18}N_2O$: N, 10.5. Found: 10.2.

3-n-Octanoyl-9-ethylcarbazole oxime. Prepared as above, it formed lustrous, silky colorless needles, m.p. 130° from ethanol.

Anal. Calc'd for $C_{22}H_{28}N_2O$: N, 8.3. Found: N, 8.1.

3-ω-Chloroacetyl-9-ethylcarbazole (IX). Prepared in the usual way from 9-ethylcarbazole (30 g.), chloroacetyl chloride (20 g.), and aluminum chloride (21 g.) in benzene, it was isolated by vacuum-distillation (b.p. *circa* 280–285° at 2 mm.), and formed long, glistening yellow-tinged needles, m.p. 115–116° (yield, 7 g.) from ethanol.

Anal. Calc'd for $C_{16}H_{14}ClNO$: N, 5.1. Found: N, 5.0.

2-(9'-Ethylcarbazol-3'-yl)pyrrocoline (XXIV). The chloroacetyl compound (1 g.) and 5 g. of anhydrous α-picoline were gently refluxed for three hours. After cooling, dry ether was added, the insoluble quaternary adduct dissolved in hot water without further purification, and sodium bicarbonate added to this solution. After a few minutes boiling, the pyrrocoline precipitated; it formed long, silky glistening colorless needles, m.p. 198° from benzene giving with sulfuric acid a deep blue coloration, and with hydrogen chloride a yellow one.

Anal. Calc'd for $C_{21}H_{18}N_2$: N, 9.3. Found: N, 9.0.

2-(3'-Chloro-9'-ethylcarbazol-3'-yl)cinchoninic acid (XXV). A mixture of 2 g. of 3-chloro-6-acetyl-9-ethylcarbazole, 1.1 g. of isatin, and 1.3 g. of potassium hydroxide dissolved in 2 ml. of water and 15 ml. of ethanol was refluxed for two days; the reaction product was diluted with water, and the neutral impurities removed by extraction with ether. The aqueous layer on acidification gave an orange-yellow precipitate (2.5 g.) which formed orange-yellow microcrystals m.p. *circa* 228–233° (decomp.) from a large amount of acetic acid.

Anal. Calc'd for $C_{24}H_{17}ClN_2O_2$: N, 6.9. Found: N, 7.0.

This substance, on heating *in vacuo* above its m.p. and purification of the resulting base through the *picrate*, gave *2-(3'-chloro-9'-ethylcarbazol-3'-yl)quinoline* in the form of faintly yellow needles (from a mixture of ethanol and benzene) m.p. 161°.

Anal. Calc'd for $C_{23}H_{17}ClN_2$: N, 7.8. Found: N, 7.5.

6-Bromo-2-(3'-chloro-9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVI). Prepared as above from 3 g. of 3-chloro-6-acetyl-9-ethylcarbazole, 2.5 g. of 5-bromoisatin, and 2 g. of potassium hydroxide (yield, 5.2 g.); crystallized from a large amount of acetic acid in microscopic orange needles melting with decomposition above 280°.

Anal. Calc'd for $C_{24}H_{16}BrClN_2O_2$: N, 5.8. Found: N, 5.5.

6-Bromo-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVII). Obtained in quantitative yield from 3-acetyl-9-ethylcarbazole (4 g.), 5-bromoisatin (4 g.), and potassium hydroxide (3 g.); from a large amount of acetic acid it gave orange-yellow microscopic needles, m.p. *circa* 272–275°.

Anal. Calc'd for $C_{24}H_{17}BrN_2O_2$: N, 6.3. Found: N, 6.0.

3-Methyl-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXVIII). From 4 g. of 3-propionyl-9-ethylcarbazole, 2.5 g. of isatin, and 3 g. of potassium hydroxide; from acetic acid it gave fine bright yellow needles (4 g.) m.p. > 310°.

Anal. Calc'd for $C_{25}H_{20}N_2O_2$: N, 7.3. Found: N, 7.2.

6-Bromo-3-methyl-2-(9'-ethylcarbazol-3'-yl)cinchoninic acid (XXIX). From 4 g. of 3-

propionyl-9-ethylcarbazole, 4 g. of 5-bromoisatin, and 3 g. of potassium hydroxide, there was obtained 5 g. of an acid which gave fine bright yellow microcrystals, m.p. 310° from nitrobenzene.

Anal. Calc'd for $C_{25}H_{19}BrN_2O_2$: N, 6.1. Found: N, 6.0.

SUMMARY

Several derivatives of 9-ethylcarbazole having substituents in the 3- and 6-positions have been prepared for biological investigation.

PARIS V, FRANCE

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. IV. SYNTHESIS OF 2,3-BENZOCARBAZOLES AND OF INDENOINDOLES[1]

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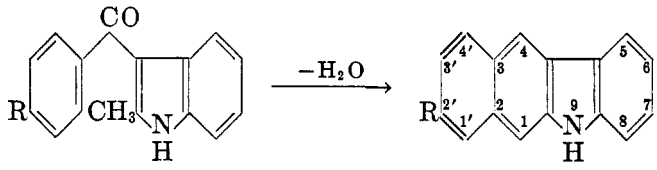
(Received August 1, 1949)

Although the Elbs reaction has been extensively used for syntheses of polycyclic hydrocarbons (1), it has hitherto rarely been applied to heterocyclic ketones with nitrogen-containing rings. To our knowledge, the only work dealing with this subject is that of Fieser and Hershberg (2), who prepared 20-methyl-4-azacholanthrene and 4′-aza-1,2-benzanthracene through pyrolysis of the suitable quinoline ketones.

We have now found that the Elbs reaction can also be performed on certain *o*-methyl ketones belonging to the indole series. Thus, 2-methyl-3-benzoylindole (I) was found to lose water rapidly on refluxing, and yielded small amounts of



I; R = H
III; R = CH_3

II; R = H
IV; R = CH_3

2,3-benzocarbazole (II). The latter is an important component of crude anthracene from coal-tar, and had previously been synthesized in various ways: (a) by thermal dehydrogenation of phenyl-β-naphthylamine in a red-hot tube (3); (b) as a by-product in the Graebe-Ullmann synthesis of 1,2-benzocarbazole from "phenylaziminonaphthalene" (4); and (c) by the Bucherer reaction (5), starting from 2-aminonaphthalene-1-sulfonic acid and phenylhydrazine.

Although the yield of 2,3-benzocarbazole obtained in our synthesis was definitely inferior to those recorded for the above methods (owing to the instability of indole ketones towards heat), it nevertheless provides a very quick procedure for the preparation of small quantities of compound II.

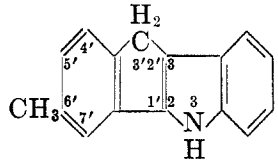
The Elbs reaction was extended to the preparation of certain homologs of 2,3-benzocarbazole which would not be readily accessible through other methods. Thus, 2-methyl-3-*p*-toluoylindole (III) could be cyclized, although in very poor yield, to 2′-methyl-2,3-benzocarbazole (IV), the methyl group being retained in the course of pyrolysis. It may be noted that the m.p. of 2′-methyl-2,3-benzocarbazole is somewhat higher than that of 2,3-benzocarbazole, a fact which is parallel to a similar difference between 2-methylcarbazole and carbazole itself.

Ketones (I) and (III) were prepared from the organomagnesium derivative

[1] For Part III, see Buu-Hoï and Royer, *J. Org. Chem.*, preceding article.

of 2-methylindole and the requisite acid chlorides in ether medium (6). 2-Methyl-3-*p*-ethylbenzoylindole, 2-methyl-3-α-naphthoylindole, 2-methyl-3-β-naphthoylindole, and 2-methyl-3-anisoylindole were also prepared in a similar way, but no pure carbazoles have yet been separated from their pyrolysis products.

A substance whose molecular form closely resembles that of 2′-methyl-2,3-



(V)

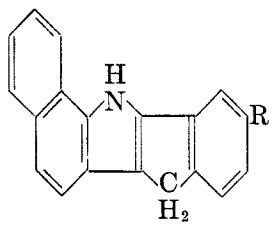
benzocarbazole is 6′-methyl-1′,2′:2,3-indenoindole (V), which we prepared by indolization of 5-methylindan-1-one phenylhydrazone; compound (V) is a homolog of indeno-1′2′:2,3-indole, already synthesized by Hausmann (7). From indan-1-one and 5-methylindan-1-one on the one hand, and α- and β-naphthylhydrazine on the other, the following substances were similarly prepared:

1′,2′:2,3-indeno(6,7-benzoindole) (VI);

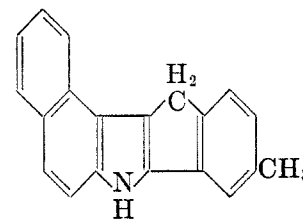
6′-methyl-1′,2′:2,3-indeno(6,7-benzoindole) (VII);

1′,2′:2,3-indeno(4,5-benzoindole) (VIII); and

6′-methyl-1′,2′:2,3-indeno(4,5-benzoindole) (IX).



VI; R = H
VII; R = CH_3



VIII; R = H
IX; R = CH_3

This group of compounds has some biological significance by virtue of its structural connection with the carcinogenic dibenzocarbazoles.

Acknowledgment. This work was carried out under a grant from the U. S. Public Health Service (Federal Security Agency); the authors convey their gratitude to the authorities concerned, and also to Professor L. F. Fieser for his kind encouragement.

EXPERIMENTAL

2,3-Benzocarbazole (II). 2-Methyl-3-benzoylindole was prepared as follows: to a solution of ethylmagnesium bromide (made from 2.4 g. of magnesium and 13 g. of ethyl bromide) in anhydrous ether (100 ml.), 13.1 g. of 2-methylindole (dissolved in ether) was added in small portions with frequent shaking. The mixture was then refluxed for thirty minutes, cooled in ice-water, and 14.1 g. of benzoyl chloride (dissolved in ether) was added dropwise. After one hour's refluxing, it was treated with a cold aqueous solution of ammonium chloride and the ether removed by evaporation. The solid precipitate was washed thoroughly with an

aqueous solution of sodium carbonate, then with water, dried, and crystallized from methanol; yield, 12 g. of ketone (I), m.p. 181°.

When 10 g. of this compound was gently boiled at normal pressure for ten minutes in a Claisen flask with a Vigreux column evolution of water and extensive carbonization was soon observed. The volatile fractions were then distilled, and the distillate treated with a large volume of methanol, which dissolved the recovered ketone and left a residue which was recrystallized from benzene. 2,3-Benzocarbazole was thus obtained in the form of grey-tinged prisms m.p. 330–331°, giving a yellow coloration with sulfuric acid (the literature indicates m.p. 330°, for this compound). The yield was 0.5 g. (*circa* 5%), barely increased by addition of zinc powder.

2-Methyl-3-p-toluoylindole (III). Obtained as above from *p*-toluoyl chloride (15.5 g.), 2-methylindole (13 g.), and ethylmagnesium bromide; from methanol it formed rose-tinged needles m.p. 210° (sublimation above 180°), giving a violet picrate; yield: 15 g.

Anal. Calc'd for $C_{17}H_{15}NO$: N, 5.6. Found: N, 5.4.

2'-Methyl-2,3-benzocarbazole (IV). Pyrolysis of the foregoing ketone (10 g.), performed as above, gave 2'-methyl-2,3-benzocarbazole in the form of almost colorless needles m.p. 343°, giving a yellow coloration with sulfuric acid (yield, 0.6 g.).

Anal. Calc'd for $C_{17}H_{14}N$: N, 6.0. Found: N, 5.8.

2-Methyl-3-p-ethylbenzoylindole. Obtained from *p*-ethylbenzoyl chloride (11.6 g.), 2-methylindole (10 g.), and ethylmagnesium bromide in the usual way. Yield, 8 g. of a ketone crystallizing from methanol in rose-tinged needles, m.p. 204°.

Anal. Calc'd for $C_{18}H_{18}NO$: N, 5.3. Found: N, 5.2.

2-Methyl-3-α-naphthoylindole. Obtained from α-naphthoyl chloride (19.3 g.), 2-methylindole (13.1 g.), and ethylmagnesium bromide in the form of colorless prisms (from methanol), m.p. 209°, giving with sulfuric acid an orange coloration (yield, 20 g.).

Anal. Calc'd for $C_{20}H_{15}NO$: N, 4.9. Found: N, 4.6.

2-Methyl-3-β-naphthoylindole. From 19.3 g. of β-naphthoyl chloride and 13.1 g. of 2-methylindole, there was obtained 14 g. of a ketone crystallizing from methanol in colorless needles, sparingly soluble in ether, m.p. 225°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{15}NO$: N, 4.9. Found: N, 4.9.

2-Methyl-3-anisoylindole. From 1.7 g. of anisoyl chloride and 1.3 g. of 2-methylindole, there was obtained 0.8 g. of a ketone crystallizing from benzene in colorless needles, soluble in ether, m.p. 206°.

Anal. Calc'd for $C_{17}H_{15}NO_2$: N, 5.2. Found: N, 5.0.

The above four ketones underwent extensive carbonization and loss of water on boiling.

6'-Methyl-1',2':2,3-indenoindole (V). 5-Methylindan-1-one (2 g.) and 2 g. of phenylhydrazine were heated at 120–130° until steam ceased to evolve; 20 ml. of acetic acid saturated with hydrogen chloride was added, the mixture was brought to the boil, and then poured into water. The solid precipitate was collected, washed, and recrystallized from ethanol, giving colorless needles, m.p. 206–207° (yield, 2 g.).

Anal. Calc'd for $C_{16}H_{13}N$: N, 6.4. Found: N, 6.3.

1',2':2,3-Indeno(6,7-benzoindole) (VI). A mixture of 1.5 g. of indan-1-one 3 g. of α-naphthylhydrazine hydrochloride, 2.5 g. of sodium acetate, and 50 ml. of ethanol was refluxed two hours, then poured into water; the precipitate was filtered off and treated with acetic acid saturated with hydrogen chloride as above. The indole (1.5 g.) crystallized from benzene in colorless prisms, m.p. 234°.

Anal. Calc'd for $C_{19}H_{13}N$: N, 6.1. Found: N, 6.0.

6'-Methyl-1',2':2,3-indeno(6,7-benzoindole) (VII). Similarly obtained from 5-methylindan-1-one (1.5 g.) and α-naphthylhydrazine hydrochloride (2.9 g.); crystallized from benzene in almost colorless needles, m.p. 223–224° (yield, 1.2 g.).

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.3.

1',2':2,3-Indeno(4,5-benzoindole) (VIII). This compound (1.2 g.), obtained from 1.5 g. of indan-1-one and 3 g. of β-naphthylhydrazine hydrochloride, formed colorless needles, m.p. 157–158° from benzene.

Anal. Calc'd for $C_{19}H_{13}N$: N, 6.1. Found: N, 5.8.

6'-Methyl-1',2':2,3-indeno(4,5-benzoindole) (IX). From 1.5 g. of 5-methylindan-1-one and 2.9 g. of β-naphthylhydrazine hydrochloride there was obtained 1.2 g. of a substance forming yellowish needles, m.p. 230° from benzene.

Anal. Calc'd for $C_{20}H_{15}N$: N, 5.2. Found: N, 5.1.

SUMMARY

1. Certain ketones belonging to the indole series are shown to be susceptible to the Elbs reaction. 2,3-Benzocarbazole and one of its methyl homologs have been obtained, although in poor yields, by that means.

2. Some new indenoindoles structurally related to 2,3-benzocarbazole have been prepared.

PARIS V, FRANCE

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. XII. SYNTHESES IN THE METHYLOCTADECANOIC ACID SERIES

JAMES CASON, ELDON L. PIPPEN,[1] PHYLLIS B. TAYLOR,[2] AND W. ROBERT WINANS[3]

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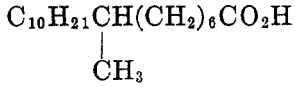
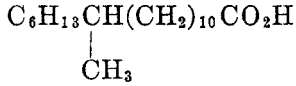
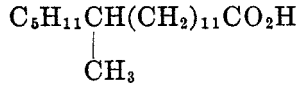
In continuation of the program of synthesis of all the monomethyloctadecanoic acids, four additional members of this series have been prepared. These are 8-methyl- (I), 12-methyl- (II), 13-methyl- (III), and 14-methyl-octadecanoic acid (IV).



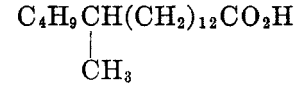
I



II



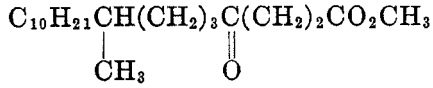
III



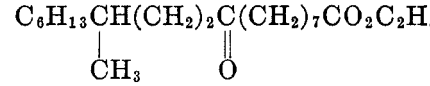
IV

Of these, the 14-methyl isomer has previously been prepared by Ställberg-Stenhagen (1), and the properties of our acid and amide are in good agreement with those reported.

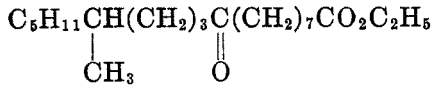
These acids were prepared by Clemmensen or Wolff-Kishner reduction of the keto esters V–VIII, and the keto esters were prepared by the previously-used (2)



V



VI



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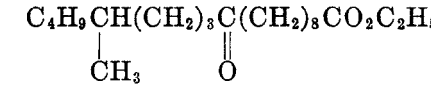

VIII

reaction between a dialkylcadmium reagent and an ester acid chloride. 1-Bromo-4-methyletradecane, used for the preparation of keto ester V, was available from previous work (3). 1-Bromo-4-methylnonane and 1-bromo-4-methyloctane, for the preparation of esters VII and VIII, were prepared from the corresponding alcohols which have been previously reported (4). 1-Chloro-4-methylnonane (4) gave about the same yield in the cadmium reaction as was obtained with the

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corresponding bromide. This is in contrast with the somewhat lower yield obtained with the chloride in the case of the *n*-butyl halides (5).

The starting point for the preparation of 1-bromo-3-methylnonane, required for synthesis of ester VI, was a Reformatsky reaction between 2-octanone and ethyl bromoacetate. The resultant ethyl 3-hydroxy-3-methylnonanoate was dehydrated, then hydrogenated at high pressure with copper chromite catalyst to yield 3-methyl-1-nonanol, and this alcohol was converted to the desired bromide.

TABLE I

KETO ESTERS

ESTER	B.P., °C.	MM.	n_D^{20}	YIELD,[a] %	ANALYSIS[b]	
					C	H
V	193–195	2.5	1.4520	38	73.21	11.52
VI	216–220	5	[c]	43		
VII	198–202	3	1.4505	46	73.74	12.37
VIII	189–190	2	1.4506	54	74.06	11.46

[a] Based on alkyl halide, the more valuable reagent. [b] Calc'd for methyl ester, $C_{20}H_{38}O_3$: C, 73.57; H, 11.73. Calc'd for ethyl ester, $C_{21}H_{40}O_3$: C, 74.07; H, 11.84. [c] Not characterized but reduced directly to the desired acid.

TABLE II

KETO ACIDS

KETO ACID FROM	SOLVENT FOR CRYST.	M.P., °C.	ANALYSIS[a]	
			C	H
Ester V	acetone	65.7–66.3	72.91	11.51
Ester VII	hexane	40.2–40.6	73.39	11.98
Ester VIII	methanol	37.4–40.4[b]		

[a] Calc'd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.61.

[b] Re-m.p. 39.2–40.0°.

EXPERIMENTAL

All melting points are corrected, while all boiling points are uncorrected. Analyses are by the Microanalytical Division of the Department of Chemistry of the University of California. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with tantalum wire spiral and partial reflux head.

Ester acid chlorides were prepared by methods previously described (2), except that thionyl chloride was used instead of phosphorus pentachloride.

Branched-chain alkyl bromides were prepared by the usual procedure (6) from the alcohols with anhydrous hydrogen bromide taken from a cylinder. 1-Bromo-3-methylnonane (7, 8), b.p. 121–122° (25 mm.), yield 86%. 1-Bromo-4-methylnonane (7), b.p. 113–114° (18 mm.), n_D^{28} 1.4538, yield 88%. 1-Bromo-4-methyloctane (7), b.p. 88–90° (12 mm.), n_D^{27} 1.4528, yield 84%.

3-Methyl-1-nonanol was prepared (with the assistance of Raylene E. Adams) by a method involving no secondary halides, in contrast to previously-reported methods (7, 8). To 18.3 g. (0.28 mole) of zinc foil (in small rolls), stirred and heated under reflux in 100 ml. of

dry thiophene-free benzene, there was added during about one hour a mixture of 25.6 g. (0.2 mole) of redistilled 2-octanone, 50.1 g. (0.3 mole) of ethyl bromoacetate, and 100 ml.

TABLE III

REDUCTION OF KETO ESTERS

ESTER REDUCED	REDUCED ESTER			
	YIELD,[a] %	B.P., °C.	MM.	n_D^{20}
V	36[b,c]	196–199	6	1.4480
VI	73[d]	183–185	2	1.4463
VII	66[b]	174–176	2	1.4459
VIII	88[d]	190–195	4	

[a] Esters V, VI, and VII were reduced by the modified Wolff-Kishner method (12), ester VIII by the modified Clemmensen method (10). [b] Methyl ester. [c] The low yields obtained in reduction of γ-keto esters is being further investigated, and this work will be reported in a later paper in this series. The modified Clemmensen reduction (10) fails almost completely with a γ-keto ester (14). [d] Ethyl ester.

TABLE IV

BRANCHED-CHAIN ACIDS AND DERIVATIVES

ACID	M.P., °C.	M.P., °C. OF AMIDE	M.P., °C. OF TRIBROMOANILIDE
I	33.9–34.7	71.0–72.6[a]	96.2–96.6
		69.0	
II	27.6–28.2[a]	86.0–88.2[b]	94.2–95.2
	36.6–37.1	87.5	
III	29.4–31.6	77.2–78.7	98.2–99.6
IV	37.2–37.6	79.3–79.6	101.0–101.6
IV	36.3–36.5	79.0–79.3	
Ref. (1)			

[a] High-melting form crystallizes from acetone, low-melting form crystallizes from the melt. [b] Crystals obtained from solvents exhibit the broad m.p. If solidified melt is placed immediately in bath at 86.8° or higher, it re-melts completely at once. If solidified melt is placed in bath at 85°, it re-melts at 87.5°.

TABLE V

ANALYSES OF ACIDS AND DERIVATIVES

ISOMER	ACID			AMIDE			TRIBROMOANILIDE		
	C	H	EQ. WT.	C	H	N	C	H	N
I	76.42	12.81	301.4	77.07	13.16				2.26
II	76.64	13.01	299.0	76.69	13.18				2.28
III	76.79	12.65	297.9			4.68			2.58
IV			297.7				49.14	6.50	
Calc'd	76.45	12.83	298.5	76.71	13.21	4.71	49.21	6.60	2.29

of benzene. After heating under reflux with stirring for an additional hour, the mixture was treated with ice and sulfuric acid; then the organic material was extracted with benzene. The extract was washed, the solvent was removed by distillation, and the residue was

heated with a few crystals of iodine for about one hour at 190–200°. Distillation from a Claisen flask gave a 55–60% yield of ethyl 3-methylnonenoate, b.p. 100–105° (10 mm.).

The unsaturated ester was immediately hydrogenated at high pressure and 250° with a copper chromite catalyst (9). In a representative run using 73 g. of ester and 22 g. of catalyst, the initial pressure at 20° was 3490 p.s.i., the maximum pressure reached at 250° was 4700 p.s.i., and hydrogenation was complete in seven hours. Distillation of the product gave an 86% yield, b.p. 108–109° (11 mm.)

Keto esters were prepared by the general procedure described previously (2), using a ratio of 1 mole of bromide, 1 atom of magnesium, 0.54 mole of cadmium chloride, and 0.8 mole of ester acid chloride. The results are found in Table I. These yields are probably not maximum, in view of results obtained more recently in this laboratory with higher molecular weight dialkylcadmium reagents. These investigations will be reported in a later paper in this series.

The keto acids were obtained from esters V, VII, and VIII by saponification in alcoholic potassium hydroxide. Their properties are included in Table II.

Reduction of keto esters. The data in Table III show that the modified Clemmensen reduction (10) is capable of at least as good yields as the modified Wolff-Kishner reduction (11), but the modified Wolff-Kishner method is faster and probably less laborious. The yield of crude acid from the Wolff-Kishner reduction was usually nearly quantitative, as reported by other workers (13), but esterification of the crude acid and distillation through a column leaves considerable residue, and the yield of pure ester is rarely greater than 80%.

Branched-chain acids were obtained by saponification of the pure esters in alcoholic potassium hydroxide, and crystallization of the acids from acetone until a constant melting point was reached (usually two or three crystallizations).

Amides were prepared by the method previously described (15), and were crystallized from acetone, methanol, or 95% ethanol.

Tribromoanilides were made by the previously-described method (16) except that acid chlorides were prepared with thionyl chloride. Crystallization was from 95% ethanol.

Data on the acids and derivatives are found in Tables IV and V.

SUMMARY

There is reported the preparation of 8-methyl-, 12-methyl-, 13-methyl-, and 14-methyloctadecanoic acid, by reduction of the keto ester obtained from the appropriate ester acid chloride and dialkycadmium reagent.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. XIII. PREPARATION OF BRANCHED AND NORMAL ACIDS FOR USE IN THE STUDY OF MELTING POINTS OF BINARY MIXTURES. COMPLETION OF THE METHYLOCTADECANOIC ACID SERIES

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The program of synthesizing all the monomethyloctadecanoic acids has been completed by preparation of 5-methyl- (I), 6-methyl- (II), 7-methyl- (III), 9-methyl- (IV), and 11-methyl-octadecanoic acid (V).

$$\begin{array}{rl} & \text{I R = } n\text{-tridecyl, n = 3} \\ & \text{II R = } n\text{-dodecyl, n = 4} \\ \mathrm{RCH(CH_2)_nCO_2H} & \text{III R = } n\text{-hendecyl, n = 5} \\ \mid & \text{IV R = } n\text{-nonyl, n = 7} \\ \mathrm{CH_3} & \text{V R = } n\text{-heptyl, n = 9} \end{array}$$

These isomers were prepared from the approprixte 1-chloro-4-methylalkanes, which were obtained by the recently-developed procedure (1) starting with the reaction between a Grignard reagent and 5-chloro-2-pentanone. The product of the Grignard reaction was allowed to react with acetic anhydride to yield a 1-chloro-4-acetoxyalkane. Removal of the elements of acetic acid, followed by catalytic hydrogenation yielded the desired branched-chain halide. This method has proved to be the most convenient yet developed for preparation of branched-chain alkyl halides from straight-chain starting materials. The branched-chain chlorides prepared for the present syntheses are represented by formulas VI–X, and the *n*-alkyl bromides required for their preparation are those containing the alkyl groups represented by R in these formulas.

$$\begin{array}{rl} & \text{VI R = } n\text{-tridecyl} \\ & \text{VII R = } n\text{-dodecyl} \\ \mathrm{RCH(CH_2)_3Cl} & \text{VIII R = } n\text{-hendecyl} \\ \mid & \text{IX R = } n\text{-nonyl} \\ \mathrm{CH_3} & \text{X R = } n\text{-heptyl} \end{array}$$

For preparation of acids I–III, there were used well-established methods for extending a chain by a few carbons. Use of the nitrile synthesis on 1-chloro-4-methylheptadecane (VI) gave 5-methyloctadecanoic acid. A high-molecular-weight aliphatic Grignard reagent gives a poor yield of acid by reaction with solid carbon dioxide. Reasonably good yields may be obtained conveniently by reaction with carbon dioxide under pressure, but much higher yields (often 90%) may be obtained by the nitrile synthesis; and the latter method has been used in the present work for most of the preparations of acids from alkyl halides.

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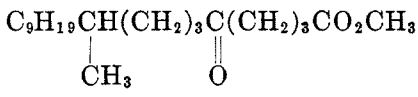
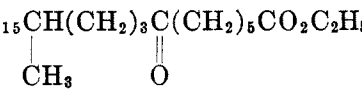
6-Methyloctadecanoic acid (II) was prepared from chloride VII by use of the malonic ester synthesis, and 7-methyloctadecanoic acid (III) was prepared from chloride VIII by two chain-extensions. 6-Methyl-1-heptadecanol was prepared by reaction of ethylene oxide with the Grignard reagent, and the corresponding bromide was converted to the desired acid, III, by use of the nitrile synthesis.

The longer chain-extensions required for isomers IV and V were accomplished by way of the keto esters XI and XII, prepared by the cadmium reaction so frequently used (2) in this work.



XI



XII

Reduction of these esters yielded the desired acids, IV and V. The 9-methyl isomer (IV) has previously been prepared by Ställberg-Stenhagen (3) using a different method of synthesis, and the properties of our acid and amide are in agreement with those reported.

In Figure 1 have been plotted the melting points of the *dl*-methyloctadecanoic acids and two of their derivatives, the amides and the 2,4,6-tribromoanilides. It is of interest that the curve through the melting points of the acids is a fairly regular line, with the exception of two points, with the minimum melting points occurring when the methyl group is near the middle of the chain. There is an uncertainty about which polymorph to consider for the three acids with methyl near the middle of the chain, but this does not affect the deduction concerning the general pattern of the melting points. In the case of the 9-methyl isomer, which falls above the regular curve, it will be noted that three adjacent isomers exist in polymorphic forms. It might be suspected that there is also a low-melting polymorph of the 9-methyl isomer, but all efforts have failed to detect such a polymorph. It might be mentioned that we were unable to prove definitely the existence of the low-melting polymorph of the 10-methyl isomer, and this form was reported by Ställberg-Stenhagen (3), but this investigator did not report a polymorph for the 9-isomer.

It will be noted that the melting points of the amides do not follow a regular pattern, but tend to fall in groups of three with nearly identical melting points. Furthermore, nearly half the isomeric amides have melting points near 80°, and it is apparent that the melting point of this derivative is less useful for characterization purposes than is the melting point of the acid. Not all polymorphic forms of the amides are indicated on the chart. Additional data are found in Table III, and in Table IV of Ref. 2.

In connection with this unusual pattern for the melting points of the amides, it should be mentioned that Weitkamp (4) has noted a periodic variation in the melting points of a homologous series of even-carbon isoaliphatic amides. Also, Velick (5) has reported a periodic sequence in the long crystal spacings of this same homologous series, and has discussed the possibility that these amides

possess a spiral chain configuration. A group of Swedish workers (6) has conducted an X-ray investigation of a homologous series of odd-carbon iso amides,

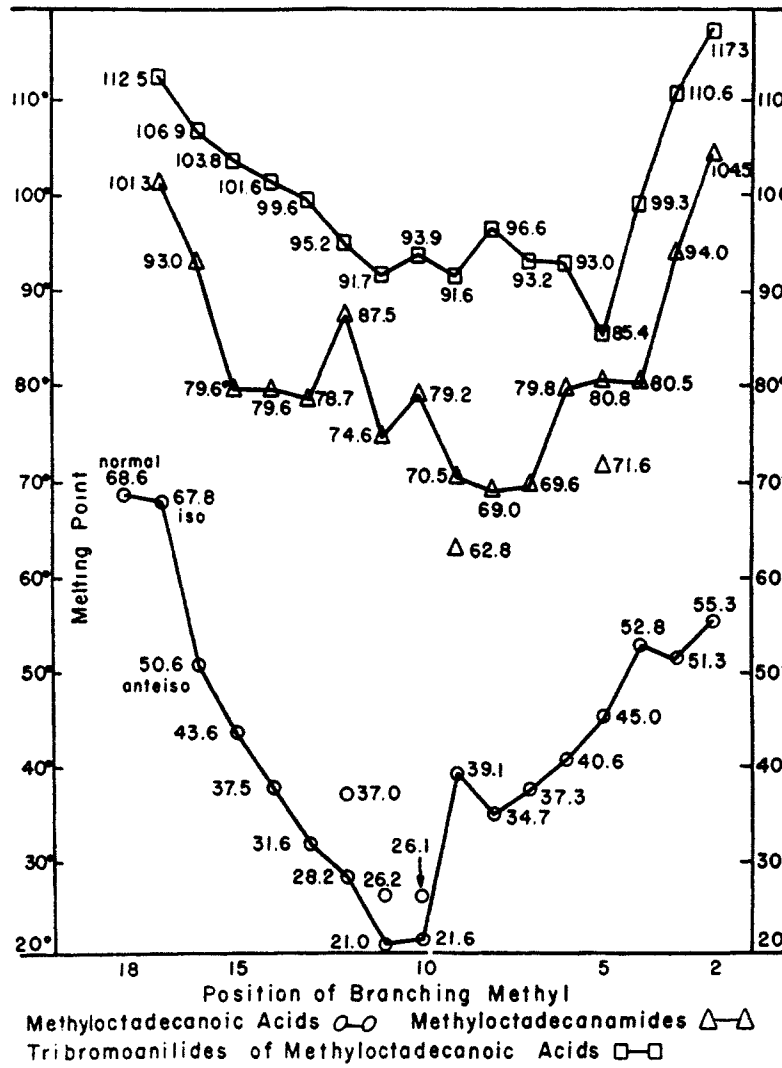


FIG. 1. MELTING POINTS OF THE METHYLOCTADECANOIC ACIDS, AMIDES, AND 2,4,6-TRIBROMOANILIDES. Data not presented in this paper were obtained from previous publications in this series, except for the low-melting polymorph of 10-methyloctadecanoic acid, obtained from Ref. 3. The points are connected by lines merely to add to clarity. In the case of polymorphs, it is not inferred that the lines connect similar crystal forms. No information concerning this matter has been sought.

as well as certain even-carbon iso amides. The latter workers found a variety of crystal structures in these amides, but stated that the evidence does not seem to support the hypothesis of a spiral chain configuration.

The melting points of the tribromoanilides decrease in a regular manner as the position of methyl approaches the center of the chain, but there is a group of six isomers with similar melting points. This derivative is more useful than the amide, and in relation to the acid has the advantage of high melting point and low solubility. Several of the tribromoanilides exhibited interesting polymorphism which is described in Table III. This behavior observed in a capillary melting point tube is presented for use in characterization of the compounds. A more careful study of the time-temperature curves obtained on freezing of larger samples is regarded as beyond the scope of this work, and not necessarily applicable to the objectives of the present investigation.

In connection with the validity of applying the observations in this series to monomethyl acids of different molecular weight, it is noteworthy that certain facts already known suggest that such an application has some validity. 12-Methyloctadecanoic acid is dimorphic (2), as is 12-methyltetracosanoic acid (7). Also, the 2,4,6-tribromoanilide of 6-methyloctadecanoic acid is definitely polymorphic, and the broad melting point of the tribromoanilide of 6-methyltetracosanoic acid (8) also suggests polymorphism. Further, the melting-point behavior of binary mixtures, as investigated by Weitkamp (4) and in the next paper of the present series, appears to depend on the position of branching and not on the molecular weight. In addition, molecular rotation of optical isomers (4) is a function of position of methyl in relation to the ends of the chain, and is nearly independent of molecular weight.

For use in the study of the melting points of binary mixtures, one additional branched-chain acid and several odd-carbon normal acids have been prepared. 16-Methylheptadecanoic (isostearic) acid was prepared *via* the 9-keto-16-methylheptadecanoic acid, hendecanoic acid was obtained by hydrogenation of undecylenic acid, and the other odd-carbon acids were prepared from the even-carbon alkyl bromides by the nitrile or the Grignard syntheses.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses are by the Microanalytical Division of the Department of Chemistry of the University of California. All distillations, unless otherwise specified, were through a half-meter Podbielniak type column with tantalum wire spiral and partial reflux head. All solid compounds were dried in a vacuum to constant weight, for analysis, and purification of the branched-chain acids was continued until the observed equivalent weights were in agreement with theory.

n-Alkyl halides, except tridecyl bromide, were distilled commercial grades or were prepared from the alcohol by the usual method (9), using hydrogen bromide gas from a cylinder.

Tridecyl bromide. To a stirred suspension of 66 g. (0.2 mole) of dried silver myristate (prepared from technical myristic acid) in 250 ml. of dried carbon tetrachloride, there was added during about ten minutes a dried solution of 32 g. (0.2 mole) of bromine in 20 ml. of carbon tetrachloride, the mixture being cooled in an ice-bath during the addition. After completion of the addition, the cooling bath was removed and stirring continued for about thirty minutes without heating, and finally with heating under reflux until evolution of carbon dioxide had ceased (about ten minutes). To the cooled reaction mixture was added 50 ml. of a 1 molar sodium carbonate solution and enough (about 1 ml.) 12 *N* sodium hydroxide to remove bromine. This mixture was stirred briefly, then 50 ml. of a 1 molar barium chloride solution was added and stirring continued for about ten minutes. The precipitate of

silver bromide and barium myristate was removed by suction filtration, and the residue remaining after removal of solvent from the filtrate was distilled in a Claisen flask to yield 37 g. (70%) of crude tridecyl bromide, b.p. 135–150° (5 mm.). This product contains a trace of hendecyl bromide and several per cent of pentadecyl bromide. Distillation through the column yields pure tridecyl bromide, b.p. 135–136° (4 mm.).

Ester acid chlorides were prepared from the dibasic acids by usual procedures (10).

1-Chloro-4-methylalkenes were prepared by the procedure described for 1-chloro-4-methylnonene, and the reaction proceeded as previously described (1) except that with the higher molecular weight compounds used in the present work a very heavy precipitate separated when the product of the Grignard reaction was treated with acetic anhydride. The mass was rendered stirrable by the addition of benzene (200 ml. for a 0.4-mole run), and the reaction completed as before.

The alkenes were hydrogenated immediately to *1-chloro-4-methylalkanes*, at room temperature and low pressure, using for each 0.1 mole of alkene 0.1 g. of commercial platinum oxide

TABLE I

1-CHLORO-4-METHYLALKANES

CHLORIDE SYNTHESIZED	CHLOROALKENE		CHLOROALKANE		OVER-ALL YIELD
	YIELD, %	B.P., °C. (MM.)	YIELD, %	B.P., °C. (MM.)	
VI	50	172–173 (4)	80	166–168 (2.4)	40
VII	71	160–161 (4)	87	160–161 (3.5)	61.5
VIII	64	152–154 (4)	89.5	153–154 (3.5)	57
IX	47	133–135 (5)	83	134–136 (5)	39
X	69	108–110 (8)	84	116–117 (10)	58

TABLE II

ANALYSES OF 1-CHLORO-4-METHYLALKANES

COMPOUND	$n^{20}D$	CALC'D		FOUND	
		C	H	C	H
VI	1.4540	74.82	12.91	74.84	12.53
VII	1.4528	74.27	12.83	75.03	12.71
VIII	1.4517	73.66	12.75	73.88	12.65

catalyst and a solvent consisting of 25 ml. of diethyl ether and 75 ml. of glacial acetic acid. The compounds were not sufficiently soluble in glacial acetic acid or ethanol. Hydrogenation was complete in twenty to forty minutes.

Data on these preparations are found in Table I. In order to make certain that these reactions had followed the same course as in the example previously described, three of the chloroalkanes were analyzed, and the data are found in Table II. In all distillations of the saturated chlorides, there was a small fore-run which was insoluble in concentrated sulfuric acid and probably consisted of the hydrocarbon resulting from hydrogenolysis at chlorine.

Methyl 5-methyloctadecanoate was prepared from 1-chloro-4-methylheptadecane (VI), by way of the nitrile, following a procedure essentially identical with that previously described (11) for ethyl nonadecanoate, except that four mole per cent of potassium iodide was added to the initial reaction mixture. The product boiled at 178–185° (3 mm.) and had n_D^{20} 1.4467.

Anal. Calc'd for $C_{20}H_{40}O_2$ C, 76.86; H, 12.90.

Found: C, 76.52; H, 13.02.

Methyl 6-methyloctadecanoate. Diethyl malonate was alkylated with 1-chloro-4-methyl-

hexadecane (VII), using potassium iodide as a catalyst, following the procedure previously described (12) for alkylation with chlorides, except that the alkylation was continued for twenty hours under reflux. The diethyl alkylmalonate obtained from the reaction was not distilled but was saponified directly with alcoholic potassium hydroxide. The resultant malonic acid was decarboxylated by heating for two hours at 180–190° at 60–90 mm., and the monocarboxylic acid was esterified by heating for two hours with twenty equivalents of methanol containing 10% sulfuric acid. The ester was obtained in 62% yield (based on chloride VII), b.p. 167–172° (2 mm.), n_D^{18} 1.4475.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.
Found: C, 77.20; H, 12.69.

6-Methyl-1-heptadecanol was prepared by the reaction of the Grignard reagent from 1-chloro-4-methylpentadecane (VIII) with 1.5 mole-equivalents of ethylene oxide which had been passed through a soda lime tube. The procedure was essentially identical with that which has been described (13) for the preparation of isononyl alcohol. In a run starting with 57 g. (0.22 mole) of chloride VIII, there was obtained 38.9 g. (66%) of 6-methyl-1-heptadecanol; b.p. 159–161° (1.8 mm.), n_D^{20} 1.4537.

Anal. Calc'd for $C_{18}H_{36}O$: C, 79.92; H, 14.16.
Found: C, 80.78; H, 13.85.

There was considerable fore-run in distilling the above alcohol, and a principal fraction (8.8 g.), b.p. 108–110° (1.8 mm.), was insoluble in concentrated sulfuric acid and yielded an analysis in agreement with *4-methylpentadecane*.

Anal. Calc'd for $C_{16}H_{34}$: C, 84.86; H, 15.13.
Found: C, 84.92; H, 15.18.

Methyl 7-methyloctadecanoate was prepared in 81% yield from the bromide (b.p. 172–173° at 1.7 mm.) of the above alcohol. The ester distilled at 170–172° (2.5 mm.), n_D^{20} 1.4465.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.
Found: C, 77.28; H, 12.96.

Methyl 5-keto-9-methyloctadecanoate (XI), prepared by the usual procedure (10) for keto esters from 1-chloro-4-methyltridecane (IX) and the ester acid chloride of glutaric acid, was obtained in 39.5% yield (based on chloride IX), b.p. 186–189° (2 mm.), n_D^{20} 1.4530.

Anal. Calc'd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73.
Found: C, 73.12; H, 11.77.

Methyl 9-methyloctadecanoate. Keto ester XI was reduced by the Huang-Minlon (14) modification of the Wolff-Kishner reduction, as previously described (15) for aliphatic keto esters. The yield of crude acid was 92%, but when this was esterified with fifteen equivalents of methanol containing 10% sulfuric acid, the over-all yield of ester was 69%, b.p. 172–173° (2.2 mm.), n_D^{20} 1.4467. This method of esterification, applied to pure acids, has repeatedly given yields of 95% or better.

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.
Found: C, 76.43; H, 12.97.

Ethyl 7-keto-11-methyloctadecanoate (XII) was obtained from 1-chloro-4-methylhendecane (X) and the ester acid chloride of pimelic acid in 49% yield (based on chloride X), b.p. 190–192° (2 mm.), n_D^{20} 1.4499.

This ester appeared to contain appreciable quantities of impurities, presumably distilling azeotropically, for the analysis for carbon was about 2% below theory, and saponification of 1 g. of ester with alcoholic potassium hydroxide yielded only 0.69 g. of crude acid. However, the *7-keto-11-methyloctadecanoic acid* was readily purified, reaching the constant m.p. of 38.8–39.5° after two crystallizations from acetone. It separated as burrs of short needles.

Anal. Calc'd for $C_{19}H_{36}O_3$: C, 73.03; H, 11.62.
Found: C, 72.97; H, 11.71.

Methyl 11-methyloctadecanoate was obtained from keto ester XII by the reduction and esterification procedure described for the 9-methyl isomer. The yield of product boiling at 170–172° (2 mm.), n_D^{20} 1.4463, was 65%.

TABLE III

METHYLOCTADECANOIC ACIDS AND DERIVATIVES

—OCTADECANOIC ACID	M.P., °C.	M.P., °C. OF AMIDE	M.P., °C. OF TRIBROMOANILIDE
5-Methyl (I)	44.5–45.0	79.6–80.8[c] 71.6	80.5–85.4[e]
6-Methyl (II)	40.0–40.6	79.1–79.8	86.0–93.0[f]
7-Methyl (III)	36.8–37.3	71.6–72.0[c] 69.6	92.5–93.2
9-Methyl[a] (IV)	38.5–39.1	69.8–70.5[c] 62.8	90.0–91.6[g]
11-Methyl (V)	21.0[b] 26.2	71.6–75.3[d] 74.6	91.0–91.7

[a] Literature (3): acid, m.p. 38.7–39.2°; amide, m.p. 70.0–70.5°, re-m.p. 61.5° (*cf.* note *c*, below). [b] These values were determined on a sample of several grams, with the thermometer in the liquid. The higher value is obtained when a sample crystallized from acetone is melted, while the lower-melting form usually separates from the melt. [c] Higher-melting form obtained on crystallization from methanol, lower-melting form separates from melt. [d] The broad m.p. is obtained on samples crystallized from a solvent, and varies somewhat with rate of heating and on different samples. The lower-melting form separates from the melt. [e] Clusters of small blades first separate from ethanol, but these rapidly change to a dense granular crystallizate. Material crystallized from ethanol always showed the broad m.p. A sample solidified from the melt re-melts at once when immediately placed in a bath at 81.5° or higher, but not in a bath at 81.4°. When placed in a bath at 81.4°, re-m.p. 83.2° (taken at once). [f] Crystallized from ethanol as small hard crystals, but fine needles separated from the melt. On slowly cooling a molten sample, re-crystallization set in at 85°, and re-melting occurred at 86°, but a sample crystallized from ethanol did not melt completely when placed in a bath at 89°. A sample which was melted, resolidified, and ground, melted in a capillary at 84.7–86.0°. [g] This m.p. was obtained on a sample which had stood overnight; freshly crystallized samples show broad melting points. A solidified sample re-melted at 90.4°.

TABLE IV

ANALYSES OF ACIDS AND DERIVATIVES

ACID	ACID			AMIDE		TRIBROMOANILIDE
	C	H	EQ. WT.	C	H	N
I	76.29	12.84	300.2	77.04	13.29	2.29
II	76.06	12.56	299.7	77.04	13.39	2.23
III	76.71	12.81	298.7	77.17	13.14	2.30
IV	76.66	12.73	298.6	76.54	13.14	2.29
V	75.95	12.64	299.1	76.92	13.16	2.29
Calc'd	76.45	12.83	298.5	76.71	13.21	2.29

Anal. Calc'd for $C_{20}H_{40}O_2$: C, 76.86; H, 12.90.
Found: C, 76.21, H, 12.72.

Methyloctadecanoic acids were obtained from the esters by saponification with alcoholic potassium hydroxide and crystallization from acetone until a constant melting point was reached. Data on these acids are found in Tables III and IV.

Amides and 2,4,6-tribromoanilides of the methyloctadecanoic acids were prepared as previously described (2), and the data are found in Tables III and IV.

Ethyl 9-keto-16-methylheptadecanoate was prepared by the usual procedure (10) from isononyl bromide (13) and the ester acid chloride of azelaic acid. The yield (based on isononyl bromide) was 55% of material boiling at 196–199° (4 mm.), n_D^{20} 1.4492.

The ester was characterized by saponification to *9-keto-16-methylheptadecanoic acid*, m.p. 70.8–73.4°, re-m.p. 72.5–73.0°.

Anal. Calc'd for $C_{18}H_{34}O_3$: C, 72.45; H, 11.48.
Found: C, 72.18; H, 11.66.

16-Methylheptadecanoic (isostearic) acid. The above keto ester was reduced by the modified Clemmensen method (16) to give a 75% yield of ethyl 16-methylheptadecanoate, b.p. 183–186° (4 mm.). Saponification of the ester and crystallization from acetone yielded isostearic acid, m.p. 68.8–69.7°, eq. wt., 282.8 (Calc'd 284.5). Literature, m.p. 67.6–68.2° (17), 69.5° (4).

Normal acids. Commercially available acids were purified by esterification and distillation of the esters, followed by saponification and crystallization of the acids (nonanoic and decanoic acids were not crystallized).

TABLE V

NORMAL ACIDS AND AMIDES

ACID	ACID	AMIDE
	M.P., °C.	M.P., °C.
Nonanoic		98.7–99.1
Decanoic		97.6–98.2
Hendecanoic	28.2–28.6	98.0–98.7
Dodecanoic	42.8–43.6	99.6–100.2
Tridecanoic	41.0–41.9	99.6–100.2
Tetradecanoic	53–54.2	102.5–103.7
Pentadecanoic	49.2–51.5[a]	102.4–103.1
Hexadecanoic	61.2–62.0	104.9–105.3
Heptadecanoic	59.2–60.5	105.0–106.0

[a] Not crystallized to constant m.p.

Hendecanoic acid was prepared by hydrogenation of a sample of distilled undecylenic acid (b.p. 139.5–140° at 3.5 mm.). Hydrogenation of 0.28 mole at room temperature and low pressure in 250 ml. of glacial acetic acid with 0.8 g. of commercial platinum oxide catalyst was complete in 33 minutes. Crystallization of the product by addition of water gave a quantitative yield of acid, m.p. 28.2–28.6°.

Tridecanoic acid was prepared by reaction of dodecylmagnesium bromide with carbon dioxide under the initial pressure from a cylinder of carbon dioxide. Shaking of the bomb was continued overnight, and the reaction was worked up as usual for a Grignard reaction. The crude (technical dodecyl bromide was used) acid was esterified and distilled to give a 55% yield of methyl tridecanoate, b.p., 130–132° (4 mm.). Saponification and one crystallization from acetone gave tridecanoic acid of m.p. 41.0–41.9°.

Pentadecanoic acid was prepared by the nitrile synthesis. The over-all yield of methyl pentadecanoate from tetradecyl bromide was 77%, b.p. 156–157° (5.5 mm.). The acid was obtained as described above.

Heptadecanoic acid was prepared by reaction of hexadecylmagnesium bromide with solid carbon dioxide. In the best run, using a very large excess of carbon dioxide added in several portions, the yield was 32%.

The data on the normal acids and their amides are found in Table V.

SUMMARY

There is reported the preparation of five methyloctadecanoic acids. This work completes the synthesis of the series of monomethyloctadecanoic acids. The melting point patterns of the acids, amides, and tribromoanilides are discussed.

A new synthesis of isostearic acid is also reported, and the preparation of pure samples of the amides of the normal acids from C_9 to C_{17} is described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED - CHAIN FATTY ACIDS. XIV. LOCATION OF BRANCHING METHYL GROUPS BY STUDY OF THE MELTING POINTS OF BINARY MIXTURES OF BRANCHED AND NORMAL ACIDS OR AMIDES

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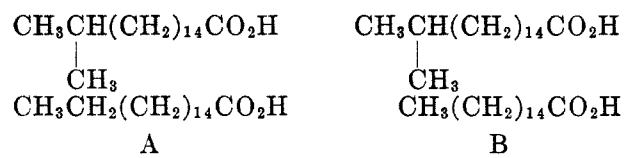
Branching methyl groups in the 2- or 3-positions of fatty acids may be definitely located by studying the rate of amide hydrolysis (1), and some information concerning the location of a branching methyl may be obtained from the melting points of the acid and its derivatives (2); however, there remains to be developed a general method for definitely locating a methyl group at any position along the chain. A promising method, which consumes relatively small quantities of materials, is the study of the melting or solidification points of binary mixtures of branched and normal acids, as introduced by A. W. Weitkamp (3).

In working with iso acids (isopropyl end-group) and anteiso acids (*sec*-butyl end-group), this investigator demonstrated the following two principles. (A) For mixtures of a branched-chain acid and a normal acid, if the total number of carbons in the normal acid is *greater than* the number of the carbon bearing the branching methyl, a melting-point diagram exhibiting *one* eutectic is obtained. (B) If the total number of carbons in the normal acid is *equal* to the number of the carbon bearing the branching methyl in the branched-chain acid, a melting-point diagram exhibiting *two* eutectics is obtained. This may be illustrated by considering the two pairs, A and B. Pair A exhibits one eutectic, pair B exhibits two.



A theoretical basis for this behavior was suggested and discussed.

Since this method seemed quite promising and was not being pursued further by Weitkamp, we have prepared the necessary acids (2) for an extension of these studies. It was of particular interest to learn whether the method could be applied to the location of branching methyl groups at positions other than the iso or anteiso positions. All compounds used in our investigations were *dl*-isomers except for *d*-10-methyloctadecanamide. Effects of stereoisomerism are discussed below.

We first repeated the determinations for a set of curves similar to those published by Weitkamp, to make certain that similar results could be obtained by

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us. Figure 1, showing our melting-point curves and the solidification-point curves of Weitkamp, demonstrates that the results are entirely consistent. The displacement of about 10% between the two sets of curves is probably caused by the known difference between the melting-point and solidification-point curves for fatty acid mixtures, although there may have been a small difference in the purity of the samples of 16-methylheptadecanoic acid. The shapes of the curves, as well as the number and location of eutectics, are very similar.

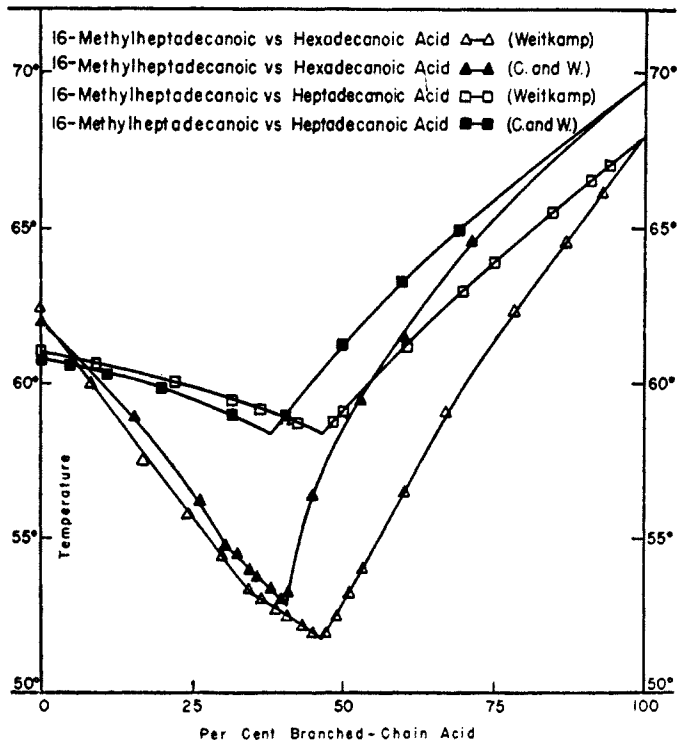

FIGURE 1

Weitkamp published one set of curves, using amides, and the results were similar to those obtained with the acids. As shown in Figure 2, we also obtained similar results with 16-methylheptadecanamide and hexadecanamide; in fact, the occurrence of two eutectics is considerably more pronounced with the amides. Also in Figure 2 is a curve showing that two eutectics are also obtained when the normal amide is shorter than the position of branching in the branched acid. The curve rises between the eutectics in this case, but the approximate compositions at the eutectics and the general trends in the two curves in this figure are similar. Since many of the acids studied in the present work have inconveniently low melting points, many of the curves have been determined on the amides.

As soon as our investigations were extended to acids with branching more remote from the end of the chain, it became apparent that the simple principles,

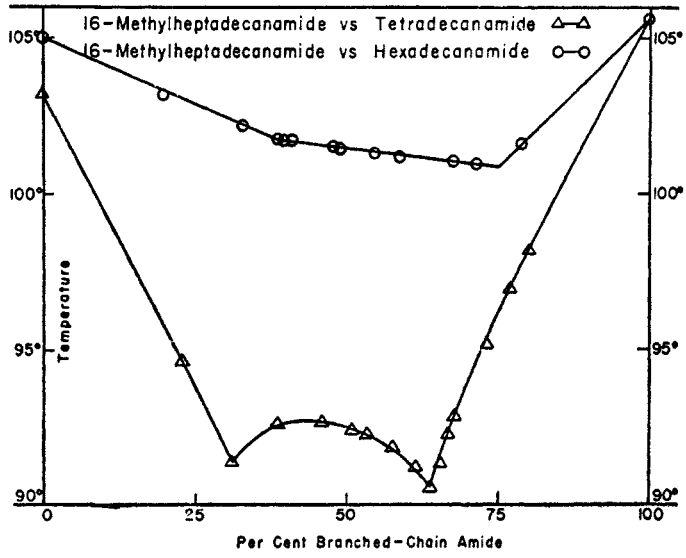

FIGURE 2

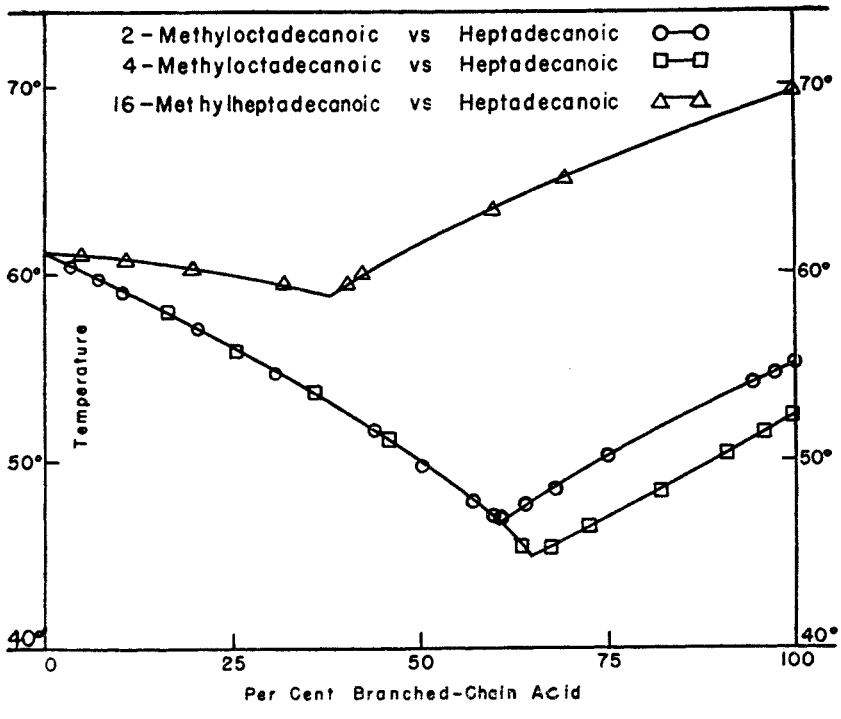

FIGURE 3

A and B, mentioned above, no longer applied. The curves were usually much more complicated, and the relationship between position of branching and chain-

length of normal acid had lost its significance. It has been possible, however, to apply a different type of analysis and to arrive at useful generalizations.

Location of methyl groups by zones. By a study of the curves obtained with branched acids (or amides) and normal acids (or amides) of approximately the molecular weight of the branched acids, it is possible to locate the methyl group in one of three zones. A fourth zone consists of the iso and anteiso positions, where a definite location is possible, as previously mentioned.

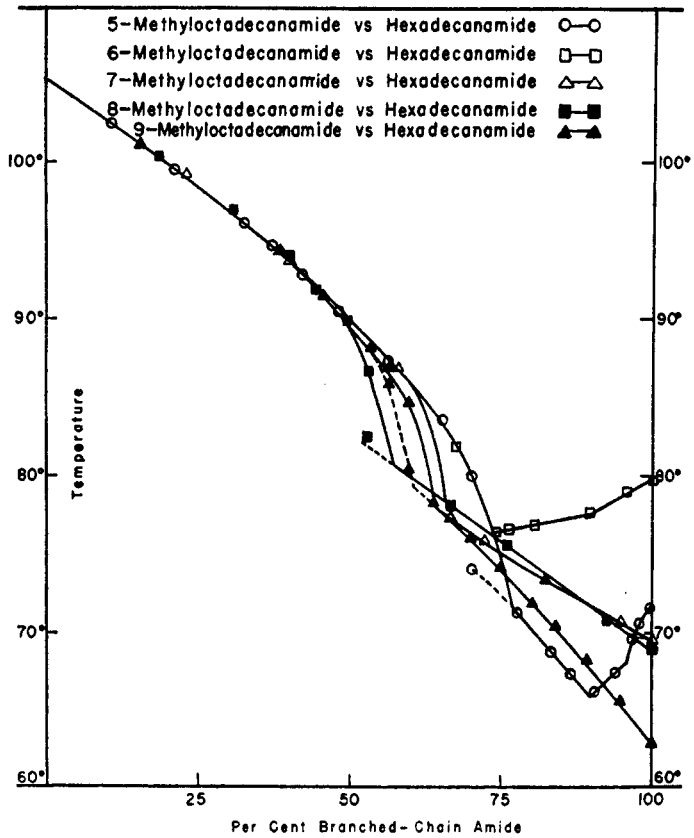

FIGURE 4

Positions 2-, 3-, and 4-. Inspection of Figure 3 shows that the curves with 2-methyl and 4-methyl acids are those characteristic of an ideal solution over the entire range. On the left of the eutectic, the species separating is heptadecanoic acid, and in the absence of solid solution this curve should be the same for any second component. This is the case for the two curves mentioned. Furthermore, the slope of the curve, in absence of solid solution, is a function of the heat of fusion[2] of the species crystallizing. Since 2-methyl- and 4-methyl-octadecanoic

[2] The data in this paper could be used to make plots for calculating heats of fusion for some of the acids studied, but this information is not regarded as of significance to the present study. The calculation would apply only in the few instances where an ideal solution over an appreciable range is indicated.

acids would be expected to have similar heats of fusion, the two curves on the right of the eutectics should be approximately parallel, and this is the case. These two curves are easily distinguished from the one-eutectic curve for 16-methylheptadecanoic acid, where there is a large deviation from ideality. It should be mentioned that distinction between substitution in positions 2-, 3-, and 4- is easily accomplished by investigation of the rate of amide hydrolysis (1).

Positions 5- and 6-. For all positions of methyl beyond the 4-position, there is a large deviation from ideality caused by both solid solution and molecular compound formation, the latter being responsible for multiple eutectics. In

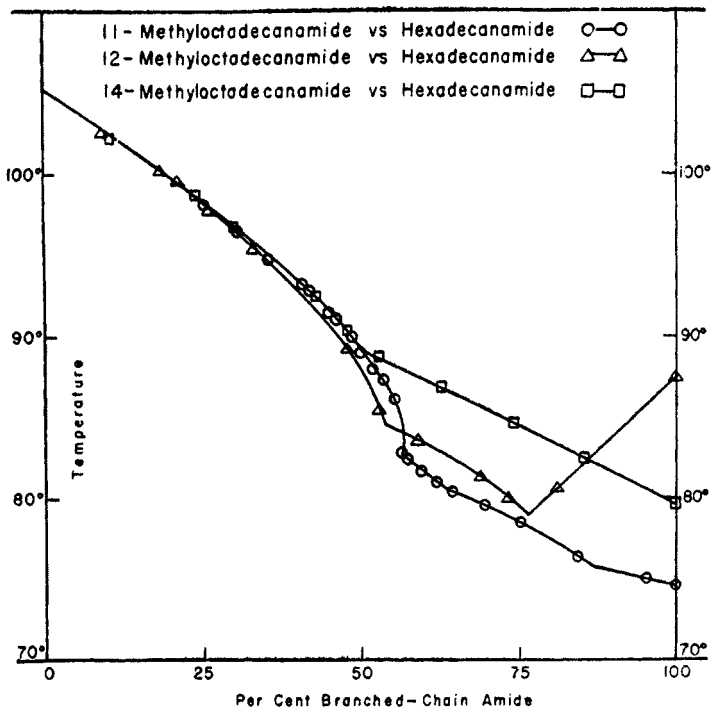

FIGURE 5

Figure 4, it will be noted that the curves for the 5-methyl and 6-methyl isomers go down from the origin at 100% branched-chain amide (right side). They differ markedly, however, from the curves described in the preceding section, in that they exhibit two and three eutectics, respectively. The eutectic at about 95% 5-methyloctadecanamide will be discussed below in the section on the effects of stereoisomerism.

In three of the curves in Figure 4 are plotted *double melting points*. The melting point obtained depended on the history of the solution prior to melting, and this is discussed in the section on experimental procedure. The lower melting point is attributed to a metastable polymorph or molecular compound, and these points have been joined by dotted lines.

Positions more remote from carboxyl than 6-. For positions more remote from carboxyl than 6-, it will be noted in Figures 4, 5, and 10 (Figure 10 is discussed in detail below) that, with one exception, the curves all *rise* from the origin at 100% branched-chain amide (right side). This is not the case in any curve with a branch nearer the carboxyl than position 7-, so these two categories are easily distinguished. The failure of the 12-isomer to follow this behavior of all its neighbors may be due to the unusually high melting point of the amide of this acid. In any case, there is no difficulty in distinguishing the 12-isomer from the 5- and 6-

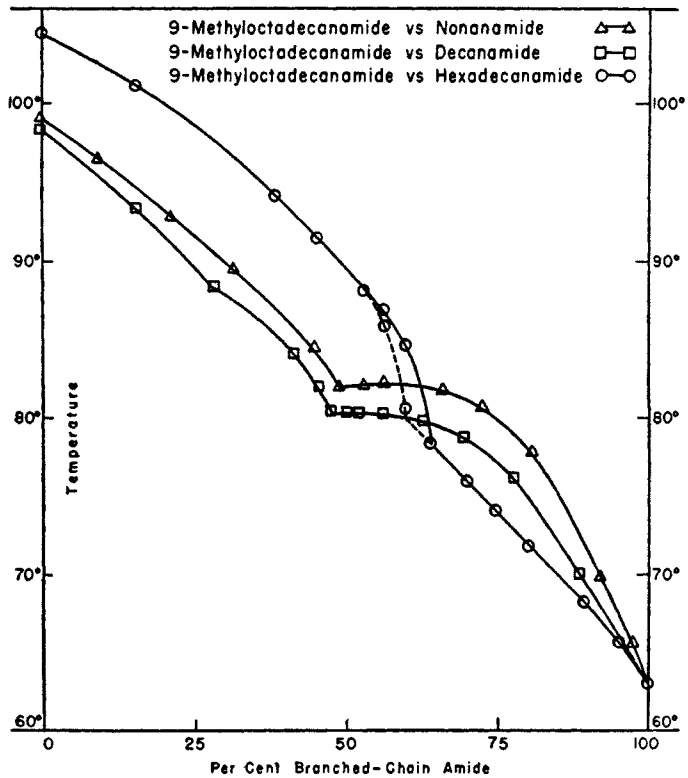

FIGURE 6

isomers, for the 12-methyloctadecanoic acid melts considerably below the 5- and 6-isomers, and is polymorphic, while the amide of the 12-methyl isomer melts unusually high. In fact, its unique properties make the 12-methyl isomer especially easy to detect.

Exact location of methyl groups. The data discussed above makes possible the exact location of methyl groups in many positions, but the positions (except 12-) between 6- and anteiso remain lumped together in one category. A study of the curves in Figures 6–10 suggests a method for locating the position of a branching methyl in this central portion of the chain. The number of curves in each figure is such that they are crowded in the diagram, but this serves to point up the

most interesting feature of these groups of curves. For each position of methyl, a curve of characteristic shape is obtained, regardless of which normal acid is used as the second component of the mixture. Thus, all curves in Figure 6 are of similar shape with a eutectic in the region between 45% and 65% branched-chain amide. All curves in Figure 7 show two eutectics, one in the region between 40% and 55%, the second at 90–95%. The curves in Figure 8 also show two eutectics, but the second is at 75–85%. The curve with tridecanamide, in Figure 8, is notable in that it is double from the first eutectic over the remainder of the curve. This is still another unique feature of the 12-methyl isomer. Finally, the

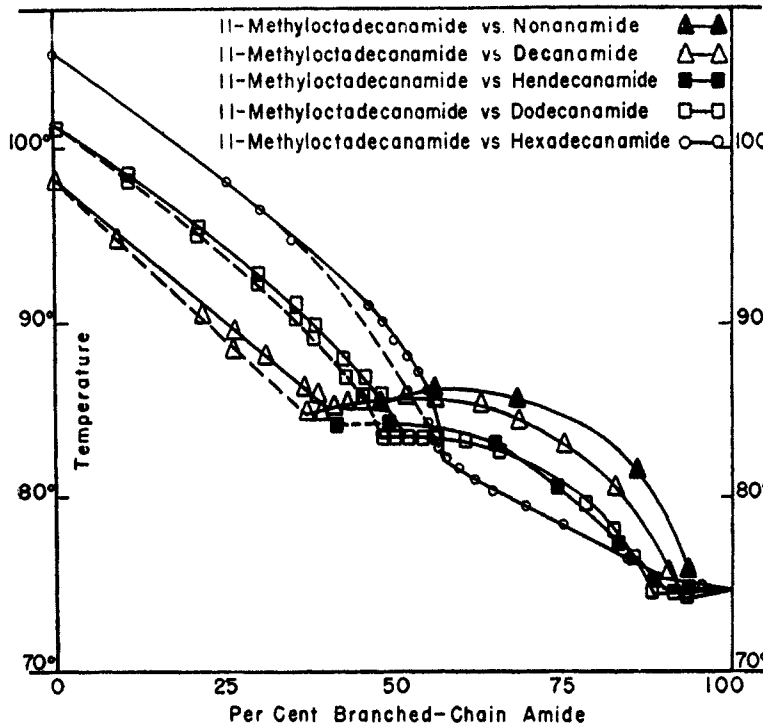

FIGURE 7

curves in Figure 9 also show two eutectics, one at 25–30%, the other at 40–55%. In Figure 9, there may be a second eutectic in the curve with hexadecanamide, at about 25%, but the inflection was so slight that its existence is doubtful, so it is not indicated on the graph. Two curves in Figure 7 and one curve in Figure 8 are left incomplete, to relieve the crowding, but the part shown is enough to demonstrate the similarity of their shape to the completed curves.

Thus, the position of a methyl in an unknown acid can be detected by constructing one curve with a normal acid of about ten carbons. By inspection, it can be determined which type of curve has been obtained, and the position of the methyl thus located. This procedure is similar to the application of ultra-violet

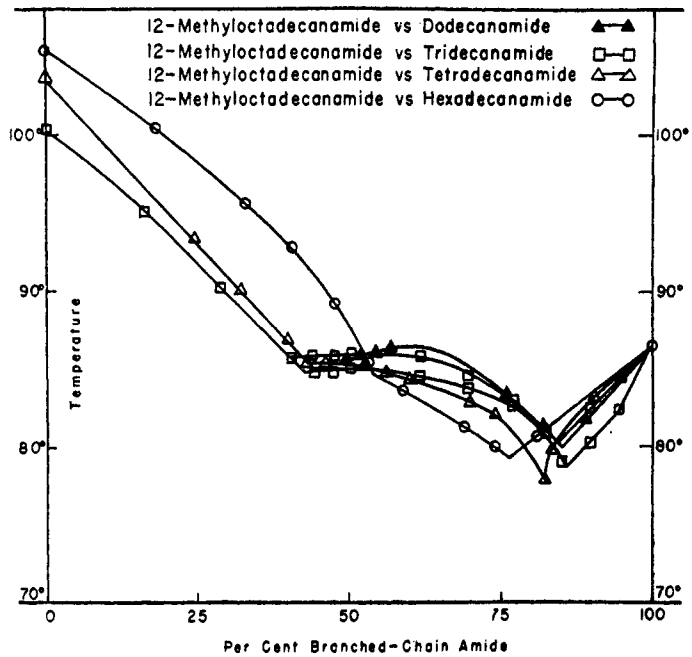

FIGURE 8

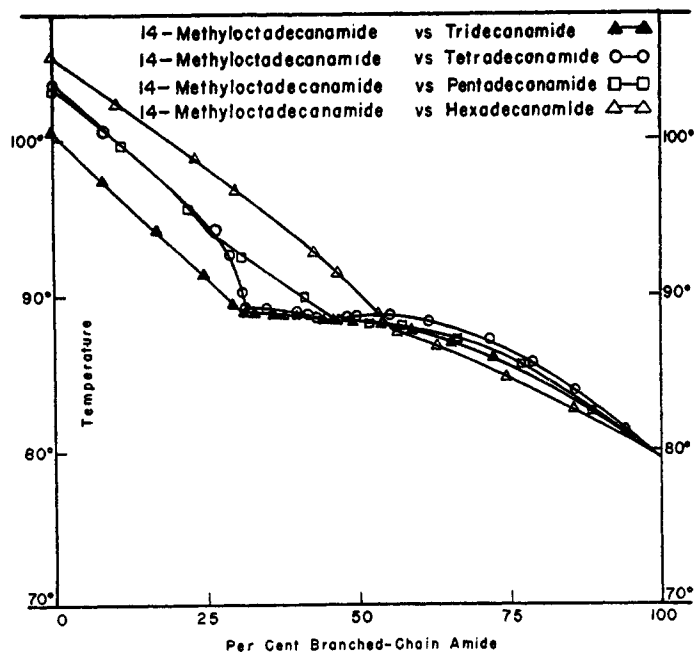

FIGURE 9

absorption spectra. There seems no probability of confusing the curves here presented. Even for adjacent positions, such as 10-, 11-, and 12-, the curves are quite different. The differences in the curves are due to molecular compound formation, and differences in solid solution, and these matters seem very sensitive to differences in the shapes of the molecules. The most similar curves obtained are those, in Figure 4, of hexadecanamide with 7-methyl- and 9-methyl-octadecanamide; however, careful inspection shows noticeable differences here. The curve for the 7-methyl isomer either has a barely perceptible eutectic at about 80%, or else it is the anomalous type shown for the *dl*-isomer in Figure 10. This feature is not present in the curve for the 9-methyl isomer. Also, the 9-methyl isomer shows

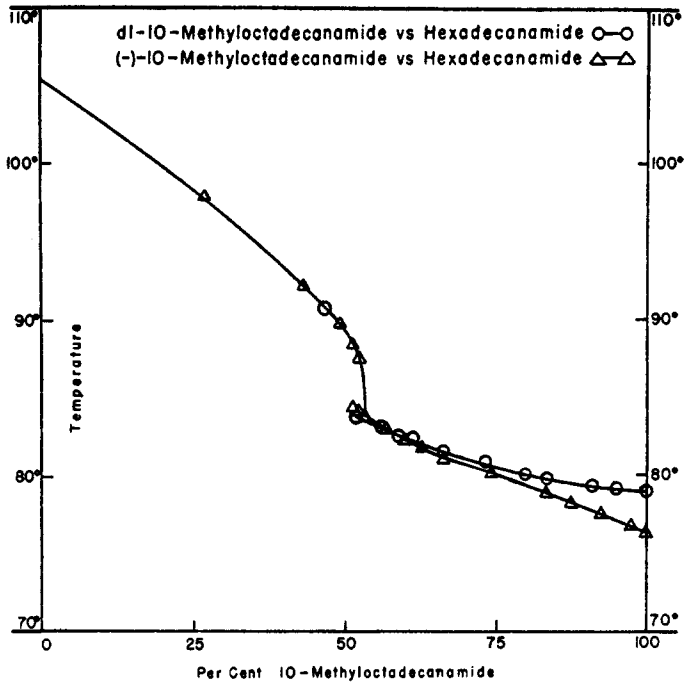

FIGURE 10

a region of double melting points, and this was not detected for the 7-methyl isomer.

Effects of stereoisomerism. Since naturally-occurring acids or acids obtained by degradation of natural products are likely to be optical isomers, it is important to consider whether differences might arise with optical isomers. Weitkamp (3) compared the curves obtained with *dl*- and *d*-16-methyloctadecanoic acids, and they were nearly identical until there was reached a mixture containing about 95% branched-chain acid. Beyond this point, the curve for the *d*-acid continued to the origin at the melting point of this isomer, while the curve for the *dl*-isomer suddenly rose to the melting point of that isomer. We have verified this sharp break in the curve for the *dl*-isomer. This behavior was attributed to the complete dissociation of the *dl*-compound as soon as a few per cent of the normal

acid was present to act as solvent. In Figure 4, the curve for 5-methyloctadecanamide and hexadecanamide shows a similar behavior, and the lower curve with tridecanamide in Figure 8 also has a eutectic near 95%. Thus, in these instances, stereoisomerism introduces no serious additional complexity.

In one instance, 10-methyloctadecanamide, a very unusual type of curve was obtained with the *dl*-isomer, as shown in Figure 10. When this curve was plotted it was realized that it was irregular, in that the portion between the eutectic and 100% branched-chain amide was bowed down instead of up, as was the case with all other curves which have been determined. Fortunately the *d*-isomer was available (4) for comparison, and determination of the curve with this isomer shows that this appears to be an unusual case in which the *dl*-compound gradually dissociates more completely into the *d*- and *l*- components, as its solution in the normal acid becomes more dilute. The two curves do not become coincident until the concentration of branched-chain amide has been reduced to about 60%. The curve for the *d*-isomer has a barely detectable, but definite, second eutectic at about 65%. In the curve for the *dl*-isomer, this eutectic is obscured by the gradual dissociation. It is noteworthy that, even in this unusual instance, the shape of this curve can hardly be confused with any of those in Figures 6–9.

Discussion of the scope of the method. It is apparent that with the data here presented, the method can be applied only to monomethyl acids. Until more data are obtained, the value of the method cannot be evaluated for acids with larger branching groups or multiple branches. However, most alkyl substituents occurring in nature are methyl, and the number of branches may be estimated by use of the data of Ginger (5), who has adapted the Kuhn-Roth method to use with high molecular weight branched-chain acids.

There is no certainty that the types of curves obtained in the methyloctadecanoic acid series will hold for acids of different molecular weight, and investigation of acids of different molecular weight is indicated as the next step in extending this method. It seems reasonable that the relationship of the branching methyl to carboxyl is the most important structural relationship, and that a few carbons more or less on the end of the chain would exert no great effect in molecules of these molecular weights. Several interrelationships between acids of different molecular weights have been mentioned in the preceding paper (2) of this series.

EXPERIMENTAL

Method and apparatus. The melting points of the mixtures were determined in tubes of about 5-mm. diameter, with walls of about 0.2-mm. thickness. A sample of 50–100 mg. (weighed accurately to 0.1 mg.) of one component was weighed in the tube and the m.p. determined as the temperature at which the last crystalline material was no longer visible. The material was stirred with a No. 18 tantalum wire during all observations of m.p. A suitable increment of the other component was weighed in a tube similar to the long-handled weighing tubes used in microanalysis (6). The melting-point tube (containing the solidified sample) was inverted over the weighing tube, the weighing tube was raised until its end was close to the solidified sample in the melting-point tube, and the tubes were inverted and the increment shaken into the melting-point tube. The weighing tube was then removed and weighed to give the weight of the increment. This technique avoided getting material on the upper parts of the wall of the melting-point tube. The new mixture was melted and stirred for several minutes with the tantalum wire; then the m.p. was deter-

mined. Another increment was then added, and the process was repeated until the mixture contained more than 50% of the component being added. This process was then repeated, starting with a sample of the other component, and the curve extended until it overlapped that determined from the other direction. In any instances where the curves from the two directions did not fit, re-determinations were made, and in places where a doubtful eutectic developed, additional points were added in that region.

The melting-point tubes were heated in an apparatus similar to the Hershberg melting point outfit (7), except that our apparatus is larger. The front tube of the apparatus is 2.4 cm. in diameter and 29 cm. high. With this larger apparatus, there was no difficulty in holding the temperture constant to ±0.1° for ten minutes or longer, but the temperature could be varied rapidly when desirable. Melting points were observed through a reading glass and a supplementary hand lens. After the melt had been stirred thoroughly, it was removed from the bath and cooled with stirring until crystallization began, then returned to the bath at a temperature below the m.p. The bath was raised slowly until melting occurred, then the temperature was lowered 0.1°, the melting point tube was removed until crystallization set in, then returned to the bath and stirred for about ten minutes or until the mixture melted. This process was repeated until it was observed that melting occurred at a given temperature and did not occur 0.1° below this temperature. Thermometers were of the Anschütz variety and were standardized against thermometers calibrated by the Bureau of Standards.

Melting points determined in this manner were easily reproducible to 0.1°, and the error in weighing increments of sample introduced a greater variation than the error of observing m.p., in regions where the m.p. changed rapidly with composition.

The greatest uncertainty exists in regions of double melting points. The behavior in these regions varied, but usually, as the composition was varied, one m.p. became less distinct as the other became more distinct. Often, there was a transition region where neither m.p. was distinct. In some cases, the lower m.p. was obtained unless the mixture was cooled considerably below this point before being returned to the bath, and sometimes standing overnight was necessary before the higher m.p. was observed. In other cases, the mixture melted at the lower m.p., then partially resolidified and re-melted at the higher point. When the higher form began to separate before the lower was completely melted the lower m.p. became rather inaccurate. In the most dubious cases it was not recorded. It will be noted that the double melting points are especially common when the branching group is near the middle of the chain. In some of these regions of double melting points, the curves also become so steep that certain regions are in doubt, for a change of a few per cent in composition changes the m.p. by several degrees.

SUMMARY

There has been determined a series of melting-point curves for binary mixtures of branched and normal acids and amides. These curves have been analyzed and used as the basis for a method of locating a branching methyl group at any position along the chain of a fatty acid. The probable scope and limitations of the method are estimated.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

ATTEMPTED PREPARATION OF 3-HYDROXYFURAN BY THE METHODS OF HODGSON AND DAVIES

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Herein are described attempts to repeat the preparation of 3-hydroxyfuran as reported by Hodgson and Davies (1). The compound was desired in order to make alkoxy and other derivatives of it and thus gain support for or against the controversial (2) formulation of Hodgson and Davies (1).

We failed in the first step which consisted of the treatment of 2-furoic acid with bromine water to give a compound formulated by Hodgson and Davies (1) as 2-bromo-3-hydroxyfuran.[1] These authors used two methods. From the first method, reported earlier by Limpricht (3) and which employed the treatment of equal quantities of 2-furoic acid and water with bromine below 30°, we obtained only 5-bromo-2-furoic acid and water-soluble products. The second procedure, which differed from the first only in the amount of water and the presence of chloroform, yielded for us only 2,3,4,5-tetrabromotetrahydro-2-furoic acid and two unstable oils. The properties of these oils were different from those reported for the crystalline 2-bromo-3-hydroxyfuran, especially in that one was infinitely water-soluble and the other, though insoluble in cold water, decomposed in hot water to give water-soluble products. Hodgson and Davies (1) recrystallized their compound from water. They were also able to steam-distill it even in the crude oily form and in the presence of the acidic reaction medium. Due to its solubility in sodium carbonate solution and its failure to give positive ferric chloride tests, our water-insoluble oil is thought to be carboxylic rather than enolic in nature.

Each of the above procedures was repeated numerous times exactly as described by Hodgson and Davies (1) and also with variations from their procedure. The difference in our results and theirs must be due either to differences in the purity of the reagents used or incompletely described procedures. An effort to obtain further details concerning the reaction was not fruitful.

EXPERIMENTAL

Materials. The furoic acid, purified by several recrystallizations from water, melted at 132–133°. The bromine was Merck's Reagent grade; the chloroform, redistilled for several of the experiments, was General Chemical's U.S.P. grade; and the water was distilled.

Reaction of 2-furoic acid with bromine water by the chloroform method. The reaction was carried out at a temperature of 25–30° using 10 g. of furoic acid as described by Hodgson and Davies (1). After 100 ml. of cold water was added, the mixture was filtered and the resulting crystals were washed with cold water and dried; yield, 4.5 g., m.p., 154–156°. The filtrate was separated, the water layer was extracted with ether, the ether extract was added to the chloroform layer and the resulting solution was washed with cold water and evaporated, yielding a water-insoluble, unstable, yellow oil (7 g.). In several runs 11 g. (0.1 mole) of

[1] A private communication from Professor George F Wright of the University of Toronto informs us that he, too, has been unable to carry out this reaction.

furoic acid was used (everything else, as before, 0.2 mole each); the yield of crystals was 9 g. and oil, 5 g. After several recrystallizations from benzene the melting point of the crystals increased to 159–160°. The material was identified as *2,3,4,5-tetrabromotetrahydro-2-furoic acid* as described later.

Anal. Calc'd for $C_5H_4Br_4O_3$: C, 13.91; H, 0.93.
Found: C, 13.93, 13.65; H, 1.57, 1.40.

In other runs, the following variations were made. The temperature was kept at 10° and 20° in two runs and no cooling was employed in another (temperature, 30–40°). Impure furoic acid (m.p. 127–129°), 10 ml. of water, tap water, traces of sulfuric acid, traces of calcium hydroxide, and chloroform saturated with water were used in other trials. In all these experiments, very little difference in results was noticed. Several runs were carried out with five times the usual amounts. Upon recrystallization of the crude tetrabromo compound, a water-soluble oil was obtained as a by-product.

The water-insoluble oil. The water-insoluble oil decomposed on standing, evolving hydrogen bromide and turning dark in color. The oil gave a negative ferric chloride test, was mostly insoluble in cold water, soluble in dilute sodium hydroxide and sodium carbonate solutions. Neutralization of these solutions gave only water-soluble materials. The oil decomposed in hot water (from the 11 g. runs, it partially crystallized to give 5-bromo-2-furoic acid, m.p. 185–186°) and during attempted steam-distillations yielding water-soluble products which reduced Fehling's solution and gave a negative ferric chloride test. Fehling-solution tests on the original oil were inconclusive due to the formation of a heavy precipitate. The oil could not be crystallized from common organic solvents, and it decomposed during attempted vacuum distillation.

The water-soluble oil. This material reduced Fehling's solution when heated, gave a positive Beilstein test for halogen, decomposed sodium carbonate solution, and gave a negative ferric chloride test. It completely resisted crystallization and slowly decomposed on standing, evolving hydrogen bromide and turning dark in color.

Reaction of 2-furoic acid with bromine water in absence of chloroform. A well-stirred suspension of 10 g. of 2-furoic acid and 10 g. of water was treated over a period of one hour with 30 g. of bromine at 25–30°. Fumes of hydrogen bromide were evolved and a yellow oil precipitated. The reaction mixture was poured into 150 ml. of cold water where colorless crystals formed (3 g., m.p. 184–186°). The filtrate was a clear solution which reduced Fehling's solution and turned dark on standing. Ether extraction of the filtrate or steam-distillation followed by ether extraction of the distillate yielded only a few additional crystals of the same material. The material was identified as 5-bromo-2-furoic acid as described later (m.p. 186–187° after water recrystallization).

Anal. Calc'd for $C_5H_3BrO_3$: C, 31.44; H, 1.58.
Found: C, 31.49; H, 1.94.

Variations in the procedure made use of crude furoic acid, tap water, and bromine mixed with 5 ml. of water. In the latter case, only an oil was obtained which resembled in behavior the water-insoluble oil described earlier.

5-Bromo-2-furoic acid. This substance was identified through its amide. A mixture of 1 g. of the acid and 5 ml. of thionyl chloride was refluxed for five minutes, cooled, and carefully poured into excess cold, concentrated ammonium hydroxide. The resulting crystals were filtered, washed, and recrystallized from aqueous ethanol solution; m.p. 141–143°. Hill and Sanger (4) reported 144–145°.

2,3,4,5-Tetrabromotetrahydro-2-furoic acid. This was identified by dehydrohalogenation according to the directions of Hill and Sanger (5) using alcoholic sodium hydroxide. The products were 4,5-dibromo-2-furoic acid (6) (m.p., 166–168°), 5-bromo-2-furoic acid (m.p. 186–187°), and 3,4-dibromo-2-furoic acid (m.p. 190–192°) as reported by Hill and Sanger (5).

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the Quaker Oats Co., Chicago, Ill., for a generous gift of furoic acid and Mr. Elias E. Kawas, research assistant, for checking our results in chloroform medium.

SUMMARY

2-Bromo-3-hydroxyfuran was not obtained from the treatment of 2-furoic acid with bromine water as reported by Hodgson and Davies. The only crystalline materials isolated were 5-bromo-2-furoic acid and 2,3,4,5-tetrabromotetrahydro-2-furoic acid.

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[CONTRIBUTION NO. 731 FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF PITTSBURGH]

CONDENSATIONS EFFECTED BY THE ALKALI AMIDES. IV. THE REACTIONS OF ESTERS WITH LITHIUM AMIDE AND CERTAIN SUBSTITUTED LITHIUM AMIDES[1]

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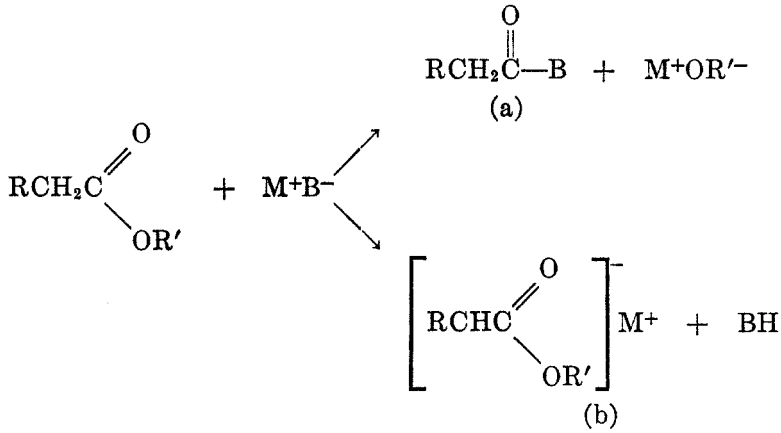
When a basic reagent reacts with an ester, the ester may be attacked at at least two different positions (1), the carbonyl carbon and the α-hydrogen as indicated by the following scheme. It has been shown earlier (2, 3) that when B^- is amide ion (from sodium amide), both (a), the amide of the starting ester, and (b), the ester anion, which is the reactive intermediate in the preparation of β-ketoesters, are formed. However, when the larger but weaker base, sodium triphenylmethide, is used in condensations apparently only α-hydrogen attack occurs (4).



M = Na or K, B = $OC_2H_5^-$, NH_2^- or $(C_6H_5)_3C^-$ etc.

The present investigation was undertaken to study the course of the reactions between a number of esters and several lithio-amides of varying sizes and basic strengths. The condensing agents used in this study were lithium amide, lithium diethylamide, lithium diisopropylamide, and lithium N-methyl-N-phenylamide.

The yields of the β-ketoesters obtained in the present investigation (Table I) using lithium amide as the condensing agent were considerably lower that those reported previously using sodium amide to effect the same condensations. As part of our investigation, we self-condensed ethyl phenylacetate by means of both sodium amide and lithium amide. We obtained a 68% yield of β-ketoester using

[1] For paper III in this series see *J. Am. Chem. Soc.*, **71**, 1120 (1949).

[2] This work is based on a thesis submitted by Matthew Hamell in partial fulfillment of the requirements for the degree of Master of Science at the University of Pittsburgh, October 1948.

sodium amide, while that reported earlier (3) was 82%. However, when lithium amide was used as the base, a considerably lower yield (47%) of β-ketoester was obtained. In order to show that the greater yield of self-condensation product obtained with sodium amide as compared with lithium amide when the reactions were carried out in the relatively polar medium, diethyl ether, was probably not due to solvation effects alone, ethyl phenylacetate was self-condensed by these

TABLE I

REACTIONS OF ESTERS WITH LITHIUM AMIDE

ESTER	PRODUCTS ISOLATED	REACTION TIME, HOURS	B.P., °C.	MM.	YIELD, %
n-Propyl acetate	*n*-Propyl acetoacetate	2	80–81	10 (3)	30
Isopropyl acetate	Isopropyl acetoacetate	3	75–79	16[a]	34
tert-Butyl acetate	*tert*-Butyl acetoacetate	12	71–75	12(19)	28
Ethyl phenylacetate	Ethyl α, γ-diphenyl-acetoacetate	2; 36	77.5–79[b] (m. p.)		47; 48
	Phenylacetamide		152–152.5 (m. p.) (20)		0.7; 0.7
tert-Butyl-propionate	*tert*-Butyl α-propionyl-propionate	3	87–89	15[c]	20
Ethyl *n*-butyrate	Ethyl α-*n*-butyrl-*n*-butyrate	2	87–95	10[d]	trace
	n-Butyramide		113–114 (m.p.) (21)		5.2

[a] Copper salt, m.p. 174–174.5° (18).

[b] Converted to 1,4-diphenyl-3-benzylpyrazalone-5, m.p. 231–232° (19).

[c] *Anal.*: Calc'd for $C_{10}H_{18}O_3$: C, 64.51; H, 9.68. Found: C, 64.10; H, 9.66.

[d] Gave a positive enol test with alcoholic ferric chloride solution.

TABLE II

SELF-CONDENSATION OF ETHYL PHENYLACETATE IN PETROLEUM ETHER (B.P. 30–36°)

BASE	REACTION TIME, HOURS	YIELD OF ETHYL α, γ-DIPHENYL-ACETOACETATE, %
$LiNH_2$	2	13.4
$LiNH_2$	6	19.2
$NaNH_2$	2	35.4
$NaNH_2$	6	50.3

two bases in low-boiling petroleum ether (b.p. 30–36°). Although the yields of β-ketoester were lower in petroleum ether than in diethyl ether, it may be seen (Table II) that sodium amide still gives the higher yield.

In attempting to explain the differences in action between lithium and sodium amides, it appears that the anion of the bases (*i.e.*, NH_2^-) is probably not independent of the cation with which it is associated when the alkali amides effect condensations. If this were not the case, then there should be no difference in the

effectiveness of lithium amide and sodium amide in the reactions studied, since the action of the amide ion should be the same regardless of its source.

Morton (5) has suggested that in spite of the ionic character of organoalkali compounds, the probability that they dissociate to any appreciable extent in organic solvents is rather remote. They probably exist and react as ion pairs rather than as the free anion and cation. The cation is in close proximity to the anion and probably has a very definite influence on it. The data obtained in the present work indicate that the concept of ion pairs is applicable to reactions effected by the alkali amides in organic solvents.

When an ester reacts with a base, it has been suggested (4) that the stronger and larger the base is, the more readily is the α-hydrogen of the ester attacked, to give the ester anion, the active intermediate in condensations. Pauling (6) has pointed out that the alkali metals decrease in electronegativity with increasing atomic weight. If, therefore, in the ion pairs $Li^+NH_2^-$ and $Na^+NH_2^-$, sodium is less electronegative than lithium, then the amide portion of the sodium amide is more electronegative than that of lithium amide. Therefore, sodium amide is probably a stronger base than lithium amide and hence the former should react with the α-hydrogen of an ester to a greater extent than does the latter. In this connection, it has been shown recently (7) that in the conversion of *o*-aroyloxyacetarones by the alkali metals into the corresponding *o*-hydroxydiaroylmethanes (these reactions may be regarded as intramolecular Claisen condensations), the yields of the β-diketones produced increase with the increasing basicity of the metal used. Thus, lithium is less effective than sodium which is less effective than potassium for these transformations. Also, these workers have shown that these conversions do not take place with lithium carbonate while with caesium and rubidium carbonates the transformations are rapid. Also, it is of interest to note that ethyllithium, ethylsodium, and ethylpotassium metalate benzofuran with increasing ease (8).

It then appeared of interest to show what effect variations in the size and basic strength of the condensing agents would have on the course of the condensations studied. Three lithio bases were used, namely the lithium derivatives of N-methylaniline, diethylamine, and diisopropylamine. On the basis of steric and electrical effects one would predict that the extent to which these reagents attack the α-hydrogen of an ester should increase in the order in which these bases are listed, *i.e.*, lithium N-methyl-N-phenylamide should give the most carbonyl carbon attack while lithium diisopropylamide should react mostly at the α-hydrogen of the ester.

These predictions have been confirmed in the present investigation (Table III). It may be seen that lithium diethylamide, prepared by the method of Ziegler and Ohlinger (9), is a satisfactory reagent for the self-condensation of *tert*-butyl acetate and ethyl phenylacetate. In all the other condensations effected by this base, the β-ketoester was contaminated with the N,N-diethylamide of the starting ester. These latter compounds were apparently formed by the attack of the base at the carbonyl carbon of the ester. The contaminated β-ketoesters were subjected to a ketonic cleavage (10) and the yields of the β-ketoester calculated on the basis of the ketone isolated.

TABLE III

REACTIONS OF ESTERS WITH SUBSTITUTED LITHIUM AMIDES

ESTER	BASE[a]	REACTION TIME, HOURS	PRODUCTS ISOLATED	B.P., °C.	MM.	YIELD, %
tert-Butyl acetate	LDEA	2	*tert*-Butyl acetoacetate	72–73	10 (19)	58.5
Ethyl phenylacetate	LDEA	2.5	Ethyl α,γ-diphenylacetoacetate	78–79.5 (m.p.[b])		95.5
Ethyl propionate	LDEA	1.5	Diethyl ketone	97–103	760[c, d]	20
	LDIA	0.5	Ethyl α-propionylpropionate	88–90	12 (23)[e]	21.3
	LMPA	0.25; 1.5	Ethyl α-propionylpropionate N-methyl-N-phenylpropionamide	80–124 57–57.5 (m.p.) (24)[g]	11[f]	trace; trace 44.4; 57
Ethyl *n*-butyrate	LDEA	1.5	Di-*n*-propyl ketone	141–147	760[h, i]	20
Ethyl isobutyrate	LDEA	3.5; 15	Diisopropyl ketone N,N-Diethylisobutyramide	121–126 192–194 76–77	760[j] 760 (26) 14	16; 3.5 —; 5.6
	LDIA	0.25; 3	Ethyl α-isobutyrylisobutyrate	87–90	14 (27)	47.1; 49.3
Ethyl isovalerate	LDEA	3	Diisobutyl ketone N,N-Diethylisovaleramide	170–174 93–95	760[k] 14[l]	46.6 6.6
Ethyl pelargonate	LDEA	1.5	Di-*n*-octyl ketone	50–50.5 (m.p.) (29)		44.1

[a] The abbreviations in this column have the following meanings: LDEA, lithium diethylamide; LDIA, lithium diisopropylamide; LMPA, lithium N-methyl-N-phenylamide. [b] See note (*b*) of Table I. [c] 2,4-Dinitrophenylhydrazone, m.p. 155–155.5° (22). [d] There was also isolated 9.7 g. of a clear, yellow, nitrogen-free oil, b.p. 90–160° at 10 mm. which gave a positive enol test with ferric chloride solution. This may have been formed by a dehydroacetic acid type of condensation. [e] There was also obtained 10.6 g. of the oil described in note (*d*). [f] Gave a red enol test with ferric chloride solution. [g] A sample was hydrolyzed to methylaniline, which was converted to its benzenesulfonamide, m.p. 78–79° [(17) p. 194]. [h] 2,4-Dinitrophenylhydrazone, m.p. 74.5–75° (22). [i] There was also obtained 11.1 g. of a clear, yellow, nitrogen-free oil, b.p. 75–142° at 4 mm. which gave a positive enol test with ferric chloride. [j] 2,4-Dinitrophenylhydrazone, m.p. 87–88° (25). [k] Semicarbazone, m.p. 121–121.5° (28). [l] *Anal.* Calc'd for $C_9H_{19}NO$: C, 68.79; H, 12.10; N, 8.92. Found: C, 68.67; H, 12.22; N, 9.18.

It may be seen (Table III) that while the reaction between ethyl isobutyrate and lithium diethylamide gives a mixture of ethyl α-isobutyrylisobutyrate (isolated as diisopropyl ketone) and N,N-diethylisobutyramide, the reaction between the more complex base, lithium diisopropylamide, and ethyl isobutyrate results apparently only in attack on the α-hydrogen of the ester with the production of a 49% yield of pure β-ketoester. It is also of interest to note that the reaction between lithium diisopropylamide and ethyl isobutyrate is a rapid one. Increasing the reaction time from fifteen minutes to three hours resulted in no substantial increase in β-ketoester formation. Finally, the relatively weak base, lithium N-methyl-N-phenylamide, has been shown to react mainly at the carbonyl carbon of ethyl propionate to give a 57% yield of N-methyl-N-phenyl propionamide.

The results reported here agree essentially with those published recently for similar condensations with the analogous magnesium bases (11, 12).

EXPERIMENTAL

REACTIONS OF ESTERS WITH LITHIUM AMIDE

(a) *Preparation of the ethereal suspension of lithium amide.* The apparatus used in this preparation is the same as that described previously for the preparation of sodium amide (13). To the reaction flask, 300 ml. of anhydrous liquid ammonia and a few crystals of hydrated iron (III) nitrate are added, and the solution stirred rapidly for ten minutes. The rate of stirring is then reduced and 0.5 mole (3.5 g.) of small pieces of lithium is added. When the lithium has been converted to lithium amide (as indicated by the disappearance of the blue color in the solution and the formation of a blue-gray sludge in the reaction flask), 250 ml. of absolute ether is added. The reaction mixture is placed on a steam-bath and the liquid ammonia evaporated. When the ether begins to reflux, indicating that no liquid ammonia is left in the flask, the reaction mixture is allowed to come to room temperature. Sufficient absolute ether is then added to the flask so that it contains about 500 ml. of liquid. In this reaction the conversion of lithium to lithium amide is assumed to be quantitative.

(b) *General procedure for the condensations.* To one equivalent of lithium amide, prepared as described above, is added 1.1 equivalents of the ester dissolved in an equal volume of anhydrous ether. After the addition of the ester is complete and spontaneous refluxing of the ether stops, the reaction mixture is stirred and refluxed on a steam-bath for the time indicated in Table I. After cooling to room temperature, the contents of the flask are stirred into crushed ice and about 100 ml. of conc'd hydrochloric acid. The chilled mixture phases are separated, the aqueous phase is extracted with several 100-ml. portions of ether, and the combined ethereal phases are dried over Drierite and the solvent distilled. Distillation is continued at atmospheric pressure to remove any unreacted ester. The residue is then distilled *in vacuo* if the product is a liquid or crystallized if the product is a solid.

REACTIONS OF ESTERS WITH DISUBSTITUTED LITHIUM AMIDES

(a) *Preparation of phenyllithium.* The procedure followed is essentially that of Gilman, *et al.* (14) except that lithium sand instead of pieces of the metal was allowed to react with the bromobenzene, using diethyl ether as a solvent. A 5-ml. portion of the reagent was standardized with 0.1 *N* hydrochloric acid after being hydrolyzed with water (15). A Gilman test (16) for the Grignard reagent was also performed on a 1-ml. sample.

(b) *Preparation of disubstituted lithium amides.* To 500 ml. of a 1 molar solution of phenyllithium contained in a 1000-ml. round-bottomed flask equipped with a mercury

sealed stirrer, a reflux condenser, and an addition funnel was added 0.5 mole of the appropriate secondary amine listed in Table III, at such a rate as to keep the ether gently refluxing. The solution was stirred for five minutes after the addition of the amine was completed and a 1-ml. sample was withdrawn and a Gilman test (16) made. If the test was negative, the solution of the lithium disubstituted amide was ready for use. The conversion of the amine to the corresponding lithium derivative was assumed to be quantitative.

(c) *General procedure for the condensations and isolation of products.* To a solution of 0.5 mole of the disubstituted lithium amide, prepared as described above, is added 0.55 mole of the appropriate ester, dissolved in an equal volume of absolute ether, just rapidly enough to keep the ether in the reaction flask gently refluxing. After the addition of the ester is complete, the reaction mixture is refluxed for the appropriate length of time (Table III). The reaction mixture is hydrolyzed as described above for the condensations effected by lithium amide. After the solvent is removed, the residue is fractionated *in vacuo* if the β-ketoester is a liquid or crystallized if it is a solid. Samples of both the β-ketoester and of any higher-boiling material are fused with metallic sodium and a qualitative test for nitrogen (17) performed.

In those cases where the β-ketoester is contaminated with nitrogenous material, the β-ketoester fraction is subjected to a ketonic cleavage according to the procedure of Hudson and Hauser (10) and the yield of β-ketoester calculated on the basis of the ketone isolated. The ketone is isolated by distillation at atmospheric pressure. In those cases where there is a significant residue after the removal of the ketone, the distillation is continued at reduced pressure and the N,N-disubstituted amide of the starting ester isolated.

SUMMARY

Lithium diethylamide has been found to be a satisfactory reagent for the self-condensation of *tert*-butyl and ethyl phenylacetate. When the ethyl esters of propionic, *n*-butyric, isobutyric, isovaleric, and pelargonic acids were treated with this base, the β-ketoesters produced were found to be contaminated with the diethylamide of the starting esters.

Lithium diisopropylamide is a satisfactory reagent for the self-condensation of ethyl isobutyrate, while lithium N-methyl-N-phenylamide reacts with ethyl propionate to give N-methyl-N-phenylpropionamide.

It has been noted that when the same esters are treated with sodium amide and lithium amide, the former base gives higher yields of β-ketoester. It is suggested that the large differences in yields may be explained on the basis that the alkali amides function as ion pairs in organic solvents.

PITTSBURGH, PA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE STATE UNIVERSITY OF IOWA]

MECHANISM OF THE FORMATION OF LEVOGLUCOSAN

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Montgomery, Richtmyer, and Hudson (1, 2) have shown that many phenyl β-D-glycosides are converted to 1,6-anhydro sugars under alkaline treatment, while the corresponding α-isomers are either unaffected or degraded to tars. In the case of the single exception, that of the conversion of phenyl α-D-galactoside to D-galactosan <1,5> β <1,6>, the reaction time was 2,688 hours as compared with eight or nine hours for most of the β-glycosides studied. Subsequently, McCloskey and Coleman (3) proposed a double inversion mechanism to explain the retention of configuration of the number one carbon atom. The reaction is pictured as proceeding through two steps. First, the inversion of carbon one with the simultaneous removal of the phenoxyl group and the formation of a 1,2-anhydro sugar; and second, the addition of the hydroxyl group on carbon six to the ethylene oxide ring when it is sterically possible. When the second step is not sterically possible, as in the case of 1,2-anhydromannose, tars are formed. To test this mechanism they treated phenyl tetramethyl-β-D-glucoside, phenyl 2,3-dimethyl-β-D-glucoside, and phenyl 3-methyl-β-D-glucoside with hot alkali. The first two compounds were recovered unchanged, presumably because the formation of the 1,2-anhydro ring is prevented by the methoxyl group on carbon two. The third compound, in which the number two hydroxyl group is free, reacted, yielding the theoretical amount of phenol and an unidentified sirup. The work with phenyl 3-methyl-β-D-glucoside has been repeated and will be described in a later paragraph. In the further study of this mechanism the present authors have made the following observations.

Hickinbottom (4) has shown that Brigl's anhydride (3,4,6-triacetyl-1,2-anhydro-D-glucose) is readily attacked at room temperature by alcohols alone, yielding the corresponding β-glucosides. In view of this, treatment of phenyl β-D-glucoside with hot alcoholic alkali should produce either the glucoside or levoglucosan. It was found that the latter product was formed in good yield in hot *n*-propanolic, ethanolic, and methanolic alkali. Either sodium hydroxide or the corresponding sodium alkoxide may be used with the same effect. Thus, if the proposed mechanism is correct, the primary hydroxyl group on carbon six rather than the solvent adds to the ethylene oxide ring.

Since Brigl's anhydride is the triacetyl derivative of the proposed intermediate, its use in testing the validity of the mechanism is at once apparent. Accordingly, Brigl's anhydride was subjected to treatment with aqueous alkali under the same conditions used for phenyl β-D-glucoside. The result was the formation of levoglucosan, isolated as the triacetate, in 25% yield. It is known

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that Brigl's anhydride reacts with water to give 3,4,6-triacetyl-D-glucose. It seems safe then to conclude that the alkali stabilizes the ring sufficiently to permit deacetylation to occur prior to the reaction of the hydroxyl group on the number six carbon atom with the 1,2-anhydro ring. That the 1,2-anhydro sugar can act as an intermediate in the formation of levoglucosan from phenyl β-D-glucoside now seems quite probable. This is consistent with the contention of Ohle and Wilcke (5) that methyl 2,3-anhydroalloside, in which the ethylene oxide ring is *trans* with respect to the primary hydroxyl group, is an intermediate in the formation of methyl 3,6-anhydroglucoside. They showed that when methyl 2-acetyl-3,5,6-tritosylglucofuranoside, from which the tosyl groups at positions five and six are difficult to remove, is treated with alkali, the product is methyl 2,3-anhydro-5,6-ditosylallofuranoside. But when methyl 3-tosyl-2,5,6-triacetylglucofuranoside, from which all three acetyl groups are easily removed, is treated with alkali, the product is methyl 3,6-anhydroglucofuranoside. However, when 3-tosyl-5,6-diacetyl-1,2-isopropylidene-D-glucose, in which the formation of a 2,3-anhydro ring is hindered by the isopropylidene group, is so treated, the only effect is deacetylation at the five and six positions. No anhydro ring is formed.

When the alkaline treatment of Brigl's anhydride was carried out in ethyl alcohol, the result was likewise the formation of levoglucosan, in 30% yield. This is consistent with our finding that phenyl β-D-glucoside is converted to levoglucosan under the action of hot ethanolic alkali.

Phenyl 3-methyltriacetyl-β-D-glucoside was treated with 2.6 *N* ethanolic alkali. Upon benzoylation of the sirupy product, a crystalline compound was obtained. Simultaneous debenzoylation and methylation of this compound by the Haworth method yielded trimethyllevoglucosan. Thus, the compound was the dibenzoyl derivative of 3-methyllevoglucosan.

The synthesis of phenyl 2-methyl-β-D-glucoside was accomplished. This compound was unaffected by boiling for forty-eight hours in aqueous alkali. A 92% recovery of the original compound was obtained.

EXPERIMENTAL

Action of alcoholic alkali on phenyl β-D-glucoside. Phenyl β-D-glucoside (2 g.) was added to 100 ml. of 2.6 *N* sodium hydroxide or sodium ethoxide in ethyl alcohol, and refluxed for forty hours. At the end of this time the solution was neutralized to methyl orange with 4 *N* sulfuric acid. The salts were separated by filtration, and the alcoholic solution evaporated under reduced pressure to a sirup. This sirup was acetylated by adding 12 ml. of acetic anhydride and heating at 100° for one hour. The excess acetic anhydride was decomposed with water and the solution was evaporated to dryness under reduced pressure. The residue was taken up with 25 ml. of chloroform. After washing with two 5-ml. portions of water, the chloroform was removed by distillation under reduced pressure. The residue (triacetyllevoglucosan) was crystallized from a small amount of ethyl alcohol. Yield, 1.3 g. (60%). The identity of the product was confirmed by a mixed melting point with an authentic sample of triacetyllevoglucosan.

When methyl alcohol was substituted for ethyl alcohol, using either sodium hydroxide or sodium methoxide in a 1.3 *N* solution, the mixture was heated for three days in an oven set at 98°. The yield was 67%.

When 1.3 *N* sodium hydroxide or sodium *n*-propoxide in *n*-propyl alcohol was used, the mixture was heated at reflux temperature for 24 hours. The yield was 60%.

Action of aqueous alkali on Brigl's anhydride. Two grams of 3,4,6-triacetyl-1,2-anhydro-D-glucose (4, 6) was heated in 100 ml. of 1.3 *N* aqueous sodium hydroxide at 90° in an oil-bath for twenty-four hours. The solution was neutralized to methyl orange with 4 *N* sulfuric acid and evaporated to dryness under reduced pressure. The salts were extracted with hot ethyl alcohol. From this point on, the procedure was the same as for the extraction of triacetyllevoglucosan from the alkaline treatment of phenyl β-D-glucoside. The yield of triacetyllevoglucosan was 0.5 g. (25%). The identity of the product was confirmed by a mixed melting point.

Action of ethanolic alkali on Brigl's anhydride. Four grams of 3,4,6-triacetyl-1,2-anhydro-D-glucose was heated in 200 ml. of 2.6 *N* sodium hydroxide in ethyl alcohol at reflux temperature for twenty-four hours. The solution was neutralized to methyl orange with 4 *N* sulfuric acid and evaporated to dryness under reduced pressure. The salts were extracted with hot ethyl alcohol. From this point on, the procedure was the same as for the preceding experiment. The yield of triacetyllevoglucosan was 1.2 g. (30%). The identity of the product was confirmed by a mixed melting point.

3-Methyl-2,4-dibenzoyllevoglucosan. A mixture of 3 g. of phenyl 3-methyl-triacetyl-β-D-glucoside (7) in 100 ml. of 2.6 *N* ethanolic sodium hydroxide was refluxed for forty hours. After neutralizing the solution and evaporating the solvent, as above, the remaining sirup was benzoylated in 13 ml. of anhydrous pyridine with 11 ml. of benzoyl chloride. The mixture was allowed to stand in an oven at 60° for two hours, and then at room temperature overnight. The next day the mixture was triturated with enough water to decompose the excess benzoyl chloride. The mixture was extracted with 80 ml. of chloroform followed by 25 ml. of water. The aqueous extract was extracted with 25 ml. of chloroform, and the chloroform extracts were combined. The chloroform solution was washed successively with 25 ml. of 6 *N* hydrochloric acid, 25 ml. of 4 *N* sodium hydroxide, and 25 ml. of water. The solvent was removed by distillation, leaving a sirup which was crystallized from glacial acetic acid. The yield was 2.4 g. (82%). After several recrystallizations from glacial acetic acid, the melting point was 134–136° (corr.)

$[\alpha]_D^{25}$ −36.0° (*c*, 1.44, USP chloroform).

Anal. Calc'd for $C_{21}H_{20}O_7$: C, 65.61; H, 5.25; OCH_3, 8.08.

Found: C, 65.57; H, 5.40; OCH_3, 8.19.

Methylation of 3-methyl-2,4-dibenzoyllevoglucosan. A mixture of 5 g. of 3-methyl-2,4-dibenzoyllevoglucosan and 65 ml. of acetone was placed in a 3-necked flask fitted with two burettes, a stirrer, and a tube arranged for downward distillation. While heating the flask in a water-bath at 50°, 33 ml. of methyl sulfate and 36 ml. of 50% sodium hydroxide were added from the burettes dropwise in ten portions at 10-minute intervals. After the last addition the temperature was raised to 75° and maintained for one hour. Then 50 ml. of water was added, and the temperature kept at 75° another hour. After cooling, the salts were removed by filtration, and the filtrate was extracted with four equal volumes of chloroform. The chloroform solution was evaporated to a sirup. Distillation of the sirup at 4 mm. (107°) yielded 1.7 g. (64%) of trimethyllevoglucosan. The distillate crystallized immediately upon inoculation with a seed crystal of trimethyllevoglucosan. The identity of the product was confirmed by a mixed melting point with an authentic sample.

Action of alkali on phenyl 2-methyl-β-D-glucoside. A solution of 2 g. of phenyl 2-methyl-β-D-glucoside in 100 ml. of 2.6 *N* aqueous potassium hydroxide was refluxed for forty-eight hours. The solution was neutralized to methyl orange with sulfuric acid and evaporated to dryness under reduced pressure. The residue was extracted with hot ethyl alcohol and evaporated to dryness. This residue was crystallized from a small amount of water and found to be identical with the original glucoside. The recovery was 92%.

2-Methyl-D-glucose. (8, 9). A mixture of 2.5 l. of water, 100 g. of mercuric chloride, and 125 g. of cadmium carbonate was heated to 50°. Under vigorous stirring, 50 g. of 2-methylglucose diethyl mercaptal was added. The stirring was maintained at 50° for three hours. The solid was then removed by filtration and washed well with water. Then 65 g. of silver carbonate was added to the aqueous solution and the suspension was stirred for two hours at room temperature. After the solid was removed by filtration, the filtrate was saturated

with hydrogen sulfide and again filtered through charcoal. Upon evaporation of the solvent a heavy sirup remained.

2-Methyltetrabenzoyl-D-glucose. The dry sirupy 2-methyl-D-glucose was benzoylated in the manner described in the paragraph headed "3-methyl-2,4-dibenzoyllevoglucosan." The proportions were: 125 ml. of anhydrous pyridine, 100 ml. of benzoyl chloride, 650 ml. of chloroform, and 220 ml. of water, etc. The product was not crystallized.

Phenyl 2-methyltribenzoyl-β-D-glucoside. The dried 2-methyltetrabenzoyl-D-glucose sirup was placed in a flask along with 185 ml. of a solution of anhydrous hydrogen bromide in glacial acetic acid (saturated at 0°), 510 ml. of dry benzene, and 140 ml. of dry ether, and allowed to stand overnight. The next day the solution was poured into ice, washed with a saturated solution of potassium bicarbonate and then dried with powdered calcium chloride. The solution was filtered and put into a flask containing 370 g. of phenol and 185 g. of powdered Drierite. After stirring the solution for about fifteen minutes, 75 g. of powdered silver carbonate was added and the mixture was stirred for 24 hours, with exclusion of moisture. The salts were separated by filtration and the solution was washed with sufficient alkali to remove the unchanged phenol, and then with water. This solution was evaporated to a sirup.

Phenyl 2-methyl-β-D-glucoside. The sirupy phenyl 2-methyltribenzoyl-β-D-glucoside was boiled for one minute in a solution of 375 ml. of methyl alcohol and 150 ml. of dioxane to which 15 ml. of a 10% solution of potassium methoxide was added. About 1 liter of water was added and the mixture was distilled until the volume of the residue was about 150 ml. Enough methyl alcohol was added to the sirup and water to effect complete solution on boiling. To the hot solution was added a solution of 23 g. of potassium hydroxide in 25 ml. of water. This solution was allowed to cool and stand overnight. The next day the solution was neutralized to litmus with 4 *N* sulfuric acid. The salts were removed by filtration and washed with hot methyl alcohol. This solution was evaporated to dryness and the residue was taken up with about a liter of water. The aqueous solution was acidified with sulfuric acid so that it was just acid to Bromophenol Blue. The precipitated benzoic acid was removed by filtration, and the last traces removed by extraction with ether. Enough potassium hydroxide was then added to the solution to render it alkaline to Bromophenol Blue. The solution was evaporated to a sirup, which was taken up with a small amount of hot water. On cooling, short needles of phenyl 2-methyl-β-D-glucoside formed. After several recrystallizations from Dimethyl Cellosolve, the melting point was 167–168° (corr.). Yield, 7 g., $[\alpha]_D^{25}$ −63.0° (*c*, 1, 95% alcohol).

Anal. Calc'd for $C_{13}H_{18}O_6$: C, 57.77; H, 6.71; OCH_3, 11.48.
Found: C, 57.93; H, 6.70; OCH_3, 12.48.

SUMMARY

Treatment of 3,4,6-triacetyl-1,2-anhydroglucose with hot alkali led to the formation of levoglucosan, showing that a 1,2-anhydrosugar is a possible intermediate in the conversion of phenyl β-D-glucoside to levoglucosan.

The action of hot alcoholic alkali on phenyl β-D-glucoside was shown to be as effective as aqueous alkali.

The dibenzoyl derivative of 3-methyllevoglucosan was prepared from phenyl 3-methyl-β-D-glucoside.

The preparation of phenyl 2-methyl-β-D-glucoside was accomplished. It was not affected by hot alkali.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY]

RHODANINE DERIVATIVES OF KETONES[1]

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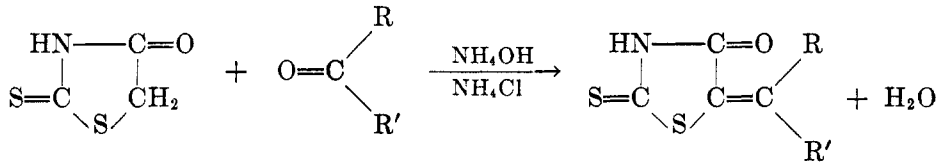
In a study of the fungicidal properties of rhodanine derivatives, an effort has been made to extend the scope of the reaction of rhodanine with carbonyl compounds. Rhodanine condenses readily with aldehydes (1) but its reaction with ketones has received little attention. Feigl (2) and Schwarz (3) state that condensations between rhodanine and ketones are possible, but neither reference contains descriptions of physical properties or analyses.[2] Certain derivatives of rhodanine with diketones have been reported (4–7) but no description of the properties of the rhodanine derivative of a simple ketone has been found in the literature.

Thirty-three representatives of various types of ketone have been condensed with rhodanine. With few exceptions, the reacting carbonyl compounds were methyl or alicyclic ketones. The second group of the methyl ketone was aliphatic, aromatic or heterocyclic.

The method of Girard (8) was used, in which the condensation takes place in an ammonium hydroxide-ethyl alcohol medium containing ammonium chloride.



EXPERIMENTAL

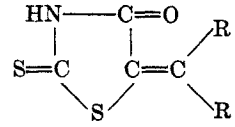
The condensation product was obtained by dissolving 0.15 mole each of the ketone and of rhodanine in 10 ml. of concentrated ammonium hydroxide and sufficient ethyl alcohol for a clear solution. Ten grams of ammonium chloride dissolved in 20 ml. of hot water was added and the resulting solution refluxed on a hot water- or steam-bath until evidence of reaction, usually the formation of a precipitate, was observed. The product either crystallized from solution or was precipitated by dilution with water. After filtration, it was recrystallized from ethyl alcohol, dioxane, acetone, benzene or a suitable mixture of solvents. No effort was made to find optimum conditions for the preparation of individual compounds. The yields varied with the nature of the ketone, being higher with the aliphatic ketones, but averaged about 30%. The melting points and analyses of the individual condensation products are recorded in Table I.

[1] The work described in this paper was done under contract with the Medical Division, Chemical Corps, U. S. Army.

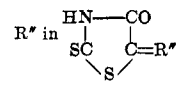
[2] A condensation product between acetone and rhodanine has been mentioned in connection with an unsuccessful attempt to synthesize penicillamine, but no description of the compound is included (9).

TABLE I

PROPERTIES OF RHODANINE DERIVATIVES



R	R′	M.P., °C. uncor.	ANALYSES			
			Calc'd		Found[a]	
			C	H	C	H
Methyl	Methyl	196–197	41.59	4.07	41.68	3.78[b]
Methyl	Ethyl	119–120	44.89	4.84	45.09	4.72[b]
Methyl	Propyl	120–121	47.73	5.51	47.84	5.63
Methyl	Isopropyl	192–192.5	47.73	5.51	47.79	5.48
Methyl	Butyl[c]	118–119	50.20	6.08	50.44	6.08
Methyl	Isobutyl	97–99	50.20	6.08	50.12	6.41[b]
Methyl	Amyl	120.5–122.0	52.38	6.59	52.52	6.51[b]
Methyl	Hexyl	107–108	54.28	7.04	54.47	7.00
Methyl	Nonyl	106–107	58.90	8.12	58.58	7.90
Ethyl	Ethyl	123	47.73	5.51	48.16	5.30[d]
Methyl	Benzyl	155[e]	57.83	4.45	57.86	4.53
Methyl	Styryl	192–194	59.74	4.24	59.66	4.15
Methyl	β-Naphthoxymethyl	188–190	60.93	4.15	60.84	4.15
Methyl	Phenyl	165–166	56.14	3.86	55.85	3.92[b]
Methyl	*p*-Tolyl	175–176	57.83	4.45	58.16	4.50[b]
Methyl	*p*-Chlorophenyl	204	48.97	2.99	49.36	3.30[b]
Methyl	*p*-Bromophenyl	215–216 d.	42.04	2.57	42.14	2.71
Ethyl	Phenyl	146–147	57.83	4.45	58.06	4.64[b]
Methyl	2-Thienyl	218–221.5 d.	44.79	2.92	45.32	2.70[b,f]
Methyl	2-(5-Chlorothienyl)	205	39.19	2.19	39.32	2.19[g]
Methyl	2-(5-Bromothienyl)	214–215 d.	33.75	1.89	33.97	2.05[g]
Methyl	2-(5-*tert*-Butylthienyl)	192–193	52.49	5.08	52.50	4.91[g]
Methyl	2-Furyl	243.5–244.5	47.98	3.13	47.60	2.63[h]
Methyl	2-(5-Methylfuryl)	248 d.	50.19	3.79	50.30	3.64[g]
Methyl	β-Furylvinyl	210–214 d.	52.57	3.61	52.69	3.73
Ethyl	Furyl	180.5–181.0	50.19	3.79	50.21	3.73[h,b]
Propyl	Furyl	159.5–160.5	52.15	4.38	52.13	4.60[h]

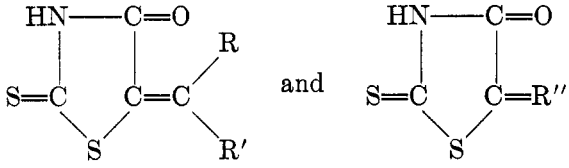


R″ in						
Cyclohexylidene		172–173	50.67	5.20	50.95	5.08
2-Methylcyclohexylidene		141–143	52.83	5.76	52.76	5.99
3-Methylcyclohexylidene		146–148	52.83	5.76	52.94	5.60
4-Methylcyclohexylidene		149–150	52.83	5.76	53.17	5.72
4-*tert*-Amylcyclohexylidene		182–183	59.32	7.47	59.45	7.37[i]
Cyclopentylidene		195–196	48.21	4.55	48.44	4.55

[a] All analyses by Clark Microchemical Laboratory unless otherwise noted. [b] Analyses by University of Pittsburgh Microchemical Laboratory. [c] Ketone prepared by R. J. Grantham. [d] S: Calc'd, 31.85; found, 31.85. [e] Some crystals, m.p. 130–134°, were also obtained. [f] S: Calc'd, 39.85; found, 39.83. [g] Ketone prepared by method of Hartough and Kosak, *J. Am. Chem. Soc.*, **69**, 3093 (1947). We are indebted to the Socony-Vacuum Co. for some of the thiophene compounds used in this work. [h] Ketone supplied by Dr. Robert Levine. [i] Ketone obtained by $K_2Cr_2O_7$-H_2SO_4 oxidation of 4-*tert*-amylcyclohexanol, following the general procedure of Grove and Bovington, *Ann. Applied Biol.*, **34**, 115 (1947) for the preparation of 4-*tert*-butylcyclohexanone; b.p., 75°/27.

SUMMARY

The condensation of rhodanine with carbonyl compounds has been extended to include derivatives of simple ketones. Products of the general formula



have been obtained.

DURHAM, NORTH CAROLINA

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY, UNIVERSITY OF ALABAMA]

DIRECT SULFURATION OF SIMPLE ORGANIC COMPOUNDS[1]

GEORGE D. PALMER AND HAROLD F. SCHAEFFER

Received August 13, 1948

Palmer and co-workers (1, 2) found that a wide variety of organic compounds reacted directly with molten sulfur to form sulfur dyes and other organic compounds. The method employed in this process consisted essentially in passing the vaporized organic reactant into molten sulfur at various temperatures (approximately 200° or above). Hydrogen sulfide was evolved in various amounts during the reactions. The sulfur compounds were produced in the excess molten sulfur at the bottom of the reactor and were purified by extraction with carbon disulfide and other solvents. The products prepared above 300° were sulfur dyes.

Heretofore all of the solid products obtained from the sulfuration of organic compound vapors have been amorphous. Recently, by modifying the apparatus and procedure we have isolated *crystalline* material formed during the preparation of a sulfur dye from nitrobenzene. The yields of the crystalline material varied from 4 to 5.5%, while at the same time about 55% of the original material was converted into an amorphous, green sulfur dye. Instead of the emission of hydrogen sulfide, sulfur dioxide was produced. Because of the exactness of technique required in obtaining the crystalline material the following procedure is given in detail.

EXPERIMENTAL

Preparation of the crystalline product. The apparatus is shown in Figure 1. The vaporization chamber, A, is a wide-mouth 500-ml. Erlenmeyer flask, provided with a good cork stopper drilled to accommodate the Y-tube B. The latter should be 18–20 mm. in diameter, with the vertical limb projecting approximately 12 cm. above the flask A. Addition of the nitrobenzene is accomplished by means of the Pyrex dropping-funnel, C. A length of tubing is sealed to the funnel stem so that the open end extends just below the end of the Y-tube. The side arm D is bent to make an angle of 45° with the upper limb of the Y-tube. The inclined condenser, E, measures 120 cm. in length. Current practice is to join the condenser to the Y-tube with a good cork stopper because ground joints occasionally have caused trouble. A tube attached to the upper end of the condenser carries the sulfur dioxide to absorbing bottles or to a fume hood. Heating is conveniently accomplished by a Wood's alloy bath.

The flask A is charged with 40 g. of flowers of sulfur, and the assembly B C E is then placed in position, taking precautions to have all joints gas-tight. Since wide-mouth Erlenmeyer flasks sometimes have imperfectly shaped necks it may be necessary to obtain a good seal by wrapping the cork with one layer of thin asbestos sheeting. When the latter is slightly moistened a good seal can be obtained by pressing the stopper firmly into the neck of the flask. After the alloy in the heating-bath has been melted the entire assembly is lowered so that the bottom of the vaporization flask A is 2.5–3 cm. below the surface of the bath. The temperature of the molten alloy is raised to 330–340°.

[1] It gives us pleasure to acknowledge the financial support of the University of Alabama Research Committee and the Office of Naval Research, Department of the Navy, in conducting this investigation.

When the flask is well filled with sulfur vapor the addition of nitrobenzene from funnel C is begun. It may require five minutes to add the first 5-ml. portion. During the addition, vapor should pass up into the condenser. While the bath temperature is kept in the 330–340° range, the remainder of the 50 ml. of nitrobenzene is added slowly. The rate should be sufficiently rapid to cause the reflux ring to gradually rise in the condenser until it has gone approximately two-thirds up the length of the tube. However, at no time should a large pool of liquid be permitted to accumulate on the surface of the sulfur.

After the reaction has been in progress for 20–40 minutes a crystalline solid begins to deposit on the wall of the condenser. Eventually, *i.e.* after about 20 ml. of nitrobenzene have been introduced, the addition of each 5-ml. portion will require from 12–20 minutes. By adopting this rate the reflux ring in the condenser will gradually recede. This is important in preventing too much of the crystalline deposit from being dislodged from the walls

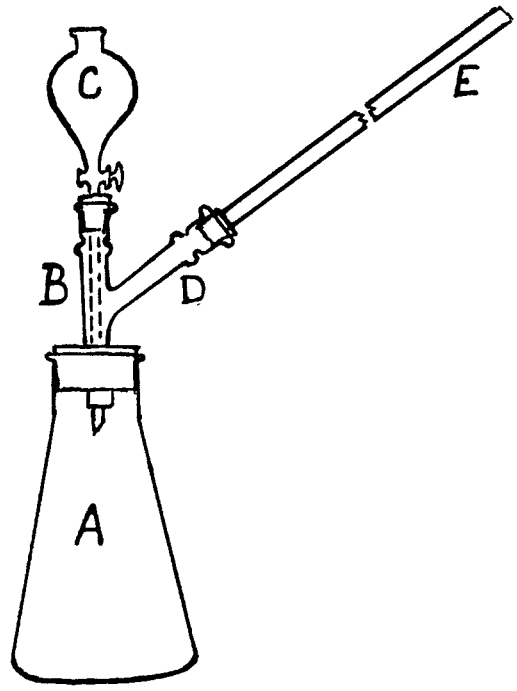

FIGURE 1.

and washed back into the vaporization flask. The time required for the addition of 50 ml. of nitrobenzene is about 2 hours (±10 minutes). Heating should be continued until reflux has practically ceased, which may require an additional period of 15–30 minutes.

The condenser is removed from the assembly and clamped in a vertical position overnight in order to permit the excess nitrobenzene to drain from the solid deposit. Final traces of the liquid are removed by drawing air through the tube for a number of hours. Finally the solid product can be scraped out by means of a heavy glass rod, the end of which has been flared to form a disc. The yield of dried, microcrystalline product is usually 5–5.5 g. In order to remove any free sulfur which might have been deposited with the crystalline material the latter is placed in a Soxhlet apparatus and subjected to prolonged extraction with C. P. benzene or with anhydrous ether.

Analyses of the crystalline material. When the crude crystals were allowed to stand exposed to air for approximately one week and recrystallized from absolute ethyl alcohol,

elemental and sulfate analyses, and molecular weight determinations showed the recrystallized substance to be practically pure aniline sulfate $(C_6H_5NH_2)_2 \cdot H_2SO_4$). The crude white crystals when freshly prepared also contained a small amount of unstable aniline-sulfur dioxide addition product (3).

TABLE I

BEHAVIOR OF THE CRYSTALLINE PRODUCT

TREATMENT GIVEN	RESULTS
1. Barium hydroxide solution	Released NH_3.
2. Potassium carbonate solution	Released NH_3.
3. Potassium ferricyanide solution	Reagent reduced.
4. Chloroplatinic acid, 2%	Solid gradually yields lathlike crystals.
5. Chloroauric acid, 2%	Reduction. Blue ppt. and metallic gold.
6. Palladium chloride, 1%	Curd-like orange-colored ppt. plus slender prismatic crystals.
7. Ferric nitrate solution	Green ppt.
8. Ferric chloride solution	Green ppt.
9. Silver nitrate solution	White ppt. which rapidly turned brown. After thorough washing the brown ppt. was identified as silver sulfide.
10. 30% Hydrogen peroxide	No visible change.
11. Oxygen gas	Bubbled through solution 25 hrs. No change observed.
12. Sodium hydroxide solution, 10%	Aniline, NH_3, and small unidentified residue.
13. Fusion with sodium hydroxide	Aniline and NH_3.
14. Ammonium hydroxide solution (conc'd)	Aniline.
15. Heated to 250°	Green sulfur dye residue, SO_2, and aniline.
16. Glacial acetic acid	H_2S evolution over a long period.
17. Benzyl alcohol	H_2S evolution.
18. 1,4-Dioxane	H_2S evolution over a long period.
19. Benzothiazole	Slight evolution of H_2S.
20. Nitrobenzene	Copious H_2S evolution; charred residue.
21. *o*-Nitrotoluene	H_2S evolution.
22. *o*-Toluidine	H_2S evolution.
23. Dimethylaniline	H_2S evolution.
24. Mesityl oxide	Slight H_2S evolution; discoloration of liquid.
25. Acetylacetone	H_2S evolution.
26. Acetonylacetone	Abundant H_2S evolution; solution becomes pink, then passes through red, carmine, purple to deep blue.
27. Diacetone alcohol	H_2S evolution; solution turns pink, finally brown.
28. Acetone	No H_2S.

The behavior of an aqueous solution of the crystalline material (crystals extracted from benzene or ether and placed in well-stoppered small bottle) toward various reagents at room temperature, the effect of boiling the material in various organic liquids, and the substances produced upon heating are given in Table I.

Similar results with the boiling organic liquids were obtained from crystals recrystallized from water.

The dried crystalline product obtained by the sulfuration of nitrobenzene had a faint odor of sulfur dioxide; even after having been extracted for 50–60 hours a trace of sulfur dioxide odor persisted. This was especially true upon opening a bottle in which the crystals had been stored for several weeks. The material gave a positive carbylamine test, indicating the presence of one or more potential amino groups. At room temperature the solubility of the material in water is a little over 7%, while in most of the common organic solvents tried, the solubility at room temperature is negligible. The material is practically insoluble in C. P. ether, benzene, toluene, chloroform, chlorobenzene, ligroin, etc. At 25°, 100 g. of absolute alcohol will dissolve 1.24 g.

Green amorphous sulfur dye (Flask A, Fig. 1). The quantity of unreacted sulfur present in different runs varies from practically 30–40% of the melt. After removal of the unreacted sulfur the color of the residue is almost black but it leaves a green streak on unglazed porcelain. Although the solid is not affected by common solvents it imparts a blue-green color to cotton. When produced at higher temperatures the nitrobenzene-sulfur dye imparts a deep green color to cotton.

SUMMARY

1. A new procedure is given for the preparation of crystals and a green sulfur dye by the sulfuration of nitrobenzene. Sulfur dioxide is also evolved.

2. Analyses, molecular weights, and certain properties of the freshly prepared crystals show the presence of aniline sulfate and a small amount of aniline-sulfur dioxide addition product.

3. The fresh crystalline product obtained by heating sulfur with nitrobenzene has the property of being converted, by treatment with alkali, chiefly into *aniline*, and some ammonia with a small amount of an unidentified solid; heat alone converts it into a *sulfur dye*, sulfur dioxide, and a small amount of aniline.

4. This apparent intermediate crystalline material should give us information about the structure of the *simplest* sulfur dyes.

UNIVERSITY, ALABAMA

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

AMINES AND IMINES OF 1,4-DIARYL UNSATURATED 1,4-DIKETONES[1]

ROBERT E. LUTZ, THAD AMACKER[1a,2], SPENCER M. KING[1b] AND N. H. SHEARER[1c]

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This investigation concerning the products of the action of amines on dibenzoylethylene dibromide (I) and dibenzoylacetylene (III) is an extension of earlier preliminary work in this field (1, 2, 3) and is related to the similar work done in the series based on benzalacetophenone (4, 5). Antimalarial tests (5, 6) in this field, which were first made on some of the dibenzoyl(dialkylamino)ethylenes[3] (*cf.* 5), added this novel type of compound to the list of those actively investigated during the war, and stimulated the synthesis of a number of new nuclear-substituted α-morpholinylbenzalacetophenones, saturated α,β-dimorpholinylketones, and related compounds, which have been considered in another paper (5).

The new mono- and di-alkylaminodibenzoylethylenes are listed in Table I in the experimental part, together with a number of their bromo derivatives. Three monoalkylamino compounds which were not obtained in crystalline form were characterized by conversion into crystalline bromo derivatives.

AMINODIBENZOYLETHYLENE

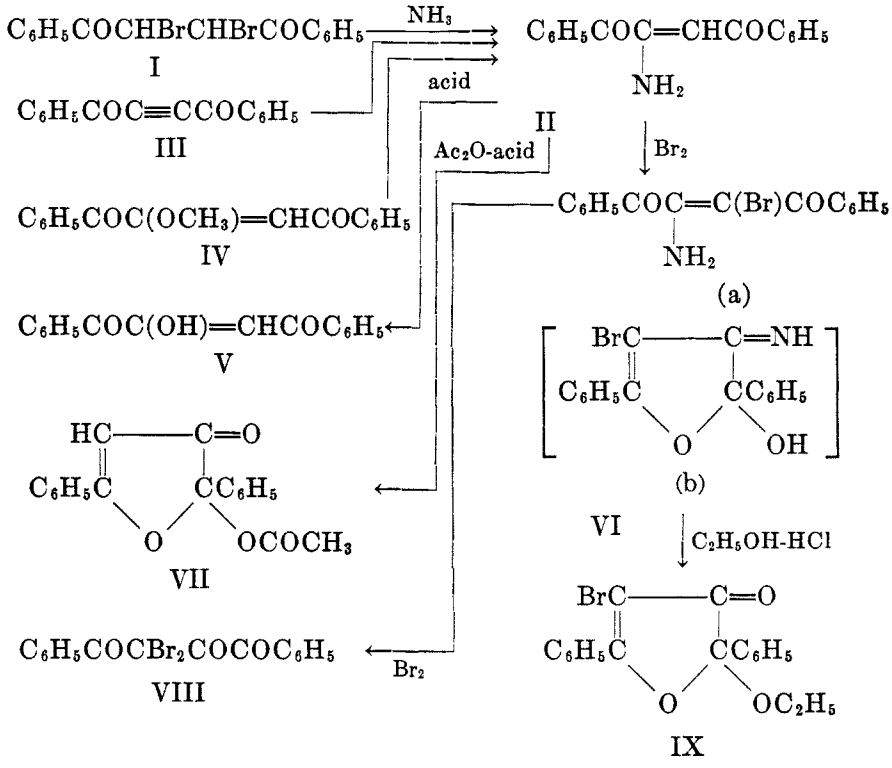
This compound, formulated as II, has been made by the action of ammonia on dibenzoylethylene dibromide (I) (1), on dibenzoylmethoxyethylene (IV) (7, 8, 9), and on dibenzoylacetylene (III) (1, 2, 10). It forms a crystalline hydrobromide which is hydrolyzed by water with regeneration of the amino compound. It is readily hydrolyzed by acids with loss of ammonia, to the triketone enol (V), in contrast with the typical substituted-amino analogs, *e.g.*, the morpholinyl (3), diethylamino, anilino, and methylanilino compounds (*cf.* XIV, XXIII), which are much more resistant toward this type of hydrolysis. The compound is not readily acylated by acetic anhydride, and it does not react with diazomethane.

The amino compound clearly must have the enamine structure (II) because of its properties, its intensely yellow color, and the synthesis from dibenzoylmethoxyethylene (IV) and from dibenzoylacetylene (III). This supposition is sup-

[1] (a) The larger part of the work reported is taken from the Doctorate Dissertation of the late Dr. Thad Amacker, University of Virginia, May 1943. (b) A number of the experiments and the ultra-violet absorptions were carried out by Mr. S. M. King. (c) A number of the derivatives in the table were made by Dr. N. H. Shearer, Master's Thesis, University of Virginia, May 1944.

[2] du Pont Co. Research Fellow, 1942–1943.

[3] In tests carried out at the Lilly Research Laboratories in the summer of 1943, dibenzoyl(dibutylamino)ethylene was found to lower the parasite count in ducks infected with *Plasmodium lophurae*. By present standards, however, (6) this compound and others of the type are regarded as "inactive."



ported by the ultra-violet absorption spectrum (Figure 1) (maxima at 259 and 360 mμ) which shows the general characteristics of those of the β-amino unsaturated ketone system, NC=C—C=O, (11), and resembles that of the reference compound, dibenzoyl(dimethylamino)ethylene (XIV) (Figure 2) (maxima at 254 and 340 mμ).

Bromination converts the amino compound (II) into the unstable hydrobromide of a monobromo derivative (VI). The crystalline material might possibly have the hydroxyfuranone-imine structure (VIb). It is colorless but dissolves to give a yellow solution. This property is analogous to that of the triketone enol (V) (7), which crystallizes from ethanol in a colorless form, but which on melting or dissolving gives the lower-melting and crystallizable enol form. The ultra-violet absorption spectrum of this amino compound (Figure 1) (maxima at 251 and 324 mμ) seems to be consistent with the open-chain structure (VIa) although the maximum at 324 mμ involves a very pronounced displacement toward the shorter wavelength relative to the corresponding maxima of II, XI, and XIV, and it is not far from the principal absorption maximum of 4-bromo-2,5-diphenyl-2-ethoxyfuranone-3 (IX) at 327 mμ (Figure 7). The large absorption maximum at 251 mμ, however, seems to be distinctive. Further data and study are obviously needed here.

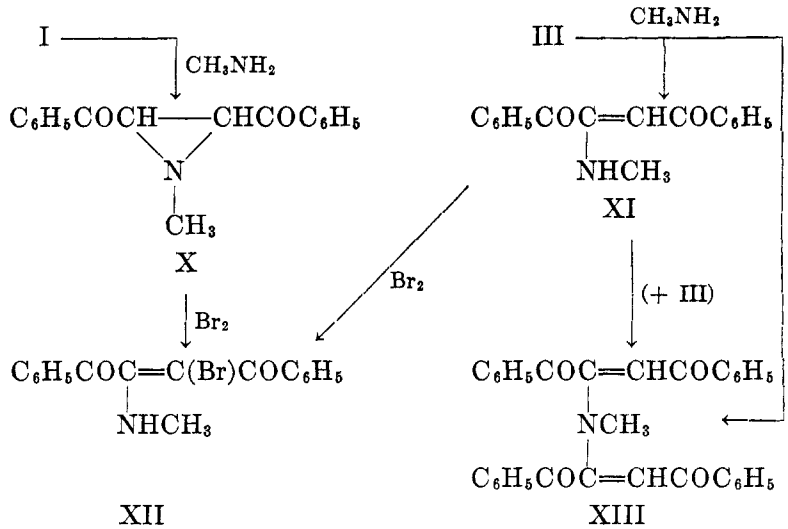
If the interpretation in terms of mobile ring-chain tautomerism is correct, then the bromo compound (VI) is less stable in the cyclic form than the oxygen analog

(4-bromo-2,5-diphenyl-2-hydroxyfuranone-3), which is believed to exist exclusively in the cyclic form (12). Whatever is the case, the bromo compound (VI) is readily converted by ethanolic hydrogen chloride into the 2-ethoxyfuranone (IX) with loss of nitrogen; bromination also involves elimination of the nitrogen but produces the dibromotriketone (VIII).

There is analogy between dibenzoylmethoxyethylene (IV) and methoxyquinones; both systems undergo similar displacement of methoxyl by amines, obviously by way of attack at the β-carbon of the β-methoxy unsaturated ketone system, —COCH=C(OCH_3)—, followed by elimination of methanol. The orienting or donor effect of the methoxyl is presumed to bar addition to the alternate α-methoxy unsaturated ketone system which is also present, —COC(OCH_3)=CH—, and to prevent the formation therefrom of isolable addition compounds. This effect is comparable with the facility of displacement of methoxyl in other simpler β-methoxy unsatuarated carbonyl systems such as that of β-methoxybenzalacetophenone (5, 13).

METHYL- AND DIMETHYL-AMINODIBENZOYLETHYLENES

Methyl- and dimethyl-amine react with dibenzoylethylene dibromide (I) to give compounds analogous to II in respect to empirical formula. The compound previously reported as the methylamino derivative (XI) is actually the dimethylamino compound (XIV) which has now been made unequivocally from pure dimethylamine.[4]



[4] The reason for the confusion in the earlier report (2) is that the commercial methylamine used then (1926) contained as a major impurity dimethylamine which apparently reacted faster than methylamine. The dimethylamine, in turn, contained a considerable proportion of methylamine. The nature of the interesting yellow byproduct of melting point 96.5° which was obtained when the dibromide (I) was treated with commercial dimethylamine is not clear; it may have been the methylamino compound (XI) which melts close to this point (101–102°) and which is now known to be formed in small amounts in the reaction between methylamine and *dl*-dibenzoylethylene dibromide (I).

The true monomethylamino product is obtained by the action of pure monomethylamine on the *meso* dibromide (I). However, in contrast with the parent amino compound (II), it is colorless and therefore appears to have the ethylenimine structure (X) [*cf.* (14, 3)] rather than the enamine structure (XI) or the hydroxyfuranone-imine structure analogous to VIb. This conclusion is supported by the isomerism of the compound with the true enamine (XI) made by the addition of methylamine to dibenzoylacetylene (III), and by the ultra-violet absorption spectrum (Figure 6) where there is observed a very high absorption only in the region 252 mμ which is characteristic of the benzoyl group. This absorption pattern is very similar to those of dibenzoyldimorpholinylethane (15) (247 mμ), bromodibenzoylmorpholinylethane (15) (251 mμ), dibenzoylethane (16) (240 mμ), and analogous N-substituted phenyl benzoyl ethylenimines (17, 18).

The true dibenzoyl-(methylamino)ethylene (XI) has now been made by the action of methylamine on dibenzoylacetylene (III). It melts at 101–102° and is bright yellow in color. Du Pont (10) has prepared a compound, supposedly this, in the same way, but reported the melting point 121°.

We obtained under some conditions a dimolecular reaction product, methylamino-*bis*-dibenzoylethylene (XIII), which was made also by the action of dibenzoylacetylene on the monomolecular product (XI).

The structures of both the mono- and di-molecular compounds (XI and XIII) are indicated by the mode of formation and are confirmed by the ultra-violet absorption spectra (Figures 2 and 5) which showed maxima at 254 and 340, and 242 and 360 mμ respectively, which resemble the absorption spectra of dibenzoyl-(dimethylamino)ethylene (XIV) (Figure 2) (maxima at 254 and 340 mμ) and of the α-(*tert*-amino)benzalacetophenones (18), where the structures are certain

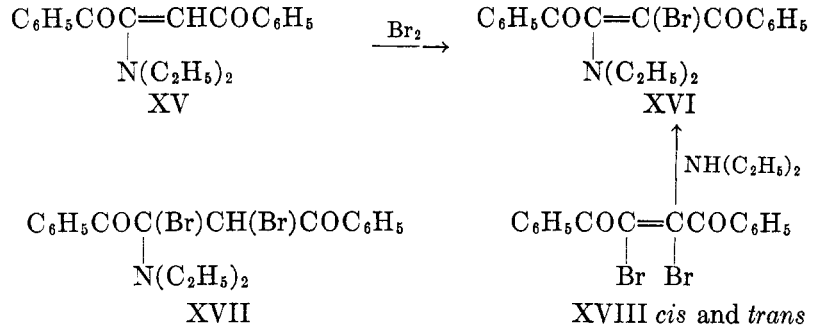
$$C_6H_5COC(N(CH_3)_2){=}CHCOC_6H_5$$

XIV

It should be noted that in the preparation of the methylimine (X) from the *dl* rather than the *meso* dibromide (I) the methyl enamine (XI) was also obtained in 25% yield. It could hardly have been formed by rearrangement of the methylimine, in view of the demonstrated stability of the imine, and it seems clearly to be the secondary product of a forked reaction.

Dibenzoyl(dimethylamino)ethylene (XIV) was made by the action of dimethylamine on either dibenzoyldibromoethane (I) or dibenzoylacetylene (III). The structure can hardly be open to question here, in view of the modes of synthesis and the non-availability of hydrogen on nitrogen for tautomerism or chelation. The ultra-violet absorption spectrum of this compound (Figure 2) therefore serves as a reference standard. It shows typical absorption at 254 mμ and also absorption in the range of 340 mμ, which is intermediate between the absorption at 300 mμ of α-*tert*-aminobenzalacetophenones and at 350 mμ for the β-*tert*-amino isomer (17, 18).

Bromination of the methylimine (X) and also of the methyl enamine (XI) gave the same monobromo compound (XII), the structure of which is established by the ultra-violet absorption (maxima at 253 and 337 mμ), which resembles those of the bromo amino compound (VIa) (maxima at 251 and 324 mμ), dimethylaminodibenzoylethylene (XIV) (254 and 340 mμ), and chlorodibenzoyl(diethylamino)ethylene (Figure 3). The bromination of the methylimine (X) poses an interesting problem of mechanism which will be investigated; for the present it may be pointed out that the methylimine is stable in refluxing methanol, and was recovered largely unchanged after standing for 24 hours in methanol containing a small amount of added hydrogen bromide.



The dimethylamino compound (XIV) reacted rapidly with bromine, as was to be expected, but hydrolysis and loss of the nitrogen occurred as well and 4-bromo-2-hydroxy-2,5-diphenylfuranone-3 was obtained.

ETHYLAMINO AND DIETHYLAMINO COMPOUNDS

Ethylamine reacted with dibenzoylethylene dibromide to give an oil which evidently consisted largely of the desired amine or imine because upon bromination it was converted into a crystalline bromo compound. No crystalline product was obtained in the reaction with dibenzoylacetylene.

Diethylamine, acting on both the dibromide and on dibenzoylacetylene, gave a crystalline dibenzoyl(diethylamino)ethylene (XV) which was converted into the bromo derivative (XVI) on bromination in chloroform. In one of the bromination experiments, however, under similar conditions, evidence was obtained of the formation of an unstable intermediate dibromide (possibly XVII) which was not analyzed. This compound was converted by the action of diethylamine into the bromo derivative (XVI) and one equivalent of diethylamine hydrobromide, and it readily lost bromine with regeneration of the starting compound (XV) when attempts were made to crystallize it from ethanol.

Bromodibenzoyl(diethylamino)ethylene (XVI) was obtained in a second way by the action of diethylamine on either *cis*- or *trans*-dibenzoyldibromoethylene (XVIII). The *cis* isomer reacted very much more readily than did the *trans*. It is noteworthy that the configurations were not consistently transmitted through to the final products.

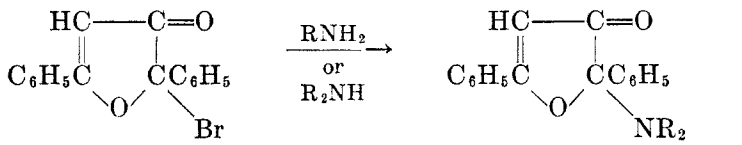
Similarly *cis*-dibenzoyldichloroethylene reacted with diethylamine to give the

chloro analog of XVI. The ultra-violet absorption spectrum of this compound (Figure 3) showed the characteristic broad maximum of the β-amino unsaturated ketone structure (255 and 330–360 mμ) (*cf.* XVI, Figure 2); the chlorine apparently had little effect on the absorption characteristics.

The above reactions of the type XVIII→XVI are of interest in connection with mechanism. Obviously the formation of an acetylenic intermediate is impossible here. The replacement of halogen must have involved 1,4-addition of the amine followed by loss of hydrogen halide. This would account for the loss of distinctive steric differences which could hardly survive the shifts of configurational centers entailed. The failure of excess amine to displace the second halogen of the dibenzoyldihalogenoethylenes (XVIII) and the isolation of only the mono-amine (XVI) under these conditions, shows that there is involved in XVI a considerably increased resistance toward addition of diethylamine; this would be expected in consequence of the donor influence of the amine nitrogen present. There is analogy here to the fact that amines add readily to dibenzoylethylene, benzalacetophenone, and to α-bromobenzalacetophenone, but do not add to α-subst.-aminobenzalacetophenones, or to dibenzoyl-(subst.-amino)ethylenes of the type XIV and XV.

2-(*tert*-AMINO)-2,5-DIPHENYL-3-FURANONES

For comparative purposes some structural isomers of the dibenzoyl-(subst.-amino)dibenzoylethylenes have been made by condensation of the 2-bromo-3-furanone (XIX) with secondary amines. From the mode of formation and the fact of isomerism with the enamines, the structures of the products are assumed to be 2-(subst.-amino)-3-furanones (XX). The ultra-violet absorption spectra of a typical one of these compounds (XXa, see Figure 7) (maxima at 242 and 312 mμ) shows a quite different type of pattern from those of most of the other compounds described above, and it shows the expected close similarities to the absorption spectrum of 2,5-diphenyl-2-methoxyfuranone-3 (maxima at 247 and 314 mμ) and 4-bromo-2,5-diphenylfuranone-3 (IX) (maxima at 253 and 327 mμ) (see Figure 7).



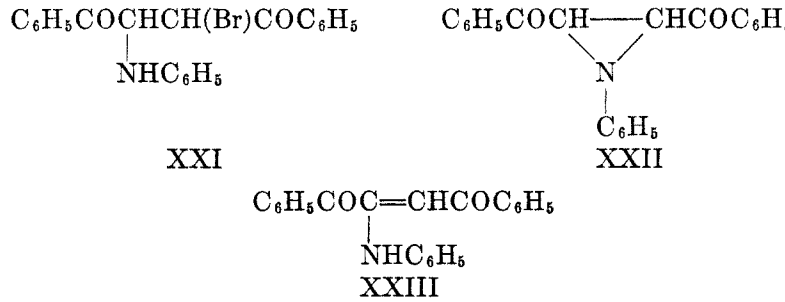
XIX XX

NR_2 = (a) $N(CH_3)_2$
(b) $N(n\text{-butyl})_2$
(c) morpholinyl

ANILINO AND METHYLANILINO DERIVATIVES

In the reaction between aniline and dibenzoylethylene dibromide (I) an intermediate monobromo monoanilino compound (XXI) was isolated when mild reaction conditions were employed. Doubtless other analogous intermediates

could be obtained in similar reactions with other amines, if special care were taken, as has been done in the reaction with morpholine (15) and as has been done in several other series, notably α,β-dibromopropiophenone (19) and benzalacetophenone dibromide (4, 5). Further treatment of the intermediate anilino bromo compound (XXI) with aniline under the usual reaction conditions caused elimination of hydrogen bromide and gave dibenzoylethylenephenylimine (XXII), the structure of which is shown by the ultra-violet absorption maximum occurring only in the region 253 mμ which is close to that expected of the benzoyl group (see Figure 6).



XXI XXII

XXIII

The isomer of the phenylimine, the true anilinodibenzoylethylene (XXIII), is obtained by the addition of aniline to dibenzoylacetylene (10). It is brilliant yellow in color and shows the expected and characteristic absorption pattern (maxima at 256 mμ and a broad band with its peak at 375 mμ) (see Figure 4). It is to be noted that the absorption in the longer wavelength involves a pronounced shift in this direction as compared with the absorption of the methyl- and dimethyl-amino compounds in the range 330–340 mμ. A similar effect was observed by Bowden (11) in the comparable series, $C_6H_5COCH{=}CHNH_2$, and its N-ethyl, N,N-diethyl, and N-phenyl derivatives.

In the reaction between dibenzoylethylene dibromide (I) and methylaniline a high reaction temperature was required to obtain the desired product which is obviously of the type of XXIII. The same compound was obtained also by the addition of methylaniline to dibenzoylacetylene. Although it must have the same enamine structure, it is, in contrast with anilinodibenzoylethylene (XXIII), practically colorless. It shows a very strong absorption maximum at 342 mμ (see Figure 4) which seems to be fully consistent with the enamine structure; in fact it is almost coincident with the absorptions of methyl- and dimethyl-aminodibenzoylethylene in the range 340 mμ. But in comparison with the anilino compound (XXIII) there is to be seen a striking shift of the maximum toward the shorter wavelength, due doubtless to steric interference with coplanarity of the N-phenyl group and the rest of the system (*cf.* ref. 11).

THE 1,4-DIMESITOYLETHYLENE SERIES

A selection of representative enamines in this series have been made and are listed in Table I. Some abnormalities in this series are worthy of note, however. The dibromide (XXIV) when treated with methylaniline gave only *trans*-bromo-

dimesitoylethylene (XXV) and not the expected dimesitoyl-(methylanilino)-ethylene. And aminodimesitoylethylene (XXVI) on bromination also gave this same *trans*-bromodimesitoylethylene (XXV).

$$C_9H_{11}COCH(Br)CH(Br)COC_9H_{11} \xrightarrow{C_6H_5NHCH_3} C_9H_{11}COC(Br)=CHCOC_9H_{11}$$

XXIV XXV *trans*

$$C_9H_{11}COC(NH_2)=CHCOC_9H_{11} \xleftarrow{Br_2}$$

XXVI

The ultra-violet absorption characteristics of certain of the compounds which were studied, are to a degree in keeping with expectations (see Figure 8). The suppression of the maximum at about 250–260 mμ which characterizes a carbonyl group conjugated with a phenyl, is doubtless caused by steric inhibition of resonance by the *ortho* methyl groups; this effect is seen also in the lack of absorption maxima in this region in the cases of dimesitoylethane, *trans*-dimesitoylethylene (*cf.* 16) (Figure 8), and of acetomesitylene (20). The curve for aminodimesitoylethylene (XXVI) (Figure 8) shows the characteristic maximum (357 mμ) which is in the expected range of the system, —C(N)=CHCO—, and which is almost identical with that of aminodibenzoylethylene itself (II) (which absorbs at 360 mμ). The dimesitoyl(diethylamino)ethylene and the bromo methylamino compounds, however, show broader patterns of absorption at shorter wavelengths in the range 270–320 mμ.

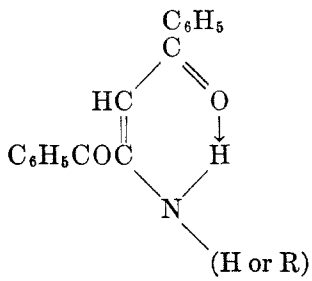
MECHANISM AND STEREOCHEMISTRY

The reaction between amines and dibenzoylethylene dibromide (I) may proceed by three paths: (a) elimination of two molecules of hydrogen bromide and addition to the resulting dibenzoylacetylene, (b) elimination of one hydrogen bromide, addition of the amine, and then loss of the second hydrogen bromide, or (c) direct displacement of one bromine followed by elimination of hydrogen bromide. Imine formation can not involve path (a). In the case of the *dl*-dibromide, to the extent that the reaction with methylamine leads to the formation of a significant proportion of the enamine, and in the reactions with ammonia, and with the secondary amines where imine formation is excluded, reaction may be by any one of these three paths. Work on these reactions and on the mechanism is in progress [*cf.* (15)].

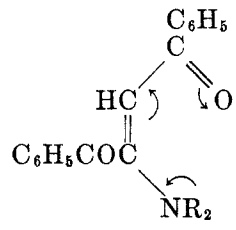
In the reaction between methylamine and the *dl* and *meso* dibromides there is some evidence of stereochemical influence affecting the course of the reactions, but at no place in the series of enamines and imines has there appeared evidence of *cis-trans* isomerism. From the nature of some of the intermediate steps involved

in the various syntheses it seems unlikely that separate and consistent configurational patterns could be retained; they certainly would be lost in paths (a) and (b) where 1,4-additions presumably occur [*cf.* (15)]. Therefore one would expect only mixtures, or as seems much more likely in view of the sharp type of differences entailed in the *cis-trans* relationship, predominantly and consistently one of the two stereoconfigurations.

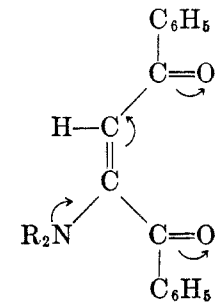
On theoretical grounds there may be a basis for postulating that certain of the enamines are *trans* (with respect to the carbonyl groups); chelation might offer a considerable stabilizing influence in those cases where nitrogen carries a free hydrogen (*cf.* II and XXVI). However, those cases where the nitrogen is tertiary cannot involve ordinary chelation (*cf.* XIV, XV); and there one can only suggest (a questionable hypothesis) that there might conceivably exist an attraction between the carbonyl and the spatially proximate amine group, related or akin to chelation, through resonance polarization which would produce opposite changes thereon (*cf.* XXVIII).



XXVII



XXVIII



XXIX

On the other hand there is analogy for a stabilizing influence in the *cis* configuration (*cis* with respect to the carbonyls) in the case of *cis*-dibenzoylmethylethylene (21, 22) and *cis*-dibenzoylphenylethylene (23)[5] where carbonyl group interaction (a quasi-chelation) has been suggested in order to account for the extraordinary relative reactivity and anomalous stability (23) (*cf.* XXIX). However the electron-repelling methyl and phenyl groups in the position *trans* to the directly-conjugated carbonyl group may play the dominant role. It would appear logical and reasonable to postulate that all of the enamines (but not necessarily the bromo derivatives), irrespective of whether or not they carry free hydrogens on the nitrogen, and also the triketone enol (V) and dibenzoylmethoxyethylene (IV), belong in this same category, with the *cis* configuration made the more stable by virtue of the *trans* relationship of the donor amine nitrogen or oxygen to the directly-conjugated and electronegative carbonyl oxygen (XXIX). Of particular significance in this connection is the fact that one typical enamine of the type under discussion, dibenzoylmorpholinylethylene (3), has been made by nitric acid oxidation of 3-morpholinyl-2,5-diphenylfuran, and dibenzoylalkoxyethylenes have similarly been made by nitric acid oxidation of the alkoxy-

[5] *Trans*-dibenzoylphenylethylene has now been made and as predicted is the *labile* stereoisomer (23).

diphenylfuranes (24); and these analogous and closely related compounds might be presumed from these syntheses to be of the *cis* configuration.

For the present, however, especially since not one *cis-trans* isomeric pair is yet known in the enamine field, it does not seem wise as yet to attempt definite

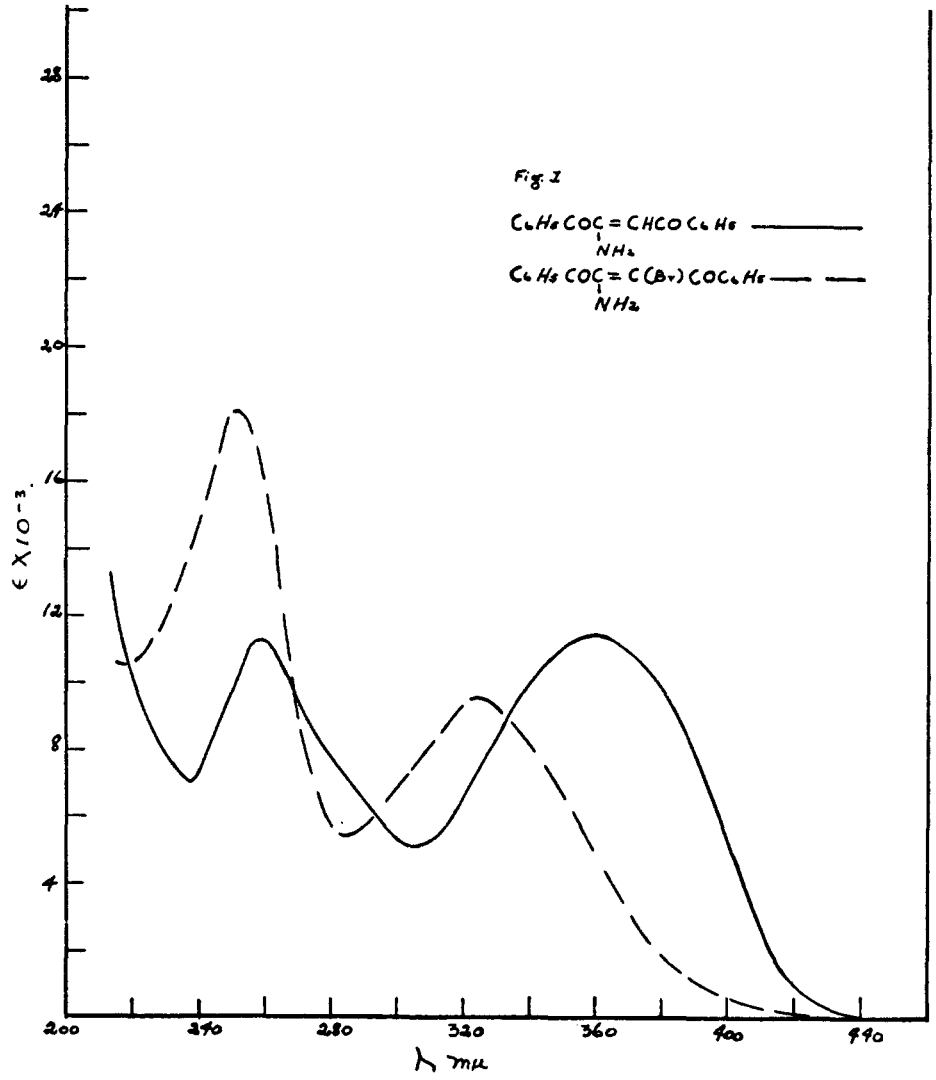


FIGURE 1

assignment of the type-configuration here, although it may be possible to do so on the basis of the ultra-violet absorptions. The ultra-violet absorption studies reported here are preliminary and are being extended in this and related fields, and consequently detailed discussion of the significance of the present results will be postponed and included in a later paper.

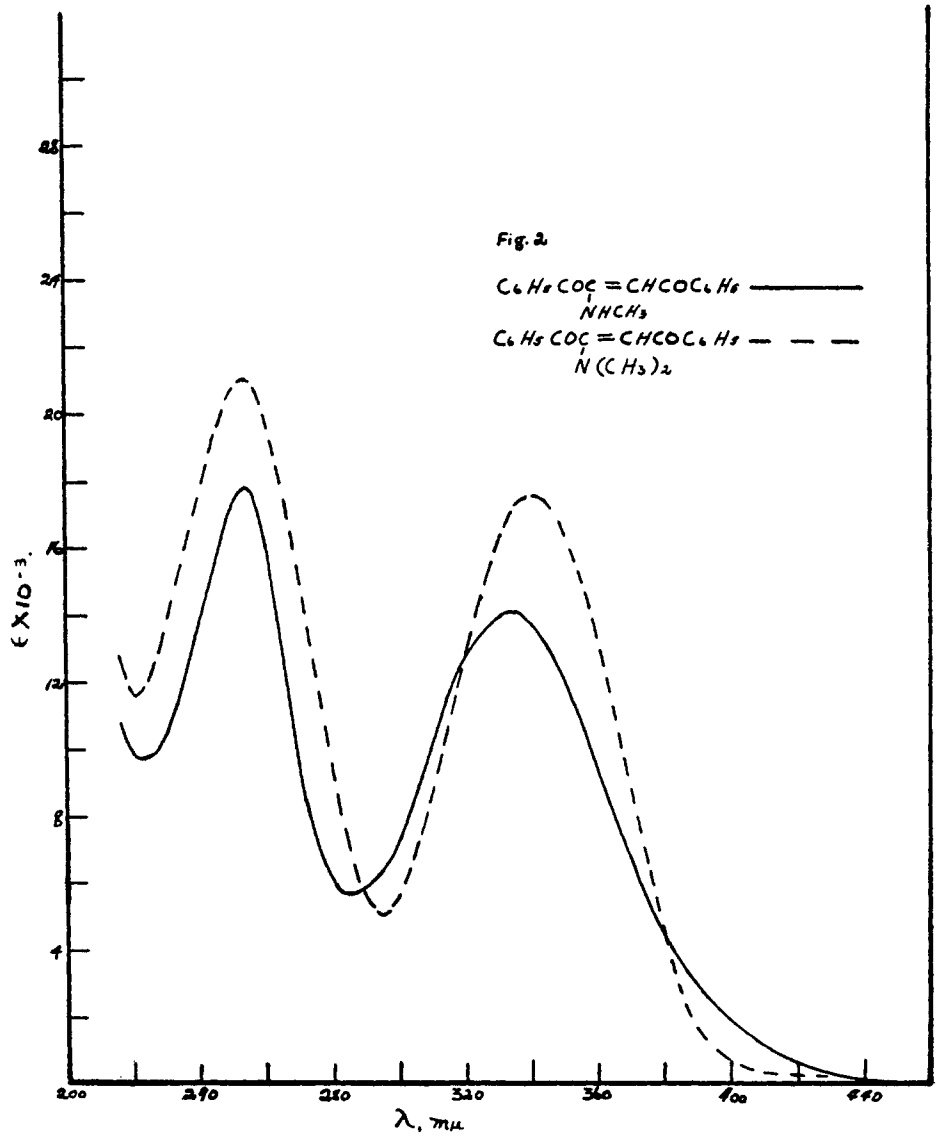


FIGURE 2

EXPERIMENTAL[6]

PREPARATION OF THE DIBENZOYL-(SUBST.-AMINO)ETHYLENES. PROCEDURES STARTING FROM DIBENZOYLETHYLENE DIBROMIDE (I).

Procedure A. Aminodibenzoylethylene (II) was best made in ethanolic ammonia at 70°. It was crystallized from ethanol and melted at 137.5–138.5°.

Procedure B. In other cases a suspension of the dibromide (I) in ethanol containing the amine in large excess was allowed to react (a) at 35° for 15 minutes, or (b) reacted at 50–65°

[6] Melting points are "corrected".

for 20–25 minutes, or (c) 70° for 15 minutes, or (d) 80° for 10 minutes, or was refluxed (e) for five or (f) twenty minutes or (g) forty minutes. In one case (h) isobutanol was used (refluxing for thirty minutes). There usually was evolution of heat and spontaneous reaction before the heating period was begun. The resulting colored (usually red) solution was cooled and diluted with water or 60% ethanol to dissolve the reagent amine hydrobromide and

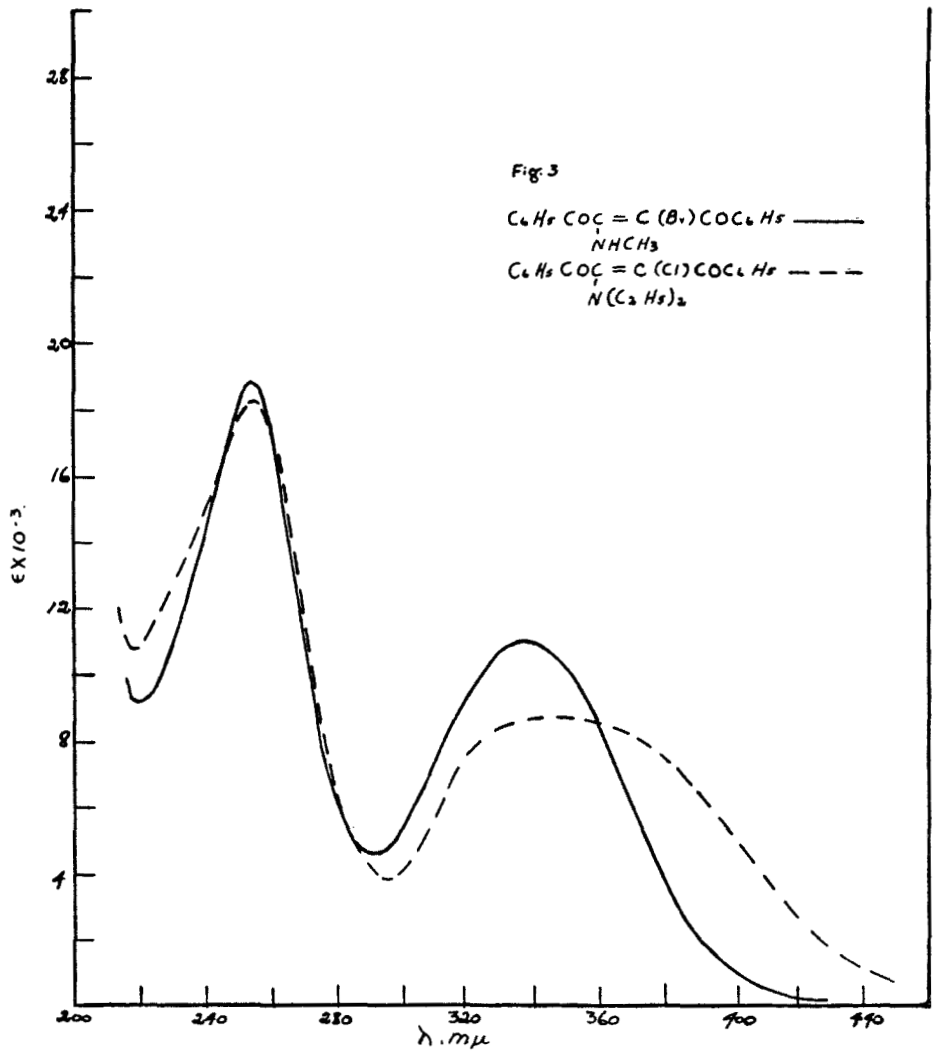


FIGURE 3

precipitate the very weakly basic product. In cases where the color of the product was dark, charcoal treatment was used in crystallization (i). In the reaction between dimesitoylethylene dibromide (XXIV) and methylaniline (in isobutanol; refluxing for 20 minutes) the product was identified as *trans*-dimesitoylbromoethylene (XXV).

Procedure C. In some cases ether was used as the solvent. Reaction was usually exothermic at the beginning. The reaction mixture was usually stirred, allowed to stand,

or refluxed gently for (a) five or (b) twenty minutes, or (c) allowed to stand overnight. The precipitated amine hydrobromide was filtered and the weakly basic product was recovered from the filtrate by (d) cooling and crystallization, or (e) concentrating and cooling. (f) In one experiment in ether as solvent using methylamine and the relatively much more soluble *dl*-dibenzoylethylene dibromide (I), the reaction proceeded more rapidly and with

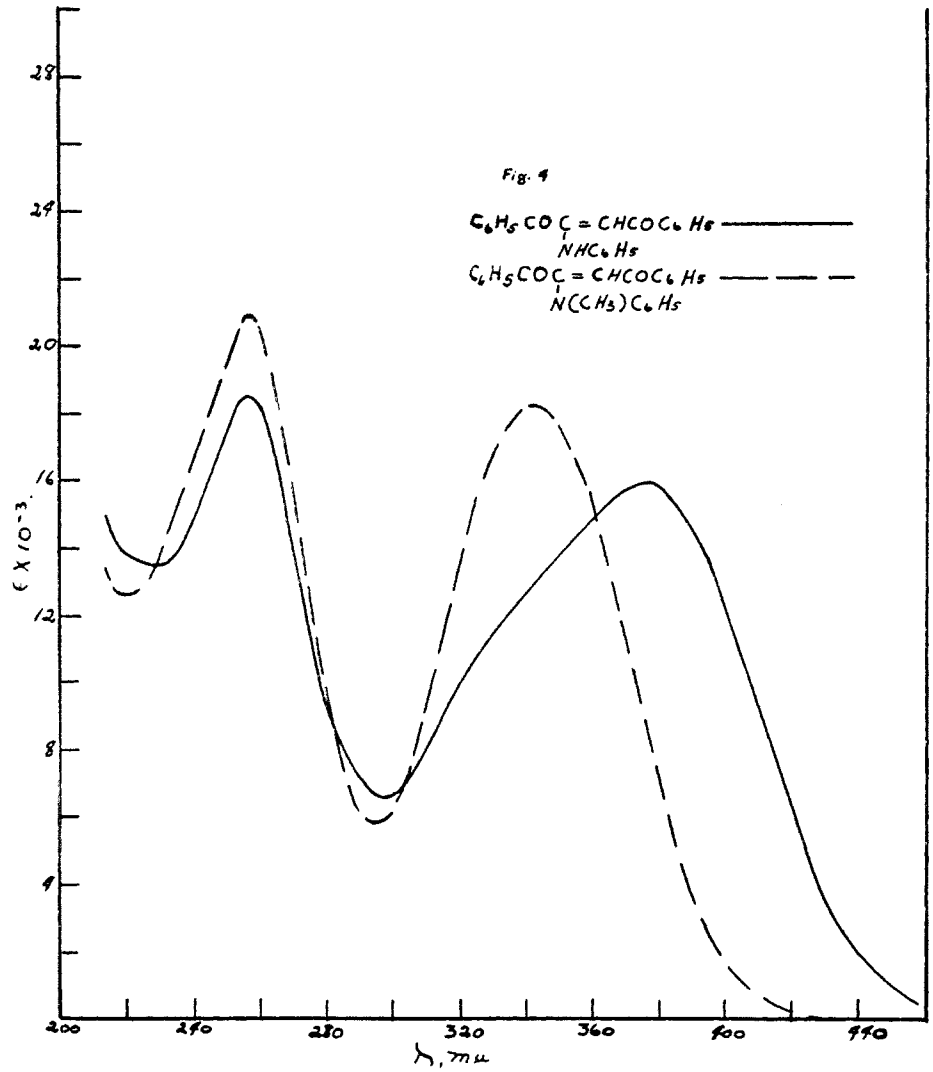


FIGURE 4

less coloration. The filtrates from crystallization of the product from 50% methanol upon concentrating and cooling gave a 25% yield of crude enamine (XI) which was purified and identified by mixture melting point with the sample made by Procedure D(a).

Procedure D started from *dibenzoylacetylene* (III). (a) In a typical experiment 1.2 g. (0.04 mole) of 25% aqueous methylamine was added to a solution of 5.6 g. (0.025 mole) of

III in 20 ml. of benzene. A vigorous exothermic reaction occurred. After ten minutes of stirring the benzene and water were evaporated at room temperature *in vacuo* and the dark red residue was crystallized from ethanol; 4.3 g. of light yellow needles, m.p. 97–99°.

(b) In the case of methylaniline a solution of 2.14 g. (0.02 mole) and 2.3 g. (0.01 mole) of III in 10 ml. of benzene was refluxed for 15 minutes. The product was precipitated by addition of isooctane.

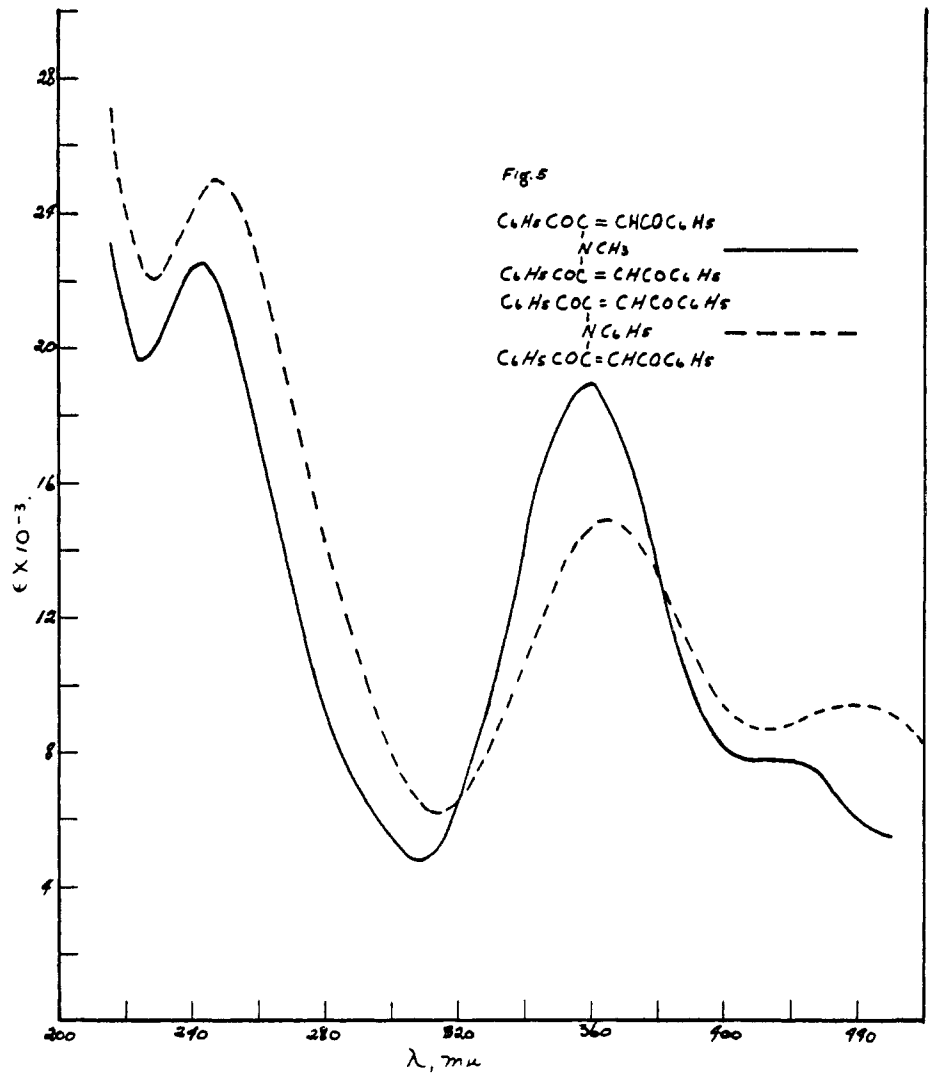


FIGURE 5

PREPARATION OF THE BROMO DERIVATIVES

Procedure E. The dibenzoyl-(subst.-amino)ethylene was dissolved in chloroform and treated by slow addition with the calculated amount of bromine. (a) The salt of the product sometimes precipitated. Water was added to the mixture or to the filtered precipitate to hydrolyze the salt and liberate the very weakly basic product. (b) When the salt did not crystallize the solution was evaporated and the residue crystallized.

In one experiment (c) on XV on a larger scale, an oil was obtained from which a small crop of crystals was isolated (it was not XVI); it appeared to be an unstable addition product (XVII). Overnight treatment with diethylamine (shaking) gave almost one equivalent of diethylamine hydrobromide; the reaction product was identified as XVI. The bulk of the non-crystalline material when treated with ethanol regenerated XV.

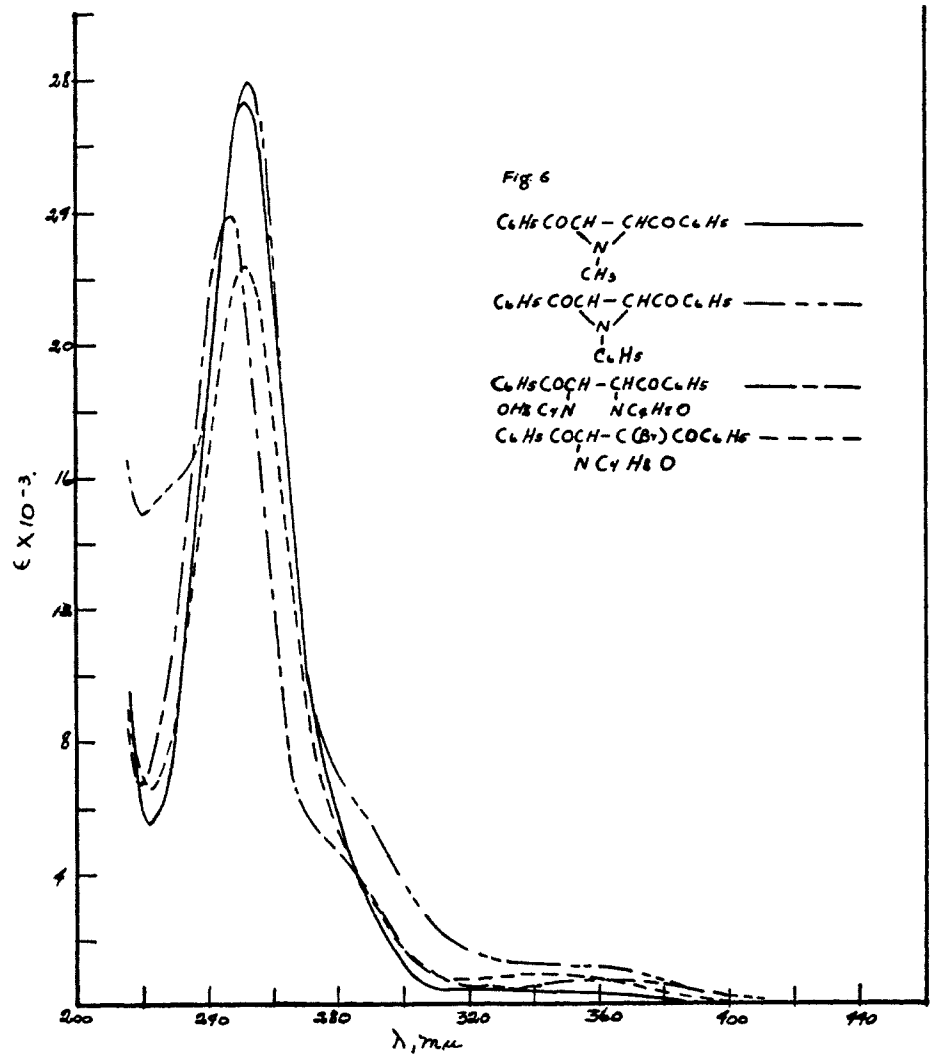


FIGURE 6

Procedure F. (a) Upon mixing 0.3 g. of *cis*-dibenzoyldibromoethylene (XVIII), 25 ml. of ethanol, and 3 ml. of diethylamine, heat was evolved and a yellow solution resulted. After heating to refluxing, the solution was diluted to the point of crystallization with water; yield of XVI, 0.2 g. (68%); m.p. 110–111°. (b) When a mixture of 5 g. of the *trans* isomer of XVIII in 50 ml. of ethanol and 20 ml. of diethylamine was refluxed for ten minutes and cooled, 4.5 g. of XVIII was recovered. From the filtrate was isolated 0.125 g.; m.p. 104–105° (identified as XVI); yield, allowing for recovery of material, 40%.

Procedure G. In the preparation of the chloro analog of XVI, the Procedure E(a) was

used, starting with *cis*-dibenzoyldichloroethylene. Crystallization of the product was brought about by dilution to the point of crystallization with dilute ethanol.

Aminodibenzylethylene hydrobromide crystallized from a solution of the base (II) in 30% hydrogen bromide-acetic acid as rectangular prisms. A crystalline sulfate (not analyzed) was obtained similarly from acetic anhydride and sulfuric acid. Hydrolysis occurred

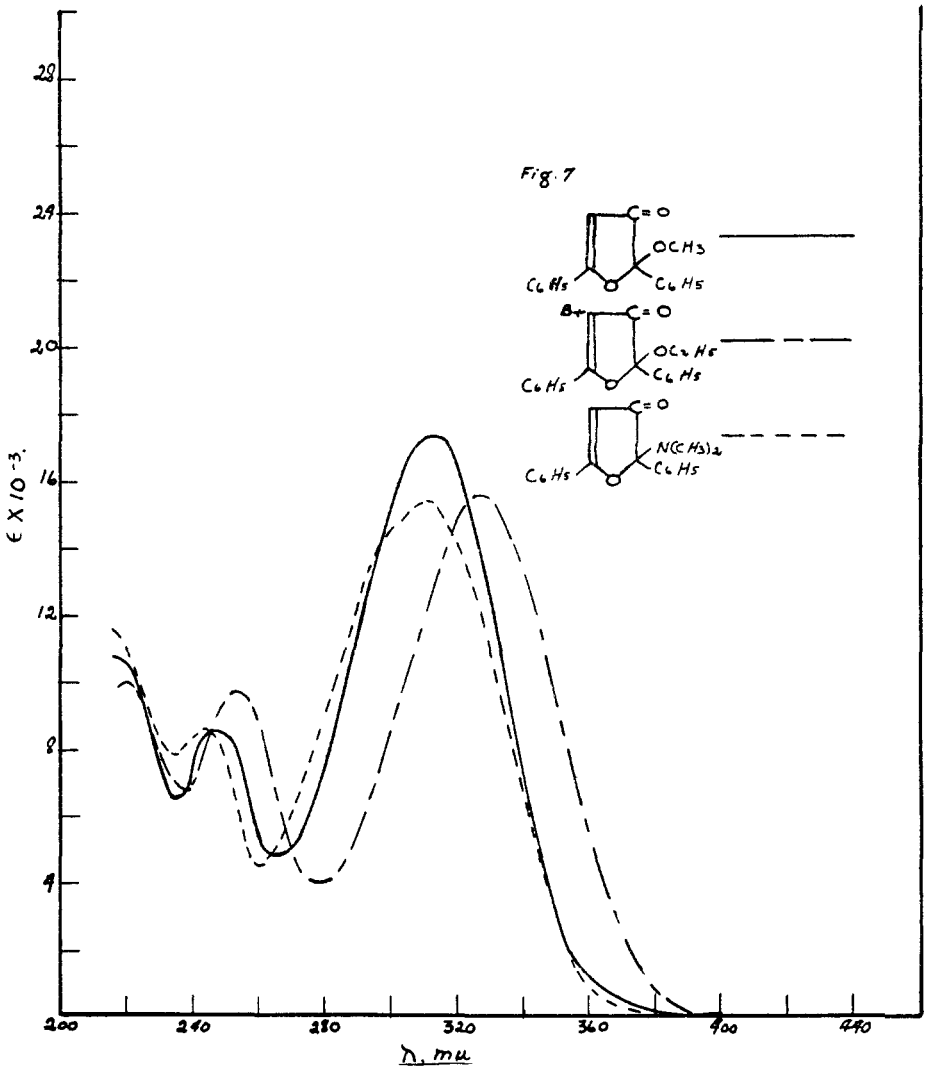


FIGURE 7

with regeneration of II in 60% ethanol or in contact with water overnight. Attempts to recrystallize resulted in hydrolysis to the triketone enol (V). Bromination of this salt in chloroform gave a white crystalline *hydrobromide* of VI (not analyzed). This salt was hydrolyzed to VI on treatment with water.

Reactions of aminodibenzoylethylene (II). *Hydrolysis* was affected by alcohol solutions containing traces of acids, on warming or standing at room temperature; the triketone enol

(V) was isolated and identified by mixture melting point with an authentic sample, and by its characteristic change in melting point upon fusion (colorless form 80–81°; yellow form 65–66°).

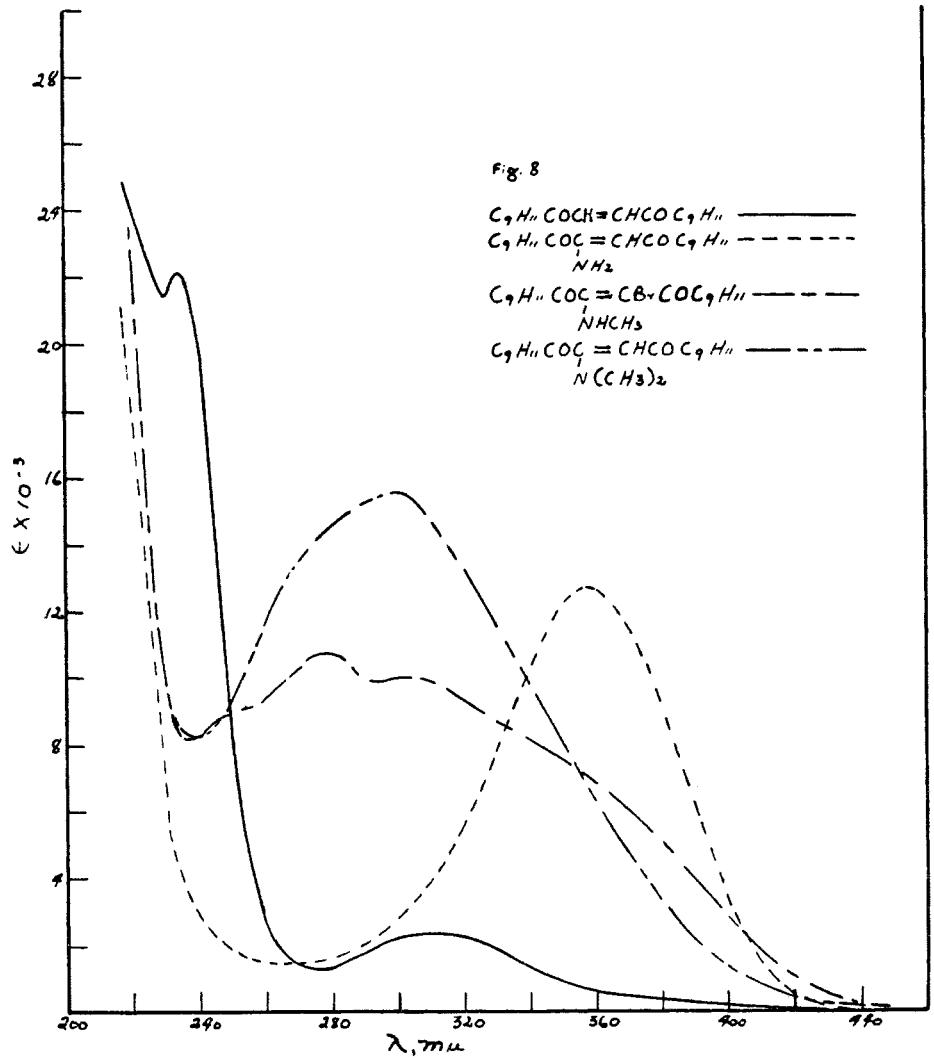


FIGURE 8

Bromination with one molecule in ethanol gave VI (identified); using two molecules, VIII was obtained (identified). *Acylation* in a 1-1 mixture of acetic acid-acetic anhydride (standing for 3 days at room temperature) gave VII. *Diazomethane* did not react with II.

Aminodimesitoylethylene (XXVI), when brominated (Procedure Db) gave, instead of the expected bromo derivative, *trans*-bromodimesitoylethylene (XXV) (yield 50%).

2-Anilino-3-bromo-1,4-diphenylbutanedione-1,4 (XXI). A mixture of 5 g. of the dibromide (I), 15 ml. of aniline, and 50 ml. of ethanol was warmed on a water-bath for 25 minutes; the dibromide was almost all dissolved during this time. The solution was filtered and

TABLE I

DIAROYL-(SUBST.-AMINO)ETHYLENES AND THE ETHYLENE IMINES

$$ArCOC\begin{pmatrix}NHR\\ or\\ NR_2\end{pmatrix} = C(X)COAr \text{ and } C_6H_5COCH\text{——}CHCOC_6H_5$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad \diagdown\ \diagup$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad N$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad R$$

(NHR or NR_2)	(X)	COLOR	PREP.[a] METHOD	YIELD, %	M.P., °C.	CRYST.[b] FROM	EMPIRICAL FORMULA	ANALYSES			
								C (or N)		H (or Br)	
								Calc'd	Found	Calc'd	Found
Dibenzoyl Series											
$-NH_2 \cdot HBr$	H	yellow	A	—[k]	195[d]	—	$C_{16}H_{14}BrNO_2$	—	—	24.07	24.01
$-NH_2$[c]	Br	none[e]	Ea	—	140–141	80% EtOH	$C_{16}H_{12}BrNO_2$	58.20	58.07[p]	3.64	3.77
$-NHCH_3$	H	yellow	D, Cf	68, 25	101–102.5	Bz-iOct.[n]	$C_{17}H_{15}NO_2$	76.98	76.66[q]	5.66	5.59
$-NCH_3$-(imine)		none	Ca, d, f	43	88–88.5	50% EtOH	$C_{17}H_{15}NO_2$	76.96	76.66	5.66	6.06
$-NHCH_3$	Br	none	Eb[l]	93	152–153	60% EtOH	$C_{17}H_{14}BrNO_2$	59.32	58.77	4.07	4.26
$-NHC_2H_5$[e]	Br	yellow	Eb	—	156.5–157	EtOH	$C_{18}H_{16}BrNO_2$	60.35	60.20	4.47	4.79
—NH(*n*-Butyl)	Br	pale yel.	Eb	—	115–116	EtOH	$C_{20}H_{20}BrNO_2$	62.16	61.88	5.23	5.25
$-NC_6H_5$-(imine)		none	Be[m]	31	143–144	EtOH	$C_{22}H_{17}NO_2$	80.73	80.39	5.19	5.56
$-N(CH_2)_2$[f]	H	yellow	Ca, e, D	51, 64	160–162	EtOH	$C_{18}H_{17}NO_2$	77.42	77.10[r]	6.09	6.49
$-N(C_2H_5)_2$[g]	H	yellow	Be	73	142.5–143	80% EtOH	$C_{20}H_{21}NO_2$	78.13	78.19[s]	6.89	7.23
$-N(C_2H_5)_2$	Br	yellow	Eb, c, F		111–112	60% EtOH	$C_{20}H_{20}BrNO_2$	62.16	62.52	5.22	5.41
$-N(C_2H_5)_2$	Cl	yellow	G	77	126.5–127.5	EtOH	$C_{20}H_{20}ClNO_2$	70.24	70.14	5.90	5.85
$-N(n\text{-Butyl})_2$	H	yellow	Bf	90	83–84	80% EtOH	$C_{24}H_{29}NO_2$	79.30	78.81	8.04	8.28
—Piperidyl	H	yellow	Ba	25	181–181.5	EtOH	$C_{21}H_{21}NO_2$	4.39	4.33	—	—
$-N(CH_2)C_6H_5$[h]	H	none	Bh, Db	–, 78	143–144	60%EtOH	$C_{23}H_{19}NO_2$	80.89	80.50	5.63	5.76

Di-(*p*-methylbenzoyl) Series											
—N(C_2H_5)$_2$	H	yellow	Bb	90	126–127	dil.EtOH	$C_{22}H_{25}NO_2$	4.18	4.24	—	—
—N(*n*-Butyl)$_2$	H	yellow	Bc	51	74.5–75	80% EtOH	$C_{26}H_{33}NO_2$	3.58	3.57	—	—
—Piperidyl	H	yellow	Bg	57	171–171.5	EtOH	$C_{23}H_{25}NO_2$	4.03	3.89	—	—
—Morpholinyl	H	yellow	Bd	35	151–152	EtOH	$C_{22}H_{23}NO_3$	4.01	4.19	—	—
Di-(*p*-methoxybenzoyl) Series											
—N(C_2H_5)$_2$	H	yellow	Bc	49	119	EtOH	$C_{22}H_{25}NO_4$	3.81	3.99	—	—
Di-(*p*-chlorobenzoyl) Series											
—N(C_2H_5)$_2$	H	yellow	Bb	70	170–171	EtOH	$C_{26}H_{19}Cl_2NO_2$	3.72	3.67	—	—
Di-(*p*-bromobenzoyl) Series											
—N(C_2H_5)$_2$	H	yellow	Bb	44	164	EtOH	$C_{20}H_{19}Br_2NO_2$	3.01	2.87	—	—
Dimesitoyl Series[i]											
—NHCH$_3$[j]	Br	none	Eb	—	142.5–143[d]	EtOH	$C_{23}H_{26}BrNO_2$	64.32	63.26	6.10	6.02
—N(CH_3)$_2$	H	yellow	Cb, e	92	149–150	60% EtOH	$C_{24}H_{29}NO_2$	79.30	79.00	8.04	8.33
—N(CH_3)$_2$	Br	pale yel.	Eb	—	140	EtOH	$C_{24}H_{28}BrNO_2$	65.01	64.49	6.34	6.45

[a] Refers to general procedures outlined in the experimental part. [b] Solvent abbreviations: EtOH = ethanol; Bz = benzene; iOct. = isooctane. [c] The hydrochloride (not analyzed) melted at 200–202° d. [d] Melts with decomposition. [e] The action of ethylamine on the dibromide (I) by Procedure Cc gave an oil which decomposed upon attempted distillation *in vacuo*; it was characterized by bromination to XVI. [f] Bromination in chloroform gave 4-bromo-2,5-diphenyl-2-hydroxyfuranone-3. [g] The hydrochloride (not analyzed) melted at 185°; it was precipitated from acetone by the addition of ethanolic-hydrogen chloride. The base was not hydrolyzed by the action of a refluxing mixture of 1 ml. of saturated ethanolic hydrogen chloride and 15 ml. of ethanol (30 minutes). [h] Not hydrolyzed by dil.-ethanolic hydrogen chloride (refluxing for 25 minutes). [i] *Cf.* Procedure Bh for the reaction between dimesitoylethylene dibromide and methylaniline. [j] The action of methylamine on the dibromide by Procedure Cb gave an oil which was characterized by bromination to this compound. This compound is unstable and difficult to purify. [k] See experimental part. [l] Forms a yellow solution but crystallizes as colorless leaflets. [m] Prepared from bromodibenzoylanilinoethane (XXI) using ethanol saturated with ammonia. [n] Crystallized also from 50% methanol. *Anal.* for nitrogen: [p] Calc'd: 4.24. Found: 3.36. [q] Calc'd: 5.28. Found: 5.35. [r] Calc'd: 5.02. Found: 5.23. [s] Calc'd: 4.56. Found: 4.55.

TABLE II

ULTRA-VIOLET ABSORPTION MAXIMA AND MINIMA FOR SOME AMINE DERIVATIVES OF SATURATED AND UNSATURATED 1,4-DIKETONES, AND RELATED COMPOUNDS, IN ABSOLUTE ETHANOL SOLUTION

COMPOUND	MAXIMA		MINIMA		FIG. NO.
	λ, mμ	ε × 10^{-3}	λ, mμ	ε × 10^{-3}	
Aminodibenzoylethylene (II)	259	11.3	238	7.00	1
	360	11.4	305	5.01	
Aminobromodibenzoylethylene (VIa)	251	18.1	217	10.6	1
	324	9.52	285	5.42	
Dibenzoyl(methylamino)ethylene (XI)	253	17.8	223	9.66	2
	334	14.0	285	5.64	
Dibenzoyl(dimethylamino)ethylene (XIV)	254	21.0	221	11.6	2
	340	17.5	295	5.00	
Bromodibenzoyl(methylamino)ethylene (XII)	253	18.8	220	9.16	3
	337	11.0	290	4.56	
Chlorodibenzoyl(diethylamino)ethylene	255	18.3	219	10.8	3
	345	8.68	295	3.80	
Dibenzoyl(phenylamino)ethylene (XXIII)	256	18.5	230	13.4	4
	375	15.9	298	6.60	
Dibenzoyl(methylphenylamino)ethylene	256	20.8	220	12.6	4
	342	18.3	295	5.8	
Methylamino-*bis*-dibenzoylethylene (XIII)	242	22.6	225	19.6	5
	360	19.0	307	4.92	
Phenylamino-*bis*-dibenzoylethylene	247	25.0	227	22.1	5
	373	14.9	315	6.24	
	440	9.48	410	8.68	
Dibenzoylethylene methylimine (X)	252	27.4	222	5.50	6
Dibenzoylethylene phenylimine (XXII)	253	27.8	220	14.8	6
	345	0.60	335	0.58	
Dibenzoyldimorpholinylethane	247	23.9	220	6.70	6
	362	0.40	327	0.28	
Bromodibenzoylmorpholinylethane	251	22.4	222	6.64	6
	345	0.48	315	0.42	
2,5-Diphenyl-2-methoxyfuranone-3	247	8.54	235	6.48	7
	314	17.4	268	4.88	
4-Bromo-2,5-diphenyl-2-ethoxyfuranone-3 (IX)	220	10.0	238	6.70	7
	253	9.76	278	3.96	
	327	15.6			
2-(Dimethylamino)-2,5-diphenylfuranone-3 (XXa)	242	8.59	235	7.80	7
	312	15.4	260	4.47	
Dimesitoylethylene (trans)	234	22.2	230	21.4	8
	310	2.48	275	1.30	
Aminodimesitoylethylene (XXVI)	357	12.7	270	14.1	8
Bromodimesitoyl(methylamino)ethylene	279	10.8	236	8.17	8
	303	10.2	295	10.0	
Dimesitoyl(dimethylamino)ethylene	300	15.6	237	8.30	8

diluted with 60% ethanol; yield 1.9 g.; m.p. 130–133° (decomp.) (40%). The compound was very unstable; several crystallizations from ethanol gave a sample melting at 139–140°d.

Anal. Calc'd for $C_{22}H_{18}BrN_2O$: C, 64.71; H, 4.44.
Found: C, 63.98; H, 4.16.

Methylamino-bis-dibenzoylethylene XIII. A solution of 1.4 g. (0.005 mole) of dibenzoyl-(methylamino)ethylene (XI) and 3.7 g. (0.016 mole) of dibenzoylacetylene in 10 ml. of benzene was refluxed for ten minutes; it turned a dark red. On cooling a crystalline precipitate was obtained, filtered, and washed with ether; yield 1.2 g. (46%); m.p. 194–197°d. After several crystallizations from a methanol-butanone mixture it melted at 202–203°d; yellow needles.

Anal. Calc'd for $C_{35}H_{25}N_2O_4$: C, 79.34; H, 5.03; N, 2.80.
Found: C, 79.12; H, 5.30; N, 3.63.

This compound was obtained as a by-product along with dibenzoyl(methylamino)-ethylene (XI) when dibenzoylacetylene (III) was treated in benzene solution with gaseous methylamine.

Anilino-bis-dibenzoylethylene was made (like XIII, above) from XXIII and III (refluxing time 20 minutes). The product was precipitated by cooling and addition of ether; yield 0.8 g. (47%); m.p. 175–185°d. Recrystallizations from ethanol-butanone mixture gave yellow needles, m.p. 194–195°.

Anal. Calc'd for $C_{33}H_{27}NO_4$; C, 81.26; H, 4.85; N, 2.49.
Found: C, 81.83; H, 4.80; N, 2.67.

This compound was also isolated from the reaction products of aniline and dibenzoylacetylene, and identified by mixture melting point with the sample above.

2-Dimethylamino-2,5-diphenylfuranone-3 (XXa). A solution of 1.1 g. of dimethylamine in dry benzene was added to a benzene solution of 2 g. of XIX under a reflux condenser, and after the vigorous reaction subsided, the mixture was refluxed for about one minute. The precipitated dimethylamine hydrobromide was filtered, the filtrate was evaporated, and the residue crystallized from 60% ethanol; colorless; yield 1.5 g. (70%); m.p. 116–117°.

Anal. Calc'd for $C_{18}H_{17}NO_2$: C, 77.40; H, 6.14.
Found: C, 77.64; H, 6.34.

2-Dibutylamino-2,5-diphenylfuranone-3 (XXb) was prepared like XXa (refluxing time 15 minutes); yield 50%; crystallized from 60% ethanol; colorless; m.p. 99.5–100°.

Anal. Calc'd for $C_{24}N_{29}NO_2$: C, 79.30; H, 8.04.
Found: C, 79.52; H, 8.14.

2-Morpholinyl-2,5-diphenylfuranone-3 (XXc) was prepared liked XXa; yield 75%; crystallized from ethanol; colorless, m.p. 148.5–149°.

Anal. Calc'd for $C_{20}H_{19}NO_3$: N, 4.34. Found: N, 4.16.

Ultraviolet absorptions were carried out in absolute ethanol as solvent, using a Beckman DU Quartz Spectrophotometer, and concentrations of about 0.00045–0.00055 molar. The solutions were made up and used as rapidly as possible to minimize deterioration of the samples. For data see Figures 1–8 and Table II.

SUMMARY

The action of ammonia and secondary amines on dibenzoylethylene dibromide and on dimesitoylethylene dibromide produces the corresponding diaroyl-(amino or subst.-amino)ethylene. In the several instances investigated the same product was obtained by addition of ammonia or the secondary amine to dibenzoylacetylene.

The action of the primary amines, methylamine and aniline, on *meso*-dibenzoylethylene dibromide produces respectively the ethylene-methylimine and -phenylimine. Methylamine reacts with the *dl*-dibromide to give the enamine as a second product. Methylamine and aniline add to dibenzoylacetylene to give the corresponding and isomeric enamines and also the dimolecular products, the amine-*bis*-dibenzoylethylenes.

The bromoamino- (and subst.-amino)-dibenzoylethylenes are obtained by bromination of the enamines. The bromo enamine was obtained in two special

cases, one by the bromination of the methylimine, and the other by the action of diethylamine on *cis*- or *trans*-dibenzoyldibromoethylene.

Three subst-aminodiphenylfuranones were made as type examples.

Abnormal reactions in the dimesitoylethylene series are cited.

Reactions of these compounds and their ultra-violet absorption spectra are considered and evidence is presented for the structures assigned. Only one configurational type seems to be involved. Some points of mechanism and stereochemistry of the reactions involved are discussed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY]

THE HYDROGENATION OF OXALOACETONE. A NEW SYNTHESIS OF β-THIOLIMIDAZOLYLPROPIONIC ACID[1]

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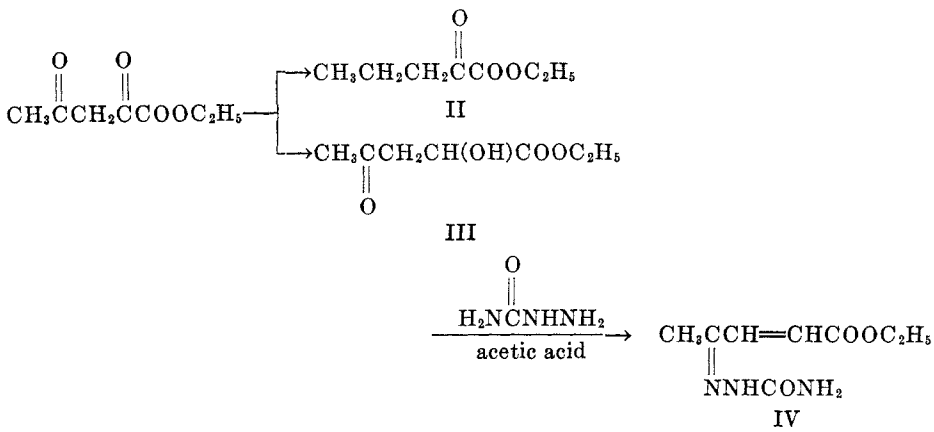
Received August 24, 1949

As a possible intermediate in the synthesis of ergothioneine we were interested in the preparation of an ester of α-hydroxylevulinic acid. Although the free acid has been prepared by Wolff (1) by the action of boiling water on bromolevulinic acid there is no record of its esters.

Attempts to add water across the double bond of ethyl acetylacrylate in a sealed tube at elevated temperatures resulted only in hydrolysis of the ester. This led us to believe that preparation of ethyl α-bromolevulinate and exchange of hydroxyl for bromine would also fail due to hydrolysis.

The hydrogenation of oxaloacetone, I (2), in absolute ethanol using platinum oxide (Adams') catalyst yielded a mixture of three products which were separated by fractionation at reduced pressure. The reaction was stopped after addition of one mole of hydrogen. The lowest-boiling fraction (79–80° at 18 mm.) was ethyl α-ketovalerate, II. It was identified by preparation of the semicarbazone, which melted at 138.5–139.5° (3). The second fraction (b.p. 60.5–61.5° at 2–3 mm.) was unreduced starting material. The highest-boiling fraction (77–78° at 2–3 mm.) was ethyl α-hydroxylevulinate. When the semicarbazone was prepared in 6 *M* acetic acid, dehydration occurred, leading to the formation of the derivative from ethyl β-acetylacrylate, IV. This was identified as the correct semicarbazone, m.p. 203.0–204.5°. The isomeric compound, ethyl α-keto-γ-hydroxyvalerate, could not have formed this semicarbazone by dehydration. These reactions are summarized in Chart I.

CHART I



[1] From the doctoral dissertation of R. W. Wynn, The Johns Hopkins University, 1947. We are indebted to the H. A. B. Dunning Foundation Fund for a grant-in-aid which partially defrayed the expense of this research.

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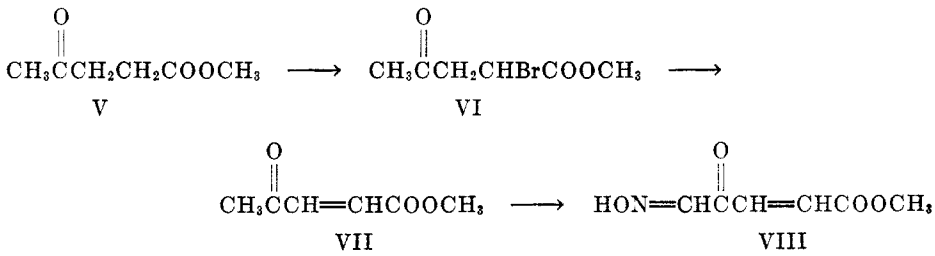
We next desired to prepare β-thiolimidazolylacrylic acid, a product of the degradation of ergothioneine by strong caustic (4). An examination of the literature revealed no synthetic source. Our attempts to nitrosate α-hydroxylevulinic ester were not encouraging but results on ethyl acetylacrylate were promising. The methyl ester was chosen because of its higher melting point and a more direct method of preparation was sought. Accordingly it was decided to attempt the synthesis from methyl acetylacrylate prepared from levulinic acid by esterification (5), bromination, and dehydrobromination (6).

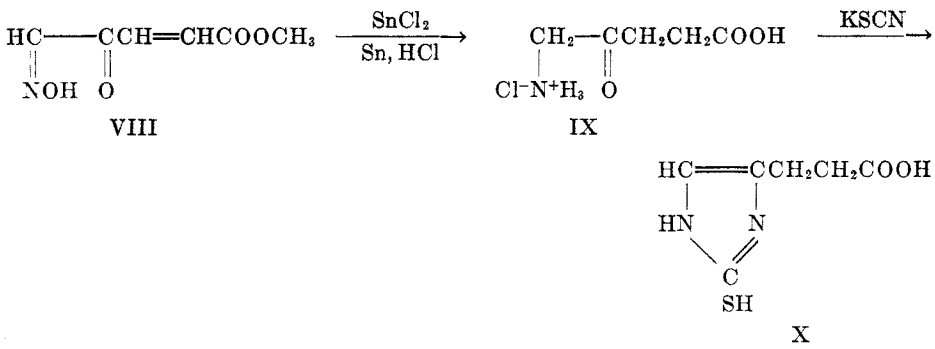
The isonitrosation of ketones is a very sensitive reaction (7). The concentration of acid catalyst is critical. Traces of water are disastrous. A scheme was finally worked out whereby yields ranging from 45–64% could be consistently obtained. The conversion of levulinic ester to the isonitroso ketone is summarized in Chart II.

CHART II



Selective reduction of the isonitroso group was attempted (8, 9). The reduction was tried chemically with two equivalents of sodium amalgam and with two equivalents of stannous chloride in hydrochloric acid. These reactions led to tarry products. Catalytic reduction with Adams' catalyst led to oils. After making a polarographic study of the reduction potentials of the various groups in the molecule (10, 11) attempts at electrolytic reduction resulted in unrecognizable oils.

CHART III



By using as reducing agent an excess of tin and stannous chloride in concentrated hydrochloric acid it was possible to isolate a white, crystalline material, δ-aminolevulinic acid hydrochloride, IX. Indirect proof of the structure of this

compound lies in the fact that on treatment with potassium thiocyanate the product obtained was β-thiolimidazolylpropionic acid, X. Thus not only the isonitroso group but also the double bond had been reduced and the reaction had taken the course shown in Chart III.

EXPERIMENTAL

Attempted hydration of ethyl-β-acetylacrylate. Five grams of ethyl-β-acetylacrylate and 55 ml. of water were sealed in a tube and heated at 135–140° for thirteen hours. The *p*H of the resulting solution was 3. This was extracted once with 25 ml. of ether. Evaporation of the ether solution yielded 1.5 g. of a solid residue, m.p. 109–120°. On recrystallizing from boiling chloroform, white crystals of acetylacrylic acid, m.p. 122–125°, were obtained.

The aqueous solution was concentrated over a free flame and dried in a vacuum desiccator. The residue was a syrupy mass containing some crystals. The crystals were triturated with ethyl acetate and recrystallized from boiling chloroform; 0.4 g. of acetylacrylic acid was recovered.

Hydrogenation of oxaloacetone. To a solution of 31.6 g. (0.2 mole) of oxaloacetone in 200 cc. of absolute ethanol was added 2 cc. of moistened Raney nickel and the mixture was shaken for five minutes. The solution was filtered and 200 mg. of Adams' catalyst (PtO_2) added. The solution was hydrogenated at 50–70 p.s.i. until 1 mole of hydrogen was absorbed (3 hours). The catalyst was filtered off and the alcohol removed on the steam cone. The residue was fractionated at 9 mm. (4-plate column) to give (a) ethyl α-ketovalerate, 6.8 g., b.p. 67–70°; (b) starting material, 7.2 g., b.p. 101–105°; and (c) ethyl α-hydroxylevulinate, 7.8 g., b.p. 122–123°.

Ethyl-α-hydroxylevulinate. An analytical sample of (c) was prepared by redistillation at 2–3 mm.; b.p. 77–78°.

Anal. Calc'd for $C_7H_{12}O_4$: C, 52.49; H, 7.55.
Found: C, 52.03, 52.04; H, 7.49, 7.52.

The technique used for weighing was as described by Niederl and Niederl (12). In order to prevent explosions it was necessary to control the temperature by using a metal block until all the sample had evaporated from the weighing tube. This required about one hour at 140°. After volatilization was complete the combustion was performed as usual.

Ethyl-α-ketovalerate semicarbazone. Ethyl-α-ketovalerate (2 cc.) was dissolved in 20 cc. of water containing just enough alcohol to make the ester completely soluble. To the solution were added 2 g. of semicarbazide hydrochloride and 3 g. of sodium acetate. It was placed in a beaker of water at 80° and allowed to cool slowly to 40°, when the tube was immersed in ice-water. The white crystals were recrystallized twice from boiling water; m.p. 138.5–139.5°.

Attempted formation of the semicarbazone of ethyl-α-hydroxylevulinate (Ethyl acetylacrylate semicarbazone). A mixture of 1 cc. of ethyl-α-hydroxylevulinte, 10 cc. of 6 *M* acetic acid, and 1 g. of semicarbazide hydrochloride was immersed in a beaker of boiling-water for five minutes and then allowed to cool slowly to room temperature. On cooling in an ice-water bath white needles precipitated; recrystallized from an alcohol-water mixture; m.p. 201.5–203.0°.

Anal. Calc'd for $C_8H_{13}N_3O_4$: N, 21.09. Found: N, 21.00.

The compound was again crystallized from an alcohol-water mixture; m.p. 203.5–205.5°.

Anal. Found: N, 21.21.

A small quantity of the material was mixed with an approximately equal amount of *ethyl acetylacrylate semicarbazone* (m.p. 203.0–204.5°) prepared as was ethyl-α-ketovalerate semicarbazone described above. The melting point of the mixture showed no depression.

Methyl-δ-isonitrosoacetylacrylate. In a 125-cc. Erlenmeyer flask fitted with a two-hole rubber stopper which had a ground-glass stopcock through one hole and through the other a glass tube drawn to a capillary reaching almost to the bottom was placed 6.40 g. (0.05 mole) of methyl acetylacrylate; 75 cc. of anhydrous ether was added through the stopcock.

On shaking at room temperature not all the ester dissolved. Through a calcium chloride tube attached to the capillary was blown in 1.01 g. of gaseous hydrogen chloride. The solution was cooled to 20° and 3.03 g. (0.04 mole) of ethyl nitrite was bubbled in over the absorbant during 1.5 hours; the temperature was maintained around 20°. The undissolved gas was released from the flask by slightly opening the ground-glass stopcock. At the end of the addition the solution had turned deep red and the solid ester had completely dissolved. The reaction mixture was stored in the dark at room temperature for 1¾ hours. It was necessary to release the pressure occasionally during this period. The reaction mixture had turned light yellow. A very small amount of insoluble material was filtered off and the ether was drawn off with an aspirator. The solid residue was dissolved in the minimum amount of ether and most of the solvent was evaporated off in an air stream and the residue cooled and filtered. On further evaporating the filtrate more crystals formed which were washed with benzene and combined with the first crop. Yield, 5.00 g. of a light yellow solid; m.p. 112–115° dec.; 64% (based on methyl acetylacrylate).

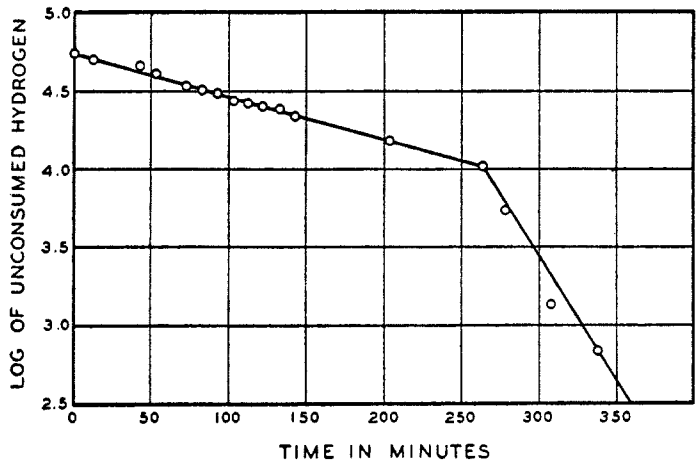


FIGURE 1.

A sample was purified for analysis by recrystallizing four times from toluene. The pure product was a very pale yellow, m.p. 114–117° dec.

Anal. Calc'd for $C_6H_7NO_4$: C, 45.86; H, 4.49; N, 8.92.
Found: C, 45.73; H, 4.45, N, 8.98, 9.05.

The compound decomposes slowly when stored in air. It is very soluble in ether and glacial acetic acid, slightly soluble in benzene and toluene, and insoluble in water. In ethanol and in concentrated sulfuric acid it turns deep red (11).

ATTEMPTED SELECTIVE REDUCTIONS OF METHYL-δ-ISONITROSOACETYLACRYLATE

(a) *By hydrogenation.* In one arm of one cup of a Warburg microhydrogenation apparatus was placed 0.532 mg. of δ-isonitrosoacetylacrylate. In the other arm a mixture of 40 mg. of Norit A, 2 ml. of distilled water, and two drops of 10% palladium chloride solution in 10% hydrochloric acid was introduced. The second capillary arm was left open to atmospheric pressure. The catalyst was hydrogenated and the solutions were then mixed and the determination started.

Figure 1 is the logarithmic plot of the unconsumed hydrogen against the time in minutes. The break in the hydrogenation occurred at 0.59 mole and the reaction ceased at 0.72 mole. This indicates partial hydrogenation of a one double bond and shows that the absorption of 2 moles required for the hydrogenation of the isonitroso group is not probable.

In spite of this, another hydrogenation was run and the product from it was treated with potassium thiocyanate. The product of the attempted condensation was a dark-colored tar from which potassium thiocyanate and no other solid material could be isolated.

(b) *With stannous chloride.* Four and one-half grams (0.02 mole) of stannous chloride dihydrate was dissolved in 8 cc. of conc'd hydrochloric acid. A solution of 1.57 g. (0.01 mole) of methyl isonitrosoacetylacrylate dissolved in 16 cc. of glacial acetic acid was poured rapidly into the hydrochloric acid solution. The mixture warmed spontaneously to about 50°. It was stirred mechanically and allowed to stand for four hours at room temperature. To the deep red solution was added 150 cc. of water and the tin precipitated with hydrogen sulfide. The tin sulfide was removed by filtration and the solvent aspirated at 40–50° until the volume was reduced to 10 cc. Then 0.97 g. (0.01 mole) of potassium thiocyanate was added and the solution evaporated to dryness on the steam-bath. The residue was a dark oil from which potassium thiocyanate could be extracted with methanol.

(c) *Electrolytic reduction.* The apparatus used for the reduction at controlled potential was a modification of that described by Lingane (10). The first reduction was run at room temperature. After orienting polarographic studies similar to those described by Hartnell and Bricker (11) a cathode potential of 0.12 volts negative to the saturated calomel electrode was chosen. The isonitroso ester (1.57 g.) was dissolved in 500 cc. of a solution 0.018 *M* in hydrochloric acid and 2.4 *M* in acetic acid. This solution, *p*H 1.5, was placed in the cathode compartment and the anode was filled with solvent only. With the cathode solution stirred vigorously, the current was 90 milliamperes. After twelve hours the current had diminished to 2 milliamperes. The reduction was stopped and the solution, which had become yellow, was drained from the cathode compartment and the water removed by sublimation. The residue was a red oil. This was dissolved in 10 cc. of distilled water and treated as above with potassium thiocyanate. The residue was a very dark viscous material from which no solid compound could be isolated.

The second reduction was performed similarly except that the temperature was maintained at 0° during the entire reduction (20 hours). The maximum current obtainable at this temperature was 55 milliamperes. One-half of the solution was dried by sublimation of the solvent and treated with potassium thiocyanate as described above. Evaporation to dryness left a red oil. The other half was reduced further at a cathode potential of 0.65 volts. When the product of this reduction was treated as described above no imidazole derivative could be isolated.

δ-Aminolevulinic acid hydrochloride. With mechanical stirring, 9.6 g. of $SnCl_2 \cdot 2\ H_2O$ was dissolved in 16 cc. of conc'd HCl and cooled to 0° when 2.30 g. of tin was added, followed by 3.14 g. of δ-isonitrosoacetylacrylate in small portions over a period of 45 minutes. The reaction mixture was stirred at room temperature for two hours, diluted with 400 cc. of water, and hydrogen sulfide blown in until all the tin was precipitated (test sample). The precipitate was filtered off and the water removed in the lyophylizer. Absolute methanol (14 cc.) was added to the residue and some undissolved ammonium chloride filtered off. The hydrochloride was reprecipitated by the slow addition of 50 cc. of dry ether; yield, 1.23 g. (34%) of white powder.

A sample was prepared for analysis by solution in the least amount of absolute methanol possible. The solution was placed in a desiccator over dry ether. The lid was clamped down and allowed to stand for several days. Slow distillation of ether into the methanol solution caused precipitation of long white needles. These were filtered off and dried in a Fischer pistol. M.p. 144–147° dec.

Anal. Calc'd for $C_5H_{10}ClNO_3$: N, 8.36. Found: N, 8.24.

β-Thiolimidazolylpropionic acid (8): A mixture of 1.23 g. (0.0067 mole) of δ-aminolevulinic acid hydrochloride, 8.00 cc. of distilled water, and 0.65 g. (0.0067 mole) of KSCN was evaporated to dryness on the steam cone. The solid residue was redissolved in 14 cc. of boiling-water, the hot solution filtered, and the filtrate allowed to evaporate at room temperature until the volume had decreased to 7 cc. During this time beautiful rosettes of crystals

formed. Further cooling in the ice box gave 0.44 g. (38%) of crude product. A sample was prepared for analysis by reprecipitating from hot water; m.p. 203–205°.

Anal. Calc'd for $C_6H_8N_2O_2S$: C, 41.85; H, 4.68; N, 16.27.
Found: C, 41.44; H, 4.61; N, 16.32.

The product showed no positive test for thiocyanate ion, decolorized ferric chloride solution slowly, and gave a gelatinous, green precipitate with cuprous chloride thiol reagent (13).

SUMMARY

1. The catalytic hydrogenation of oxaloacetone is described and the structure of the products determined.

2. A new synthesis of β-thiolimidazolylpropionic acid is outlined.

3. Several new intermediate compounds have been synthesized and described and their structures established.

BALTIMORE, MARYLAND

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[CONTRIBUTION NO. 194 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

PYRIDINDENE DERIVATIVES. I

JOHN T. PLATI AND WILHELM WENNER

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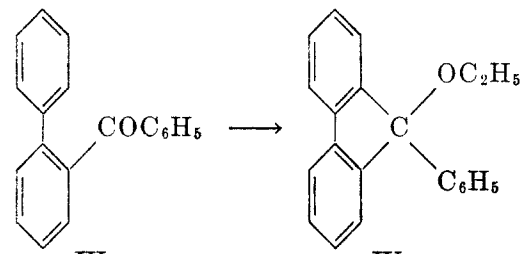
In previous papers (10, 11) we have described convenient methods for the preparation of 1,3,4-trisubstituted piperidine derivatives. The reactions of these amines have since been studied in detail. The present communication deals with an interesting intramolecular cyclodehydration of these piperidine derivatives.

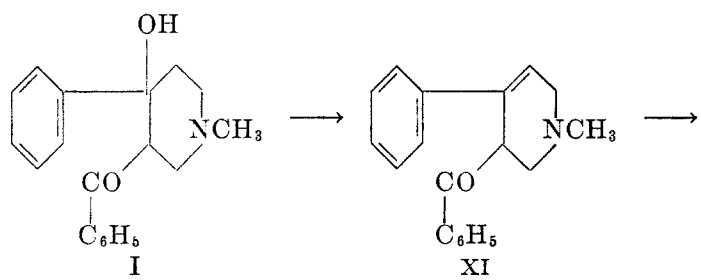
When 1-methyl-3-benzoyl-4-hydroxy-4-phenyl-piperidine, I (6, 10, 12), is subjected to the action of strong hydrobromic acid (40–48%) at temperatures ranging from approximately 100° to reflux temperature, a yellow, well crystallized compound of m.p. 202–203° is formed. It does not contain oxygen. From the complete elementary analysis, the empirical formula $C_{19}H_{17}N \cdot HBr$ can be derived. The identical base $C_{19}H_{17}N$ is obtained when I is treated with strong sulfuric acid at elevated temperatures. Hydrochloric acid, phosphorus oxychloride, and phosphoric acid, however, do not convert I into the new base. The properties and reactions of the base $C_{19}H_{17}N$ lead to the conclusion that it has the formula II and is formed by the removal of two molecules of water from I. One molecule of water is eliminated with the formation of a double bond; the second is lost in a cyclodehydration, a reaction for which numerous examples have been reported in the aromatic series (2).

Our reaction seems to be the first instance of such a cyclodehydration where a hydrogenated heterocyclic ring system is involved. A similar ring closure without dehydration occurs in the case of *o*-phenylbenzophenone, III (3), which is converted into 9-phenyl-9-ethoxy-fluorene (IV) by refluxing with hydrobromic acid and then with alcohol.

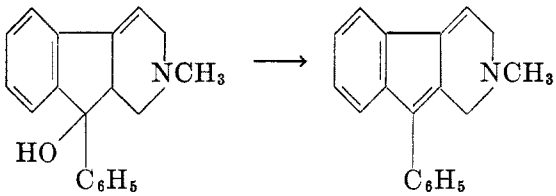


III IV

In our reaction the presence of additional hydrogen makes possible a further loss of water leading to the formation of a double bond. Schematically the sequence of reactions involved in this case may be depicted as follows:

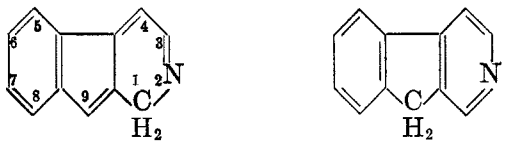


I XI



XII II

The base $C_{19}H_{17}N$ is a derivative of the ring system V. This is isomeric with the

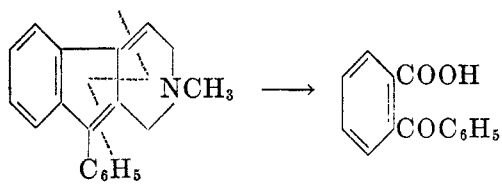


V VI

system VI which is the skeleton present in several aromatic compounds described in the literature (1, 8). This latter system has been called pyridofluorene (8) and 2-azafluorene (1). The official name is 9*H*-indeno[2,1-*c*]pyridine (9). In accordance with this nomenclature, the ring system V should be called 1*H*-indeno[2,1-*c*]pyridine.

Indene and pyridine rings can be fused in several ways leading to different tricyclic ring systems all of which are classified as indenopyridines. They are differentiated by the use of the appropriate figures and letters within the brackets. Three of these fused ring systems are listed in the Ring Index (9) under No. 1760–1762. For the purpose of easy reference and in order to avoid the cumbersome use of letters and figures within the brackets, we decided to assign the simple name "1-pyridindene" to the ring system V. Thus compound II becomes 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene.

The structure of compound II was proved by oxidation. When it was treated with potassium permanganate in alkaline solution, *o*-benzoylbenzoic acid (VII) was formed. The acid VII was identified by a mixed melting point determination with an authentic sample of this acid and by the preparation of the amide (4) and of the anilide (7). The oxidation is illustrated by the scheme:



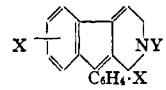
II VII

The dotted line indicates the manner of degradation. The isolation of *o*-benzoylbenzoic acid is conclusive proof that the two phenyl groups, originally separated as shown in formula I, have become attached to the same carbon atom in compound II, and furthermore, the attachment has taken place *ortho* to the substituent in one of the phenyl nuclei. These requirements are met by formula II.

The reaction is not confined to the piperidine derivative I. Other 1,3,4-trisubstituted piperidines of the general formula VIII undergo the ring closure to IX in the same way. The resulting tricyclic compounds are listed in Table I.

TABLE I

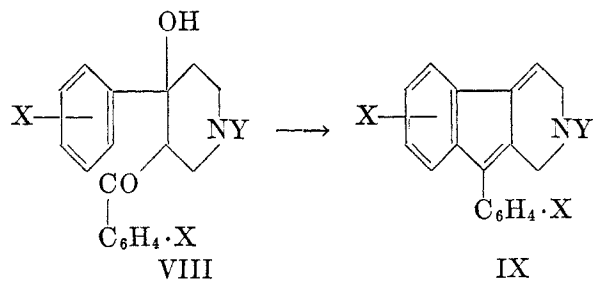
1-PYRIDINDENE DERIVATIVES



FORMULA	X	Y	EMPIRICAL FORMULA	HYDROBROMIDE M.P., °C.
II	H	CH_3	$C_{19}H_{17}N$	201–204
XIII	H	C_2H_5	$C_{20}H_{19}N$	202–204
XIV	H	$CH(CH_3)_2$	$C_{21}H_{21}N$	243–245
XV	H	n-C_4H_9	$C_{22}H_{23}N$	193–195
XVI	CH_3	CH_3	$C_{21}H_{21}N$	200–203[a]
XVII	OCH_3	CH_3	$C_{21}H_{21}NO_2$	209–210

[a] Semi-hydrate.

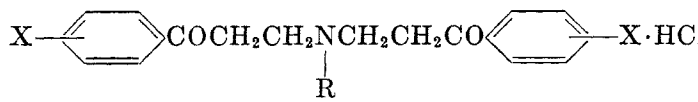
The resulting 1-pyridindene derivatives were isolated as hydrobromides which crystallize readily from the appropriate solvents. The hydrobromides are quite stable in contrast to the free bases which discolor soon on standing.



VIII IX

The ease with which the piperidine bases are converted into 1-pyridindene derivatives prompted an investigation of the behavior of the original Mannich compounds X, from which the piperidine bases are obtained, toward hydrobromic acid.

As discussed in the previous papers (10, 11) the reaction products of the Mannich condensation between acetophenone, alkylamine hydrochlorides, and formaldehyde are hydrochlorides of the formula X.



X

The corresponding bases are not stable and, when liberated from the salts, they undergo rearrangement into piperidine derivatives of the type I. This reaction

involves an intramolecular aldol condensation. Inasmuch as aldol condensations are frequently brought about in acid as well as in alkaline solution, it was felt that treatment of the Mannich product X with hydrobromic acid should also give initially the piperidine compound II which would then undergo further cyclization to the pyridindene derivative II. This assumption proved to be correct. By treatment with hydrobromic acid, not only *bis*-(β-benzoylethyl)methylamine hydrochloride, but also *bis*-(β-benzoylethyl)ethylamine hydrochloride, and *bis*-(β-*p*-toluylethyl)methylamine hydrochloride are converted into the corresponding pyridindene derivatives.

By the outlined reactions, derivatives of dihydro-1-pyridindenes have become one of the most easily accessible classes of polynuclear heterocyclic compounds.

EXPERIMENTAL

The melting points are uncorrected.

PART I: 1-PYRIDINDENES FROM PIPERIDINE DERIVATIVES

A. *2-Methyl-9-phenyl-2,3-dihydro-1-pyridindene* (II). 1. *With hydrobromic acid.* Seven-hundred-fifty grams of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (5, 6, 12) and 2500 cc. of 48% hydrobromic acid are distilled through a twenty-plate distillation column over a period of about one hour. The temperature rises by this time to 124°. Distillation is discontinued, and the remaining dark yellow solution is poured into 8000 cc. of water with stirring. An oily precipitate forms which soon solidifies. The crystals are recrystallized from 3400 cc. of alcohol to yield 610 g. of yellow crystals, m.p. 201–204°. Additional amounts are obtained from the filtrate. The total yield averages 700–720 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide. The melting point varies somewhat with the rate of heating.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33; N, 4.12; Br, 23.49.
Found: C, 66.77; H, 5.26; N, 4.32, Br, 23.99.

The same compound is obtained when the starting material is heated to 90–100° with six times its weight of 48% hydrobromic acid for 10–12 hours.

2. *With 65.6% sulfuric acid.* A mixture of 10 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 50 cc. of 65.6% (by weight) sulfuric acid is refluxed for twenty minutes. The solution is poured into 100 cc. of cold water, and the base is liberated by the addition of 10% sodium hydroxide at 20–30°. The base is extracted with ether and treated with hydrogen bromide gas. The hydrobromide separates immediately. It is digested with 75 cc. of hot acetone. On cooling, about 3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–203° is obtained.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33.
Found: C, 67.26; H, 5.15.

3. *With 47% sulfuric acid.* A mixture of 20 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine and 80 cc. of 47% sulfuric acid is refluxed for three hours and then treated as in the preceding experiment. Yield, 13.3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 202–204°. Recrystallization from methanol gives a product of m.p. 201–203°.

Anal. Calc'd for $C_{19}H_{17}N \cdot HBr$: C, 67.06; H, 5.33.
Found: C, 67.57; H, 5.13.

B. *2-Ethyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIII). A mixture of 46 g. of 1-ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) and 185 cc. of 48% hydrobromic acid is distilled for thirty minutes through a twelve-plate column. The temperature rises to 122°. The mixture is poured into 370 cc. of water. The oily precipitate is crystallized from 150 cc. of alco-

hol, yielding 40 g. of 2-ethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–204°.

Anal. Calc'd for $C_{20}H_{19}N \cdot HBr$: C, 67.80; H, 5.69.
Found: C, 68.05; H, 5.48.

C. *2-Isopropyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIV). A solution of 40 g. of 1-isopropyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) in 170 cc. of 48% hydrobromic acid is distilled through a twelve-plate column until the boiling point reaches 122°. The solution is then poured into 350 cc. of water. The precipitate is refluxed with 400 cc. of alcohol to remove impurities. The undissolved crystals are filtered hot and washed with ether. Yield, 41 g. of 2-isopropyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 243–245°.

Anal. Calc'd for $C_{21}H_{21}N \cdot HBr$: C, 68.48; H, 6.02.
Found: C, 68.73; H, 5.99.

D. *2-n-Butyl-9-phenyl-2,3-dihydro-1-pyridindene* (XV). A mixture of 20 g. 1-*n*-butyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (11) and 80 cc. of 48% hydrobromic acid is distilled through a twelve-plate column until the temperature rises to 121–122°. The solution is poured into 160 cc. of water. The precipitate is filtered and recrystallized from about 100 cc. of acetone. Yield, 11.4 g. of 2-*n*-butyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 193–195°.

Anal. Calc'd for $C_{22}H_{23}N \cdot HBr$: C, 69.11; H, 6.33.
Found: C, 69.08; H, 6.40.

E. *2,7-Dimethyl-9-p-tolyl-2,3-dihydro-1-pyridindene* (XVI). A solution of 20 g. of 1-methyl-3-*p*-toluyl-4-hydroxy-4-*p*-tolylpiperidine (11) in 80 cc. of 48% hydrobromic acid is distilled slowly through a twelve-plate column over a period of thirty minutes. The water is thereby removed. The mixture is then poured into 160 cc. of water. The precipitate (18 g.) is crystallized, first from alcohol and then from acetic acid, yielding 2,7-dimethyl-9-*p*-tolyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–203°. It contains one-half molecule of water of crystallization.

Anal. Calc'd for $C_{21}H_{21}N \cdot HBr \cdot \frac{1}{2} H_2O$: C, 66.84; H, 6.14.
Found: C, 67.12; H, 6.42.

F. *2-Methyl-6-methoxy-9-m-methoxyphenyl-2,3-dihydro-1-pyridindene* (XVII). To 12 cc. of conc'd sulfuric acid, maintained at 5–9° by means of an ice-bath, 2 g. of 1-methyl-3-*m*-methoxybenzoyl-4-hydroxy-4-*m*-methoxyphenylpiperidine (11) is slowly added in about twenty minutes. After standing for approximately ten minutes, the solution is poured into cracked ice and treated below 30° with 30% sodium hydroxide solution until distinctly alkaline. The liberated base is extracted with ether, and the ethereal solution is treated with gaseous hydrogen bromide. On standing in the refrigerator, 2-methyl-6-methoxy-9-*m*-methoxy-phenyl-2,3-dihydro-1-pyridindene hydrobromide gradually crystallizes. Recrystallization from alcohol yields the pure product, m.p. 209–210°.

Anal. Calc'd for $C_{21}H_{21}NO_2 \cdot HBr$: C, 63.00; H, 5.54.
Found: C, 62.68; H, 5.35.

PART II: 1-PYRIDINDENES FROM "MANNICH BASES"

A. *2-Methyl-9-phenyl-2,3-dihydro-1-pyridindene* (II). A mixture of 250 g. of *bis*-(β-benzoylethyl)methylamine hydrochloride and 1000 ml. of hydrobromic acid 48% is refluxed with stirring for one hour. The hydrochloride dissolves slowly. Hydrogen chloride is formed and escapes through the condenser. After standing overnight, 1000 cc. of water is added with stirring. Crystallization starts slowly but proceeds rapidly as soon as crystals are present. After stirring for two hours, the mixture is filtered, washed with 50 cc. of water, and dried. The crude hydrobromide (250–255 g.) is recrystallized from 2000 cc. of boiling alcohol, yielding 200–220 g. of pure 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide of m.p. 202–204°. The synthesis of the 1-pyridindene compounds proceeds in the same manner if *bis*-(β-benzoylethyl)methylamine hydrobromide of m.p. 182° is used in place of the hydrochloride. This hydrobromide is obtained directly when the Mannich reaction is carried

out with methylamine hydrobromide instead of methylamine hydrochloride as found by Mr. Weinhagen.

B. *2-Ethyl-9-phenyl-2,3-dihydro-1-pyridindene* (XIII). Twenty-five grams of *bis*-(β-benzoylethyl)ethylamine hydrochloride (11) is refluxed in 100 cc. of 48% hydrobromic acid. After cooling, 200 cc. of water is added with stirring; an oil separates. The supernatant liquid is poured off, and the oil is dissolved in about 50 cc. of alcohol. On standing in the refrigerator, 2-ethyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide crystallizes slowly. Recrystallization from alcohol yields the pure compound, m.p. 201–203°.

C. *2,7-Dimethyl-9-p-tolyl-2,3-dihydro-1-pyridindene* (XVI). Twenty grams of *bis*-(β-*p*-toluylethyl)methylamine hydrochloride is suspended in 80 cc. of 48% hydrobromic acid. The mixture is distilled through a twelve-plate column until the vapor temperature reaches 122–123°. The remaining solution is then poured into 160 cc. of water. A gummy precipitate appears from which the supernatant liquid is poured off. The material is dissolved in 60 cc. of boiling alcohol. On cooling, 14 g. of crystals of m.p. 174–190° is obtained. Recrystallization from about 200 cc. of glacial acetic acid yields pure 2,7-dimethyl-9-*p*-tolyl-2,3-dihydro-1-pyridindene hydrobromide, m.p. 200–203°.

PART III: OXIDATION OF 2-METHYL-9-PHENYL-2,3-DIHYDRO-1-PYRIDINDENE

A mixture of 3 g. of 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene hydrobromide, 12 g. of potassium permanganate, and 15 cc. of 10% sodium hydroxide was heated on the steam-bath with occasional shaking for about 5 hours. Sulfur dioxide was then passed into the mixture until only a gummy precipitate remained. This material was separated and digested with 50 cc. of 5% sodium hydroxide. The solution was filtered. The filtrate was acidified with conc'd hydrochloric acid, and the gummy precipitate was digested with 50-cc. portions of boiling water. Each time the hot supernatant solution was decanted and filtered with a little charcoal. On cooling the first portion gave crystals which, after drying at 70°, melted at 126–127° and weighed 0.07 g. The second portion yielded 0.1 g. of m.p. 128–129°. Recrystallization of the combined crops of crystals from water gave a product of m.p. 128–129°. It showed no depression in melting point when mixed with an authentic sample of *o*-benzoylbenzoic acid. The melting points of the amide and of the anilide, prepared by conventional methods, were substantially identical with those reported in the literature; the amide melting at 161–163° (4) and the anilide at 192–194° (7). The anilide was analyzed to establish its structure.

Anal. Calc'd for $C_{20}H_{16}NO_2$: C, 79.45; H, 5.34.
Found: C, 79.40; H, 5.29.

Acknowledgment. We thank Dr. A. Steyermark for the microanalyses and Mr. P. Bevilacqua for technical assistance.

SUMMARY

1-Alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines and their ring-substituted derivatives are converted by cyclodehydration into derivatives of 1-pyridindene (1*H*-indeno[2,1-*c*]pyridine). The same compounds are formed when diketone-amine hydrochlorides, obtained by Mannich reactions from acetophenone, are refluxed with strong hydrobromic acid.

NUTLEY, N. J.

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[CONTRIBUTION FROM L'INSTITUT DE CHIMIE, UNIVERSITY OF MONTREAL AND THE DIVISION OF CHEMISTRY OF THE NATIONAL RESEARCH COUNCIL]

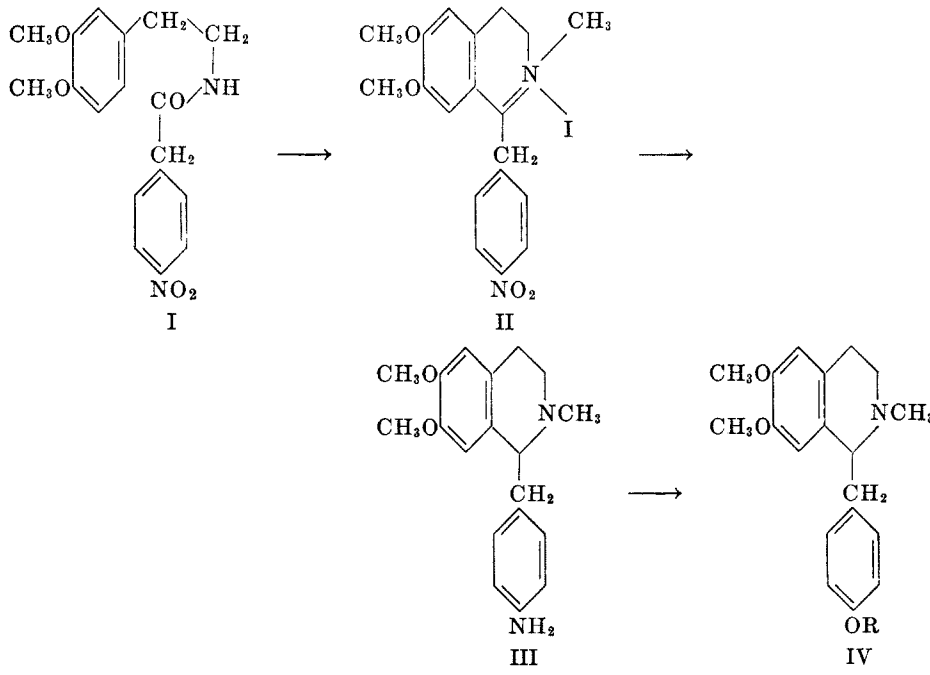
THE SYNTHESIS OF *dl*-ARMEPAVINE[1]

LÉO MARION, LIONEL LEMAY, AND VINCENT PORTELANCE

Received September 6, 1949

Armepavine is a levorotatory alkaloid ($C_{19}H_{23}NO_3$) obtainable from two species of *Papaver*, *i.e.*, *P. armeniacum*, Lam., (1) and *P. floribundum*, Desf. (2). On oxidation the base gives rise to 1-keto-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V) (3). Armepavine contains a phenolic hydroxyl and forms a methyl ether which, in the final step of the Hofmann degradation, produces a trimethoxystilbene. The substituted stilbene is scinded by oxidation into anisic acid and *meta*-hemipinic acid. On the basis of these results armepavine has been represented by formula IV (R = H), *i.e.*, 6,7-dimethoxy-1-(*p*-hydroxybenzyl)-2-methyl-1,2,3,4-tetrahydroisoquinoline (3). This structure has now been confirmed by a total synthesis of *dl*-armepavine. Although it has not yet proved possible to resolve the racemic base, its degradation to the same products as those obtained from the naturally occurring alkaloid leave no doubt as to the structural identity of the synthetic base with armepavine.

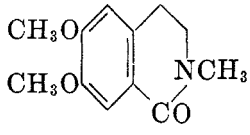
p-Nitrophenylacetyl chloride and 3,4-dimethoxyphenylethylamine were condensed to (*p*-nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide (I) and this was cyclized by the Bischler-Napieralski reaction to 1-(*p*-nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. The methiodide (II) of the cyclized product



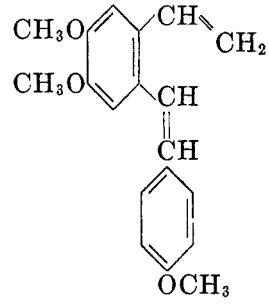
[1] Published as National Research Council Bull. No. 2052.

was reduced to 1-(*p*-aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (III) which was diazotized and converted to *dl*-armepavine (IV, R = H).

Oxidation of the racemic base with potassium permanganate produced the expected 1-keto-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (V). Synthetic armepavine formed an O-methyl derivative (IV, R = CH_3), the methiodide of which was converted by the action of alkali to *des*-O,N-dimethylarmepavine.



V



VI

This last compound, in turn, formed a methiodide which, by the action of hot alkali, gave rise to 4,4′,5-trimethoxy-2-vinylstilbene (VI). The structure of this substituted stilbene was confirmed by its oxidation with potassium permanganate to anisic acid and *meta*-hemipinic acid. These various degradative reactions have all been carried out previously with the naturally occurring alkaloid (3) and the properties of the many compounds isolated in the course of these degradations agree with those already on record (3).

Acknowledgment. The authors wish to express their gratefulness to the National Research Council of Canada for the award of a Fellowship to one of them (V. P.).

EXPERIMENTAL

The synthesis first involved the preparation of the starting materials. 3,4-Dimethoxyphenylethylamine was prepared from veratraldehyde by the method used by Marion and Grassie for the synthesis of 3,4-methylenedioxyphenylethylamine (4). *p*-Nitrophenylacetic acid was obtained from benzyl chloride by standard procedures (5, 6).

(p-Nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide (I). To a solution of *p*-nitrophenylacetic acid (7.3 g.) in chloroform (53 cc.), phosphorus pentachloride (18.7 g.) was added gradually. The resulting solution was added dropwise to a mixture of 3,4-dimethoxyphenylethylamine (9 g.), chloroform (45 cc.), 2 *N* aqueous sodium hydroxide (240 cc.), and water (375 cc.), kept stirred mechanically and cooled under the tap. After completion of the addition, stirring was continued for 30 minutes. The chloroform layer was separated and the aqueous solution was extracted with three more portions of chloroform. Successively, the combined chloroform extract was washed with 1:1-hydrochloric acid, with a saturated sodium carbonate solution, and with water; dried over sodium sulfate and distilled to dryness. The residual amide was crystallized twice from boiling methanol from which it separated as colorless scales, melting at 120°,[2] wt. 8.7 g., average yield, 65%.

Anal. Calc'd for $C_{18}H_{20}N_2O_5$: C, 62.79; H, 5.81; N, 8.11.
Found: C, 62.81, 62.70; H, 5.77, 5.93; N, 7.98, 7.94.

[2] All melting points are corrected.

1-(p-Nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline. To the above amide (5 g.) dissolved in chloroform (20 cc.) was added phosphorus oxychloride (15 cc.) and the resulting solution allowed to stand at room temperature for one week. The chloroform and excess phosphorus oxychloride were evaporated under diminished pressure and the light yellow solid residue was dissolved in warm dilute (1:1) hydrochloric acid. The solution was diluted with water, filtered to remove a small quantity of gum, and alkalized with ammonium hydroxide to liberate the base. The precipitated base was filtered, washed with water, and crystallized from boiling methanol from which it separated as small colorless needles, m.p. 122°; yield, 71%.

Anal. Calc'd for $C_{18}H_{18}N_2O_4$: C, 66.26; H, 5.52; N, 8.59.
Found: C, 66.10; H, 5.52; N, 8.38.

1-(p-Nitrobenzyl)-6,7-dimethoxy-3,4-dihydroisoquinoline methiodide (II). A mixture of the substituted dihydroisoquinoline (5 g.), methyl iodide (25 cc.), and methanol (75 cc.) was refluxed on the steam-bath for six hours. The crystalline methiodide which separated was filtered and washed with absolute ether. After recrystallization from boiling methanol it consisted of small yellow prismatic needles, m.p. 194°. Yield, 95%.

Anal. Calc'd for $C_{19}H_{21}IN_2O_4$: C, 48.71; H, 4.49.
Found: C, 48.80, 48.78; H, 4.63, 4.63.

1-(p-Aminobenzyl)-2-methyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline dihydrochloride. The methiodide (II) (10 g.) was dissolved in a mixture of water (100 cc.) and conc'd hydrochloric acid (200 cc.) with the aid of heat. To the solution kept mechanically stirred on the steam-bath, zinc dust (30 g.) was added in small quantities in the course of 45 minutes. The resulting mixture was filtered, the cooled filtrate alkalized with ammonium hydroxide, and extracted with four portions of ether. The combined extract was dried over potassium hydroxide pellets and the solvent subsequently distilled off on the steam-bath. The white, crystalline, residual base was immediately dissolved in a mixture of absolute methanol and absolute ether and the solution saturated with dry hydrogen chloride. The precipitated dihydrochloride was filtered and recrystallized from methanol-acetone from which it separated as small, colorless prisms, m.p. 268°. Yield, 70%.

Anal. Calc'd for $C_{19}H_{26}Cl_2N_2O_2$: C, 59.21; H, 6.75; Cl, 18.44.
Found: C, 59.61, 59.44; H, 6.82, 6.70; Cl, 17.88, 18.34.

dl-Armepavine (IV, R = H). The amine dihydrochloride (5 g.) was dissolved in sulfuric acid (10 cc.) previously diluted with water (100 cc.) and the solution cooled to 0° in an ice-bath. A cold solution of sodium nitrite (1 g.) in water (50 cc.) was then added at such a rate that the temperature did not rise above 5°. After the addition of the sodium nitrite had been completed the reaction mixture was allowed to stand ten minutes, during which the diazo compound crystallized. The resulting mixture was cautiously added to a boiling mixture of water (375 cc.) and conc'd sulfuric acid (125 cc.) and boiling continued for fifteen minutes after completion of the addition. The solution was cooled, filtered through charcoal to remove a quantity of gum which had separated, and the filtrate alkalized by the slow addition of ammonium hydroxide while cooling and stirring. The liberated base was extracted with four portions of ether and the combined extract dried over sodium sulfate. Distillation of the ether by heating the extract on the steam-bath left a residue consisting of small, yellow prisms. After recrystallization from acetone-ether, synthetic *dl*-armepavine was obtained as small, colorless rhombs, m.p. 166°. Yield, 65%.

Anal. Calc'd for $C_{19}H_{23}NO_3$: C, 72.84; H, 7.35; N, 4.47.
Found: C, 72.70, 72.87; H, 7.39, 7.27; N, 4.50, 4.41.

O-Methyl-dl-armepavine (IV, R = OCH_3). A solution of *dl*-armepavine (1.0 g.) in ether, to which an excess of diazomethane had been added, was allowed to stand overnight at room temperature. The ether and excess diazomethane were distilled off on the steam-bath and the residue dissolved in 5% hydrochloric acid (50 cc.). The filtered solution was alkalized with sodium hydroxide and extracted with ether. After removal of the solvent by distillation, the extract yielded an oil which was dissolved in absolute ether. On standing, this solution deposited colorless prismatic needles, m.p. 92°. Wt. 0.82 g.; yield, 78.3%.

Anal. Calc'd for $C_{20}H_{25}NO_3$: C, 73.40; H, 7.64, N, 4.28.
Found: C, 73.51, 73.47; H, 7.59, 7.50; N, 4.19, 4.16.

O-Methyl-dl-armepavine methiodide. O-Methyl-*dl*-armepavine when refluxed for three hours with methanol and excess methyl iodide gave a quantitative yield of the corresponding methiodide which crystallized from methanol as small yellow prisms, m.p. 135–136°.

Anal. Calc'd for $C_{21}H_{28}INO_3$: C, 53.73; H, 5.97; N, 2.98.
Found: C, 53.01, 53.14; H, 6.09, 6.06; N, 3.15.

Des-O,N-dimethylarmepavine. The methiodide of O-methyl-*dl*-armepavine (0.2 g.) was added to methanol (10 cc.) containing sodium hydroxide (0.8 g.) and the solution heated on the steam-bath for ninety minutes. This solution was subsequently evaporated to dryness, the residue dissolved in water (20 cc.), and the resulting aqueous solution extracted with ether. The extract was dried over potassium hydroxide pellets and distilled on the steam-bath to remove the solvent. It yielded a colorless oil (wt. 0.15 g.) which crystallized from petroleum ether as fine colorless needles, m.p. 87°; yield, quantitative. The similar compound obtained from *l*-armepavine had m.p. 86–87° (3).

Anal. Calc'd for $C_{21}H_{27}NO_3$: N, 4.10. Found: N, 4.16, 4.21.

Des-O,N-dimethylarmepavine methiodide. This methiodide was prepared by refluxing a mixture of the above methine (90 mg.), methanol (10 cc.), and methyl iodide (2 cc.) for ninety minutes. The resulting solution was concentrated to a small volume and allowed to stand. The methiodide which separated was recrystallized from methanol after which it consisted of small, colorless prisms, m.p. 234°; wt. 95 mg. The methiodide obtained from the natural base had m.p. 233–234° (3).

Anal. Calc'd for $C_{22}H_{30}INO_3$: C, 54.67; H, 6.22.
Found: C, 54.79, 54.71; H, 6.16, 6.14.

4,4',5-Trimethoxy-2-vinylstilbene. *Des-O,N*-dimethylarmepavine methiodide (0.2 g.) was added to methanol (5 cc.) containing potassium hydroxide (1 g.) and heated on the steam-bath for 1¾ hours. The solution was evaporated to dryness, water (15 cc.) was added to the residue, and the mixture extracted with ether (four portions). The combined extract was washed with two 50-cc. portions of 5% hydrochloric acid and with water. It was then dried over potassium hydroxide pellets and evaporated to dryness when it yielded a colorless oil which crystallized in contact with petroleum ether (2–3 cc.). Wt. 0.12 g., yield, 95%. After recrystallization from a mixture of anhydrous ether and petroleum ether, the product consisted of colorless rods, m.p. 79.5°. Literature, m.p. 79–79.5° (3).

Anal. Calc'd for $C_{19}H_{20}O_3$: C, 77.02; H, 6.76.
Found: C, 76.77, 76.95; H, 6.77, 6.75.

Oxidation of 4,4',5-trimethoxy-2-vinylstilbene. To a stirred solution of the substituted stilbene (0.5 g.) in purified acetone (100 cc.), 1% potassium permanganate in purified acetone (150 cc.) was added in the course of two hours at 20–22°. The reaction mixture was stirred a further two hours after which a little alcohol was added to destroy the excess potassium permanganate. The precipitated manganese dioxide was filtered and washed with hot water (200 cc.). The aqueous washings which had been kept separate were evaporated to dryness *in vacuo* on the steam-bath, the residue shaken with 10% hydrochloric acid (50 cc.), and the mixture extracted with five portions of ether. The combined extract was concentrated to 3–4 cc. and allowed to stand when it deposited a mixture of small, brownish warts and colorless needles. This was shaken with ether until all the needles had dissolved and the mixture filtered to remove the less soluble warts which were washed with a few drops of ether (wt. 0.116 g.). On recrystallization from boiling anhydrous ether, the filtered product yielded small colorless needles, m.p. 185–186° either alone or in admixture with an authentic sample of *meta-hemipinic acid.* The acetone liquor, from which the manganese dioxide had been filtered, was evaporated to dryness *in vacuo.* It left a residue which was shaken with 15% hydrochloric acid (50 cc.); the mixture was extracted with four portions of ether. When concentrated to a small volume, the combined extract deposited a crystalline substance which, after recrystallization from anhydrous ether, consisted of colorless needles (wt. 0.116 g.) m.p. 183.5–184.5° either alone or after admixture with an authentic sample of *anisic acid.*

6,7-Dimethoxy-2-methyl-1-keto-1,2,3,4-tetrahydroisoquinoline (V). To a solution of *dl*-armepavine (0.4 g.) in purified acetone (75 cc.) kept at 25–27°, was added dropwise, in the course of ninety minutes, a solution of potassium permanganate (0.7 g.) in purified acetone (90 cc.). This solution was allowed to stand with occasional stirring for a further hour and the excess potassium permanganate was destroyed by the addition of a little methanol. The manganese dioxide was then filtered and washed with acetone (50 cc.) and the combined filtrate and washings were evaporated to dryness *in vacuo*. A yellowish, solid residue was left which was dissolved in warm 10% hydrochloric acid (100 cc.). The solution was cooled, filtered, alkalized with ammonium hydroxide, and extracted with ethyl acetate. On evaporation to dryness *in vacuo* the extract left a residue which was dissolved in warm 0.5% hydrochloric acid (100 cc.). The solution was cooled, extracted with four portions of ether and the extract dried over potassium hydroxide pellets and distilled to dryness. There was left a crystalline residue which, after recrystallization from anhydrous ether, consisted of small colorless needles, m.p. 124–125°, wt. 0.15 g. Literature, m.p. 124–125° (3).

Anal. Calc'd for $C_{12}H_{15}NO_3$: C, 65.16; H, 6.79; N, 6.33.
Found: C, 65.20; H, 6.92; N, 6.40.

SUMMARY

The structure assigned to armepavine has been confirmed by a total synthesis of the racemic base. This synthesis has been effected from (*p*-nitrophenylaceto)-β-3,4-dimethoxyphenylethylamide which was cyclized to the corresponding dihydroisoquinoline, the methiodide of which was reduced and the product converted to *dl*-armepavine by diazotization. The structural identity of the synthetic base with the naturally occurring alkaloid has been confirmed by a comparison of the properties of the oxidation product and of the products of the Hofmann degradation with the recorded properties of the corresponding derivatives obtained from the alkaloid.

OTTAWA AND MONTREAL, CANADA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

STUDIES ON γ-PYRONES. I. DERIVATIVES OF KOJIC ACID[1]

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The varied reactivities of γ-pyrones (1,2), together with the ready availability of some of them such as kojic acid and maltol make these substances interesting starting materials for synthesis. In this paper we are reporting several syntheses based on kojic acid, as shown in the Flow Sheet.

Yabuta (3) and Armit and Nolan (4) found that selective methylation of the phenolic hydroxyl group of kojic acid could be achieved by the use of diazomethane, but Yabuta reported that methyl sulfate attacked both hydroxyl groups and led to the dimethyl ether. We have reinvestigated this reaction and found that even with methyl sulfate the phenolic hydroxyl group is attacked first, and good yields of the monomethyl ether, II, can be obtained if an excess of methyl sulfate is avoided.

2-Chloromethyl-5-methoxy-4-pyrone (III) is obtained easily and in good yield from kojic acid monomethyl ether. Although the chlorine atom in III is reactive, the compound does not undergo most replacement reactions normally. Thus treatment with alkali cyanides (4) causes tar formation, and similar results were obtained in the present work when cuprous cyanide was used. When attempts were made to prepare a Grignard reagent from III the magnesium dissolved, but on hydrolysis only an intractable gum was obtained. The chloro compound does react normally with tertiary aliphatic amines to give quaternary salts (VI) in good yield, but attempts to react it with N-β-dimethylaminoethylaniline were unsuccessful. The halogen atom of III can be replaced by hydrogen by use of zinc and acetic acid (5) or tin and hydrochloric acid, but catalytic hydrogenation of III over Raney nickel is not selective.

2-Chloromethyl-5-methoxy-4-pyridone (VIII) was prepared from 2-hydroxymethyl-5-methoxy-4-pyridone (VII) by the action of thionyl chloride in chloroform. The structure of VIII was established by hydrogenation to 2-methyl-5-methoxy-4-pyridone (V), identical with the substance prepared from 2-methyl-5-methoxy-4-pyrone (IV) and ammonia. The m.p. of V (105–106°) and its picrate (180°) found in this work are not in agreement with those reported by Yabuta (3) (115° and 200°, respectively); this discrepancy may be due to varying degrees of hydration.[4] 2-Chloromethyl-5-methoxy-4-pyridone gave only tars on treatment with sodium cyanide, cuprous cyanide, and sodioacetoacetic ester. It re-

[1] The material in this paper is abstracted, in part, from the Ph.D. Dissertation of Joseph F. Ackerman, University of Notre Dame, June, 1949.

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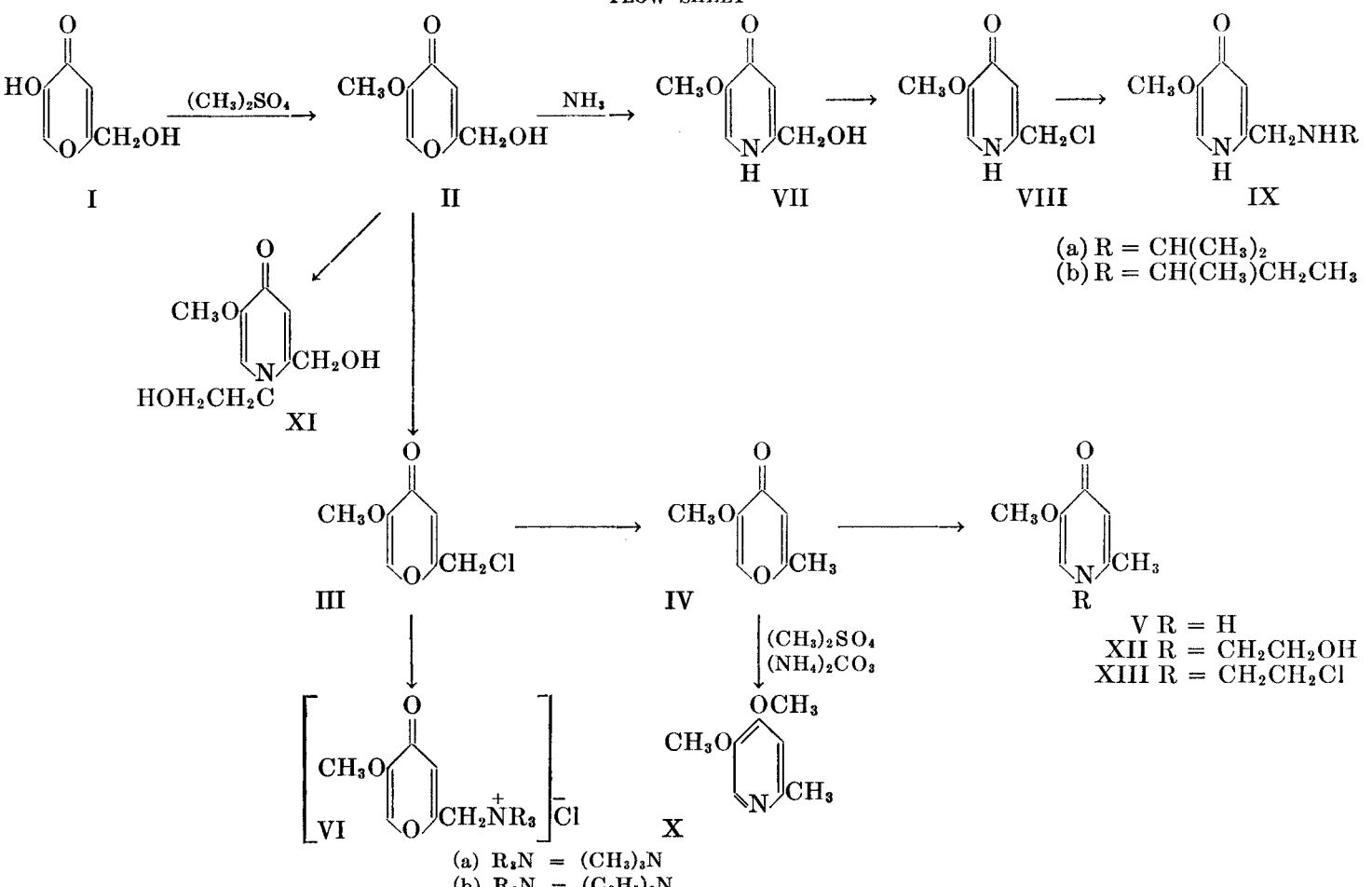
[4] The 4-pyrones and 4-pyridones form hydrates very readily, and other cases of discrepancies in melting points due to hydration have been observed; thus, 5-methoxy-2-hydroxymethyl-4-pyridone has been reported to melt at 95°, 111°, and 173–175° (2).

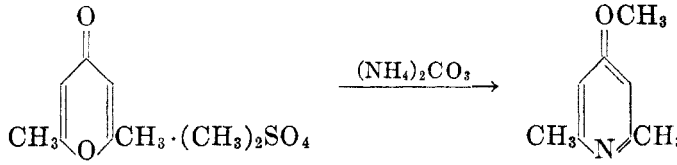
FLOW SHEET


HO
O
CH2OH
(CH3)2SO4
CH3O
NH3
N
H
CH2Cl
CH2NHR
I
II
VII
VIII
IX
(a) R = CH(CH3)2
(b) R = CH(CH3)CH2CH3
HOH2CH2C
XI
III
IV
V R = H
XII R = CH2CH2OH
XIII R = CH2CH2Cl
(CH3)2SO4
(NH4)2CO3
OCH3
CH2N+R3 Cl-
VI
X
(a) R3N = (CH3)3N
(b) R3N = (C2H5)3N

acted normally with primary amines, however, to form the 2-alkylaminomethyl-5-methoxy-4-pyridones (IX).

5-Methoxy-2-hydroxymethyl-4-pyrone and 5-methoxy-2-methyl-4-pyrone on treatment with ethanolamine gave the corresponding 1-(β-hydroxyethyl)pyridones, but pyridones were not obtained when the ethyl ester of glycine was used as the amine. 5-Methoxy-2-methyl-N-(β-hydroxyethyl)-4-pyridone (XII) was converted to the β-chloro compound (XIII) with thionyl chloride, but when this same reaction was applied to 5-methoxy-2-hydroxymethyl-N-(β-hydroxyethyl)-4-pyridone (XI) only one of the two hydroxyl groups was replaced.

Von Baeyer (6) observed that when 2,6-dimethylpyrone methyl methosulfate was treated with perchloric acid and then with ammonium carbonate it formed 2,6-dimethyl-4-methoxypyridine rather than the N-methylpyridone:



We have found that this reaction can also be carried out on 5-methoxy-2-methyl-4-pyrone, to give 4,5-dimethoxy-2-methylpyridine. Attempts to replace the perchloric acid with other strong acids such as *p*-toluenesulfonic acid or trichloroacetic acid were unsuccessful and neither the pyrone methiodide nor the methosulfate could be converted to the pyridine by treatment with ammonium carbonate.

EXPERIMENTAL[5,6]

2-Hydroxymethyl-5-methoxy-4-pyrone (II). To a well-stirred solution of 114 g. (0.8 mole) of kojic acid[7] in 500 ml. of 10% potassium hydroxide there was added 101 g. (0.8 mole) of redistilled dimethyl sulfate in portions over a period of thirty minutes. The temperature was kept below 25° by occasional cooling in an ice-bath. Stirring was continued for an additional fifteen minutes and the mixture was cooled in an ice-bath and filtered. The product weighed 90 g. (72%) and after recrystallization from methanol melted at 157–158° and was pure enough for subsequent reactions. Recrystallization from a 1:1 mixture of ethanol and ether raised the melting point to 161°, in agreement with Yabuta's value (3).

2-Methyl-5-methoxy-4-pyrone (IV). 2-Chloromethyl-5-methoxy-4-pyrone (III) was prepared from the hydroxy compound (II) and thionyl chloride, as described by Yabuta (3) for 2-chloromethyl-5-hydroxy-4-pyrone. Yield about 65%, m.p. 118°. Attempts were made to remove the halogen by catalytic hydrogenation over Raney nickel, but the reaction was not sufficiently selective. Reduction of III by tin and conc'd hydrochloric acid gave a 40% yield of IV.

The best results were obtained when the chloro compound was reduced with zinc and acetic acid, essentially as described by Yabuta (5). The average yield was 87%, m.p. 69–70°.

2-(Trimethylaminomethyl)-5-methoxy-4-pyrone chloride (VIa). A mixture of 6 g. (0.035 mole) of 2-chloromethyl-5-methoxy-4-pyrone, 18 g. (0.08 mole) of 30% aqueous trimethyl-

[5] Analyses for C, H, and N by Clark Microanalytical Laboratory, Urbana, Ill.

[6] All melting points are uncorrected.

[7] We wish to thank the Northern Regional Laboratory and the Corn Products Refining Co. for their generous gifts of kojic acid.

amine, and 50 ml. of ethanol was heated at 90° for 2½ hours in a closed container. Evaporation of the resulting solution under reduced pressure yielded a brown, oily residue which was triturated with dry acetone until crystallization occurred. Recrystallization from a methyl alcohol-acetone mixture yielded 5 g. (63%) of the quaternary salt, m.p. 209° (dec.).

Anal. Calc'd for $C_{10}H_{16}ClNO_3$: C, 51.39; H, 6.90; N, 5.99; Cl, 15.20.
Found: C, 51.84; H, 7.11; N, 5.75; Cl, 15.32.

2-(Triethylaminomethyl)-5-methoxy-4-pyrone chloride (VIb). A mixture of 5 g. (0.028 mole) of 2-chloromethyl-5-methoxy-4-pyrone and 6 g. (0.06 mole) of triethylamine in 50 ml. of 95% ethanol was refluxed for four hours. Evaporation of the reaction mixture under reduced pressure left a brown oil which crystallized on trituration with dry acetone. Recrystallization from a methyl alcohol-acetone mixture yielded 5 g. (65%) of hygroscopic plates, m.p. 72–74°.

Anal. Calc'd for $C_{13}H_{22}ClNO_3 \cdot \frac{1}{2} H_2O$: C, 54.82; H, 8.14; N, 4.92; Cl, 12.45.
Found: C, 54.91; H, 8.29; N, 4.98; Cl, 12.86.

2-Methyl-5-methoxy-4-pyridone (V). 2-Methyl-5-methoxy-4-pyrone (2 g.) was heated with 10 ml. of conc'd ammonium hydroxide at 90° for two hours. The product after recrystallization from a mixture of acetone and ethyl acetate melted at 105–106° and formed a picrate, m.p. 178°. Yabuta (3) who made V by this same reaction reported the m.p. as 115°, and that of the picrate as 200°.

5-Methoxy-2-chloromethyl-4-pyridone hydrochloride (VIII). 5-Methoxy-2-hydroxymethyl-4-pyridone (VII) was prepared by treating pyrone II with ammonia at 90°, as described by Armit and Nolan (4); the yield of material with m.p. 171–172° was 75%. Redistilled thionyl chloride (15 ml.) was added in portions to a solution of 5 g. of VII in 20 ml. of chloroform, cooled in an ice-bath, and the mixture was refluxed for an hour to complete the reaction. The product separated on cooling and was recrystallized from an absolute alcohol-acetone mixture. Yield of product with m.p. 152–153°, 70%.

Anal. Calc'd for $C_7H_9Cl_2NO_2$: C, 40.02; H, 4.32; N, 6.67.
Found: C, 40.09; H, 4.41; N, 6.90.

Reduction of 5-methoxy-2-chloromethyl-4-pyridone. A solution of 0.01 mole of VIII in 50 ml. of absolute ethanol containing 0.02 mole of potassium hydroxide was shaken with hydrogen in the presence of Raney nickel. The calculated amount of hydrogen (0.01 mole) was absorbed in forty-five minutes and absorption then ceased. The product (V) isolated from the solution melted at 102–103° after recrystallization from ethyl acetate, and formed a picrate, m.p. 180°. These substances did not depress the melting points of V and its picrate prepared from 2-methyl-5-methoxy-4-pyrone.

2-Isopropylaminomethyl-5-methoxy-4-pyridone dihydrochloride (IXa). To 10 g. (0.047 mole) of 2-chloromethyl-5-methoxy-4-pyridone hydrochloride (VIII) dissolved in 50 ml. of absolute ethanol there was added 15 g. (0.25 mole) of isopropylamine and the mixture was heated for 3 hours at 100° in a closed container. After cooling, the solution was evaporated to dryness under reduced pressure and 50 ml. of 18% hydrochloric acid was added. The solution was again evaporated to dryness and the residue after washing with 50 ml. of cold *n*-propyl alcohol was recrystallized from a methyl alcohol-acetone mixture. Colorless plates weighing 9.4 g. (75%) were obtained, m.p. 235° (dec.).

Anal. Calc'd for $C_{10}H_{18}Cl_2N_2O_2$: C, 44.62; H, 6.74; N, 10.41; Cl, 26.34.
Found: C, 44.95; H, 6.64; N, 10.94; Cl, 26.21.

2-sec-Butylaminomethyl-5-methoxy-4-pyridone dihydrochloride (IXb). This was prepared as described above, using 8 g. of IV and 10 g. of *sec*-butylamine. The product weighed 7.5 g. (70% yield) and melted at 231° (dec.).

Anal. Calc'd for $C_{11}H_{20}Cl_2N_2O_2$: C, 46.65; H, 7.12; N, 9.89; Cl, 25.04.
Found: C, 46.87; H, 7.26; N, 9.74; Cl, 24.87.

1-(β-Hydroxyethyl)-2-methyl-5-methoxy-4-pyridone. A solution of 13 g. (0.21 mole) of ethanolamine in 25 ml. of water was added with stirring to 30 g. (0.21 mole) of 2-methyl-5-methoxy-4-pyrone (IV) in 150 ml. of water over a period of fifteen minutes. The reaction mixture was refluxed for 3 hours and then evaporated under reduced pressure. The residue

was dissolved in a small amount of absolute ethanol and again evaporated under vacuum. An oil remained which crystallized upon trituration with isopropanol. The product after recrystallization from isopropanol had m.p. 166° and weighed 21 g. or 58% of the theoretical.

Anal. Calc'd for $C_9H_{13}NO_3$: C, 58.99; H, 7.15; N, 7.64.
Found: C, 58.69; H, 7.15; N, 7.58.

1-(β-Hydroxyethyl)-2-hydroxymethyl-5-methoxy-4-pyridone. To a solution of 29 g. (0.186 mole) of II in 100 ml. of water was added 10.2 g. (0.20 mole) of ethanolamine. The mixture was stirred for two hours at room temperature and was then refluxed for one hour and evaporated under reduced pressure. Trituration of the residue with a small amount of isopropanol gave cream-colored crystals; m.p. 167–168° after recrystallization from absolute ethanol yield 15 g.

Anal. Calc'd for $C_9H_{13}NO_4$: C, 54.25; H, 6.58; N, 7.03.
Found: C, 54.04; H, 6.49; N, 7.18.

1-(β-Chloroethyl)-2-methyl-5-methoxy-4-pyridone hydrochloride. To 5 ml. of purified thionyl chloride there was added in small portions, 8 g. of 1-(β-hydroxyethyl)-2-methyl-5-methoxy-4-pyridone. A vigorous reaction occurred and after the evolution of gas had ceased, the excess thionyl chloride was removed under reduced pressure. The residue solidified to a buff-colored powder on trituration with acetone. The product was treated with propanolic hydrogen chloride and 6.5 g. of buff-colored plates were obtained, m.p. 208° (dec.).

Anal. Calc'd for $C_9H_{13}Cl_2NO_2$: C, 45.40; H, 5.50; N, 5.88.
Found: C, 45.81; H, 5.49; N, 5.94.

Reaction of 1-(β-hydroxyethyl)-2-hydroxymethyl-5-methoxy-4-pyridone with thionyl chloride. To 2 ml. of purified thionyl chloride was added one gram of the pyridone. A vigorous reaction occurred and when the evolution of gas had stopped, the excess thionyl chloride was removed by evaporation. The residue was triturated with acetone and colorless crystals, m.p. 121–122° were obtained. Analysis indicated that one of the hydroxyl groups had been replaced by chlorine.

Anal. Calc'd for $C_9H_{13}Cl_2NO_3$: C, 42.56; H, 5.16; N, 5.52.
Found: C, 42.59; H, 5.11; N, 5.34.

2-Methyl-4,5-dimethoxypyridine (X). A mixture of 30 g. (0.21 mole) of 2-methyl-5-methoxy-4-pyrone and 31 g. (0.25 mole) of dimethyl sulfate was heated for two hours at 50°. The resulting oily, red liquid was cooled in an ice-bath and added to a twofold excess of cold 20% perchloric acid. After standing for two hours, the mixture was filtered and the crystalline methoperchlorate was added in portions to 175 ml. of cold 10% ammonium carbonate solution. The mixture was allowed to warm to room temperature and after saturation with ammonium sulfate, the solution was extracted with ethyl acetate. The extract yielded 20 g. of reddish-brown oil which was distilled *in vacuo*, b.p. 78–80°/1 mm. The *hydrochloride* melted at 164°.

Anal. Calc'd for $C_8H_{12}ClNO_2 \cdot \frac{1}{2}H_2O$: C, 48.35; H, 6.59; N, 7.05.
Found: C, 48.18; H, 6.64; N, 6.82.

SUMMARY

1. A new procedure has been developed for the preparation of kojic acid monomethyl ether.

2. Several derivatives of 5-methoxy-2-chloromethyl-4-pyrone and the corresponding pyridone have been prepared.

3. 5-Methoxy-2-methyl-4-pyrone has been converted to 4,5-dimethoxy-2-methylpyridine by the Baeyer reaction.

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[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY OF THE UNIVERSITY OF SZEGED]

CONFIGURATION OF DIASTEREOISOMERIC 3-METHOXY-4-HYDROXYPHENYLPROPANOLAMINES

GABOR FODOR, J. KISS, AND MÁRIA SZEKERKE

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In a previous communication (1) a synthesis of 1-(3-methoxy-4-hydroxyphenyl)-2-aminopropanol-1 (IVa) was described; this proceeded from isoeugenol benzyl ether *via* IA → IIa → III → IVa (route *A*). The hydrochloride of IVa melted at 205°. Other investigators (2) had prepared an amino alcohol of the same structure by a method analogous to ours, from isoeugenol acetate *via* IB → Va → IV (route *B*), but they recorded m.p. 176° for the hydrochloride of IV. We assumed that the compounds are diastereoisomers (1).

By the same type of synthesis, two closely related starting materials led to two end-products of assumedly different configuration. The reason for this discrepancy remained still to be elucidated. This seemed all the more interesting, as Welsh (3) called our attention to the same problem. He thought that IV obtained by route *B* would possess the same configuration as ephedrine, whereas using method *A*, deacetylation of IIa to III would result in a change of configuration, so that IVa would belong configuratively to ψ-ephedrine.

We record briefly our investigations, which afforded elucidation of the question, as follows. The acetamido derivative IIa was converted by hydrogenolysis into the phenolic compound VIa, and this, in turn, was acetylated to Va. The latter proved to be identical with the diacetyl derivative Va, obtained from isoeugenol acetate by route *B*. Consequently, IIa and Va are of the same configuration. As in our experiments both acetamides IIa and Va underwent an instantaneous N → O acetyl migration by the action of alcoholic hydrogen chloride,[1] they probably are related configurationally to ψ-ephedrine (4, 5).

Change of this configuration could occur either (a) in converting IIa into III, or (b) during deacetylation of Va to IV.

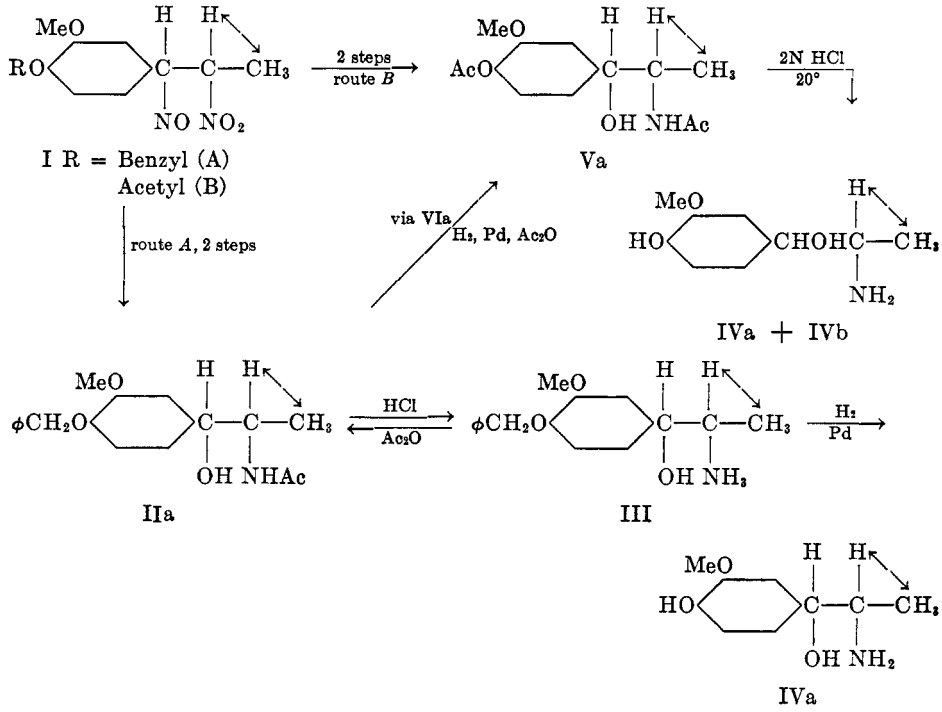
We deacetylated IIa to III, according to (1) by heating the nearly neutral aqueous solution of the corresponding O-acetyl amino alcohol; III was then reacetylated with acetic anhydride in pyridine to give IIa in nearly quantitative yield, but no trace of its diastereoisomer IIb. It was thus proved that the isolated product III (1) of the deacetylation of IIa retained the configuration of ψ-ephedrine. Since III afforded by hydrogenolysis (1) IVa, the latter must have the same configuration, as hydrogenolysis never effects a change of configuration.

In order to determine the correctness of our second assumption (*i.e.*, that deacetylation of bis-acetyl-ψ-ephedrine derivative Va would be associated with Walden inversion, and lead to the hydrochloride of IV of ephedrine configuration)

[1] Bruckner and Krámli (2) carried out an acetyl migration experiment by adding the calculated 1 mole of hydrochloric acid in small portions to an acetone solution of Va in the course of 24 hours to avoid deacetylation. Acyl migration completed, therefore, only after the full amount of acid was added. This slow reaction prompted Welsh (3) to assume ephedrine configuration as well for Va as for the product of its deacetylation, IV.

we synthesized 1-(3-methoxy-4-hydroxyphenyl)-2-aminopropanol-1 by a method which led with analogous compounds selectively (6, 7) to norephedrine derivatives. This end-product should be identical with either the amino alcohol obtained by route *A*, or with that produced by method *B*.

We started with 3-methoxy-4-hydroxypropiophenone[2], prepared in a good yield from guaiacol and propionic acid with boron trifluoride. This ketone was, in turn, converted into the oximino ketone VII. With thionyl chloride the latter underwent secondary Beckmann rearrangement (9) to furnish, after hydrolysis,



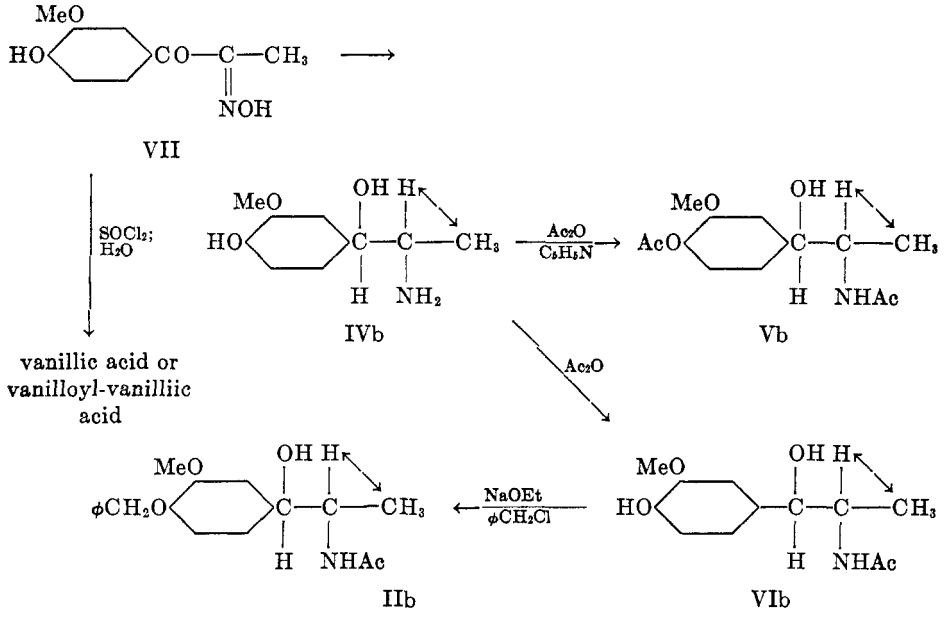
vanillic acid (under more energetic conditions vanilloylvanillic acid was formed. *para*-Position of the ketonic group to the phenolic hydroxyl was therefore proved. Reduction of the oximino ketone under Hartung's conditions furnished the hydrochloride of IVb, m.p. 217°, which gave a strong m.p. depression with IVa-hydrochloride from isoeugenol benzyl ether, m.p. 206°. The free base showed m.p. 170°; IVa melted at 149–150°. Methylation with diazomethane gave 3,4-dimethoxynorephedrine (10) while IVa gave on similar treatment 3,4-dimethoxynor-ψ-ephedrine (1), obtained also from the corresponding 1-nitroso-2-nitro compound (11).[3]

[2] Marshall (8) recorded Fries rearrangement of guaiacol propionate to this ketone in the presence of $AlCl_3$.

[3] Regarding the configuration of some amino alcohols produced by this type of synthesis compare (6).

Acetylation of IVb with 2 moles of acetic anhydride in pyridine yielded a 4,N-diacetyl derivative Vb, not identical with Va obtained from isoeugenol acetate and from isoeugenol benzyl ether through the corresponding 1-nitroso-2-nitro compounds. This acetamide, under mild conditions, did not undergo acyl migration N → O, proving thus its ephedrine configuration (4, 5).

Acetylation of IVb with one mole of anhydride gave rise to an alkali-soluble N-monoacetyl derivative VIb, which, in turn, was benzylated to IIb, not identical with IIa, produced by route *A*. Compound IIb did not undergo acyl migration spontaneously.



All these facts suggest that: 1. Synthesis of IVa starting from the nitroso-nitro compound IA led to a compound which is related configurationally to ψ-ephedrine, whereas reduction of oximino ketone VII produced the appropriate ephedrine derivative IVb. Therefore our earlier paper (1) must be modified, as the therein described compounds are "synthetic ψ-norephedrine derivatives" and not "synthetic norephedrine derivatives".

2. Synthesis of Va from nitroso-nitro derivative IB led similarly to a ψ-ephedrine derivative. However, this latter underwent an inversion during its hydrolysis to IV, so that the hydrochloride m.p. 176° (2) must therefore consist of a difficultly separable mixture of both diastereoisomeric amino alcohols IVa (m.p. 206°), and IVb (m.p. 217°).

EXPERIMENTAL

3-Methoxy-4-hydroxypropiophenone. A solution of 12.4 g. (0.1 mole) of guaiacol in 14.8 g. (0.2 mole) of propionic acid was saturated with boron trifluoride while cooling with ice.

In five hours the weight increased 15 g. The sirupy reddish mixture was heated at 70° for 90 min. in a water-bath, then poured with stirring into a solution of 22 g. of anhydrous sodium acetate in 90 cc. of water; the separated oil was extracted with a total of 150 cc. of ether. The solvent was then evaporated and the residual oil distilled *in vacuo*, b.p. 165–175° (5–7 mm.). Thirteen grams (77.4%) of crystals, m.p. 48–50°, was obtained, suitably pure for the preparation of the oximino ketone. Marshall *et al.* (8) recorded m.p. 60–62°.

3-Methoxy-4-hydroxy-α-oximinopropiophenone (*VII*). To a solution of 26 g. (0.14 mole) of 3-methoxy-4-hydroxypropiophenone in 120 cc. of benzene, 23.8 g. (0.13 mole) of 20% hydrogen chloride in dry ether, then 16.7 g. (0.16 mole) of isobutyl nitrite, were added in 30 min. while cooling with ice. After standing for a few hours in the ice-box, 20 g. of crystals was obtained; evaporation of benzene *in vacuo* furnished a further crop, 2 g., (a total of 84%); m.p. 144° after recrystallization from 50% ethanol.

Anal. Calc'd for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3.
Found: C, 57.1; H, 5.4.

Degradation. (a) Treatment of 1 g. (0.048 mole) of oximino ketone with 5 cc. (0.071 mole) of thionyl chloride under stirring caused a rise in temperature; the reddish-brown solution was evaporated, and the residual oil heated with 50 cc. of water. One cc. (0.005 mole) of 5 *N* sodium hydroxide was added and the undissolved part, 0.2 g., was filtered and the filtrate acidified; the radial needles which separated, 0.3 g., melted at 222–223°. Analysis gave data corresponding to those for vanilloylvanillic acid.

Anal. Calc'd for $C_{16}H_{14}O_7$: C, 60.4; H, 4.4.
Found: C, 60.1; H, 4.55.

(b) The above experiment was repeated, but addition of thionyl chloride was carried out dropwise under cooling with ice, and removal of excess thionyl chloride took place at 15–20°. The crystalline residue yielded on recrystallization from water pale yellow needles, 0.76 g. (94.5%) of vanillic acid, m.p. 205–206°, which was raised by further purification to 207–208° (12).

Anal. Calc'd for $C_8H_8O_4$: C, 57.1; H, 4.8.
Found: C, 56.8; H, 5.1.

3-Methoxy-4-hydroxy-dl-norephedrine (*IVb*). A solution of 31.5 g. (0.15 mole) of oximino ketone in 380 cc. of absolute alcohol was hydrogenated in the presence of 69 cc. of 5 *N* hydrogen chloride in absolute alcohol and 10 g. of Pd-charcoal (7% PdO). Absorption of hydrogen: 6750 STP-cc. (2 moles) in six hours. The excess of hydrogen chloride was neutralized with 20% sodium hydroxide solution, the catalyst-free solution evaporated to 60 cc. volume, and diluted with 170 cc. of water and hydrogenated with 5 g. of Pd-charcoal; uptake of hydrogen: 3350 STP-cc. in 5 hours. The residue from the solution was dissolved in 150 cc. of anhydrous alcohol, filtered from sodium chloride and concentrated to a 20–30 cc. volume; the crystals of IVb-hydrochloride were transferred to a filter with 20 cc. of ether, and washed with alcohol-ether; 19 g., 55%, m.p. 217° (dec.). Fodor (1) recorded m.p. 206° for IVa; a mixture melted from 184–192°.

Anal. Calc'd for $C_{10}H_{15}NO_3 \cdot HCl$: C, 51.37; H, 6.90.
Found: C, 51.53; H, 7.52.

Free base. Liberation was carried out in absolute alcohol using sodium ethoxide, and the resulting base was recrystallized from toluene; yellowish crystals, m.p. 169–170°.

Anal. Calc'd for $C_{10}H_{15}NO_3$: C, 60.9; H, 7.7.
Found: C, 60.5; H, 7.7.

3,4-Dimethoxy-dl-norephedrine (*methyl ether of IVb*). To a solution of 0.8 g. of base IVb in 20 cc. of absolute methanol an ethereal diazomethane solution was added until nitrogen evolution ceased. The methylated amino alcohol, 0.8 g., was recrystallized from benzene; after washing with alkali, nearly colorless crystals were obtained, m.p., alone and in mixture with an authentic specimen (10) 139–140°.

N-Acetyl-3-methoxy-4-acetoxy-dl-norephedrine (*Vb*). To a solution of 0.6 g. (0.003 mole) of amino alcohol IVb in 20 cc. of pyridine, 0.65 cc. of acetic anhydride (0.0065 mole) was added. The solvent was removed after a day; the residue gave white needles from benzene, 0.52 g., m.p. 135–136°. The diastereoisomer melted at 164–165° (2).

Anal. Calc'd for $C_{14}H_{19}NO_5$: C, 59.8; H, 6.8.
Found: C, 60.0; H, 6.9.

From 0.28 g. of Vb, 0.22 g. was recovered unchanged after standing ten hours with 0.2 cc. of 4 *N* alcoholic HCl in 2 cc. of absolute alcohol.

N-Acetyl-3-methoxy-4-hydroxy-dl-norephedrine (VIb). To 0.805 g. (0.004 mole) of the amino alcohol IVb, 0.86 cc. (0.008 mole) of acetic anhydride was added; an immediate reaction took place and the temperature rose to 40°. The crystals were collected after keeping the mixture for a day at room temperature; yield 0.758 g., m.p. 138–141°, raised to 142–143° after recrystallization from toluene.

Anal. Calc'd for $C_{12}H_{17}NO_4$: C, 60.2; H, 7.2.
Found: C, 60.15; H, 7.2.

N-Acetyl-3-methoxy-4-benzyloxy-dl-norephedrine (IIb). A solution containing 0.24 g. (0.0012 mole) of the acetamido alcohol VIb, 25 cc. of anhydrous ethanol, 0.15 cc. (0.0012 mole) of benzyl chloride, and 0.024 g. (0.0012 atom) of sodium was refluxed for 20 hours and the filtered solution evaporated to dryness. The residue was recrystallized from 30 cc. of benzene to give 0.16 g. of white plates, m.p. 145–146°, mixed m.p. with IIa (m.p. 138°) 125–130°, From 0.15 g. of IIb, 0.13 g. was recovered unchanged after standing ten hours with 0.2 cc. of alcoholic 4 *N* HCl in 2 cc. of anhydrous alcohol.

Anal. Calc'd for $C_{19}H_{23}NO_4$: C, 69.3; H, 7.0.
Found: C, 69.4; H, 7.2.

Conversion of IIa into Va. One gram of N-acetyl derivative IIa in 15 cc. of absolute alcohol absorbed 70 cc. of hydrogen (calc'd for 1 mole, 68 STP-cc.) in the presence of 0.4 g. of Pd-charcoal in 30 min. The filtrate was evaporated, the residue, 0.32 g. of amorphous VIa, was dissolved in 1 cc. of dry pyridine, 0.15 cc. of acetic anhydride was added, and kept for 24 hours at room temperature. The solvent and acetic acid were removed *in vacuo* at 25° and the crystalline residue, 0.2 g., was recrystallized from alcohol; m.p. 163°, also in mixture with authentic Va from isoeugenol acetate (2). *Acyl migration* N → O. A solution of 0.1 g. of diacetyl product Va in 2 cc. of absolute alcohol was treated with 0.1 cc. of 4 *N* HCl in alcohol and the solution evaporated after 15 min. to dryness. The residual crystalline hydrochloride showed m.p. 192° (2). *Acyl migration* O → N. This hydrochloride (0.05 g.) was dissolved in 3 cc. of water and the N-acetyl derivative, 0.03 g., precipitated by sodium carbonate.

N-Acetyl-3-methoxy-4-benzyloxy-dl-nor-ψ-ephedrine (IIa) from 3-methoxy-4-benzyloxy-nor-ψ-ephedrine (III). Three tenths gram of III, prepared according to (1) with 40% yield, m.p. 129°, was added to 1 cc. of acetic anhydride with shaking. An exothermic reaction took place and the acetyl derivative crystallized from the solution, yield 0.25 g. after washing with a small amount of cold acetic acid, m.p. 138°, also in mixture with an authentic specimen of IIa (1).

Deacetylation of Va. 1. According to (2), 0.25 g. of Va, m.p. 165°, prepared by route *B* from isoeugenol acetate *via* IB, was added to 2.5 cc. of 2 *N* HCl and kept for 4 days at room temperature with occasional shaking. In 2 days the amide dissolved completely. The solution was evaporated *in vacuo* at 25° and 5 mm.; the amorphous residue could, however, not be crystallized. 2. A solution of 0.113 g. of Va in 0.86 cc. of *N* HCl (1.1 mole) was kept for 20 hours at room temperature, then heated for an hour on a steam-bath. Evaporation under 1–2 mm. pressure afforded a crystalline residue which could be recrystallized from alcohol-ether to furnish colorless prisms, m.p. 184–187°. This mixture of the assumed diastereoisomers proved to be unseparable by recrystallization.

Action of alcoholic hydrogen chloride upon IVb. 1. To a solution of 0.185 g. of IVb hydrochloride, m.p. 217°, in 20 cc. of alcohol, 0.6 cc. of 4 *N* HCl (3 moles) in absolute alcohol was added and the mixture refluxed for 3 hours. Evaporation gave 200 mg. of ammonium chloride, formed by a hydramine cleavage during the heating. 2. A solution of 0.032 g. of IVb-HCl in 10 cc. of absolute alcohol was refluxed for 46 min. with 0.06 cc. (1.5 mole) of 4 *N* HCl in absolute alcohol. Evaporation afforded an assumed mixture of diastereoisomers, m.p. 184–188°. Longer heating yielded a product, m.p. 170–184°.

The phenolic amino alcohol is obviously very sensitive towards acids, and apparently tends to undergo inversion easily.

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SUMMARY

Analogous syntheses (1, 2) of IV led to different products. It could be proved by synthesis of the ephedrine derivative of IVb and by several interconversions that both syntheses starting with 1-nitroso-2-nitro compounds Ia and Ib, respectively, led primarily to nor-ψ-ephedrine derivatives IIa and Va, respectively.[3] However, deacetylation of Va resulted in a partial inversion, leading to a mixture of IVa and IVb, whereas hydrolysis of IIa and subsequent hydrogenolysis of III furnished with retention of configuration the ψ-ephedrine derivative IVa.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF SOUTHERN METHODIST UNIVERSITY]

THE KOLBE-SCHMITT REACTION. I. VARIATIONS IN THE CARBONATION OF *p*-CRESOL

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In order to carry out a certain study made in our laboratory some time ago it became necessary to prepare several aromatic hydroxy acids. The possibility of employing the traditional Kolbe-Schmitt reaction (1) suggested itself early in this work. Upon an examination of the literature one is faced with a wide variation in possible procedures (2, 3, 4, 5, 6). By far the most simple technique reported consists in heating the phenol with potassium carbonate and carbon dioxide under pressure, a procedure apparently first used by Marassé (7). It was evident that, while a large number of compounds have been prepared by the Kolbe-Schmitt reaction, no general study of the relative merits of these several modifications has been reported.

In this paper we attempt to show the effect of variations in temperature, reaction time, carbon dioxide pressure, and the particular alkali metal or compound thereof on the yield of *p*-cresotinic acid (2-hydroxy-5-methylbenzoic acid) prepared from *p*-cresol. This particular phenol was selected for study since the possibility of forming more than one acid is remote. No attempt has been made to interpret the results of our study to support any of the theories related to the mechanism of this reaction (8), but it is felt that further work using a wide variety of different phenols may justify this.

The procedure mentioned under reference (7) was chosen for this preliminary work since it did not involve the initial preparation and isolation of an extremely hygroscopic metallic cresoxide. The number of operations involved in the reaction was thereby reduced to a minimum, thus making the comparison of yields under different conditions more valid. Table I shows the variation in yield of *p*-cresotinic acid at various temperatures and pressures when the reaction is carried out for different lengths of time. The examples that appear in the table are typical of those resulting from several hundred runs made during this study and all reported yields have been checked by duplicate runs. Details concerned with the control of temperature and pressure are described under Experimental.

From the results shown in Table I (Part A) it is evident that no appreciable amount of acid (less than 1%) will be formed at a temperature lower than 100° regardless of the pressure and time of reaction. A very high yield of product may be secured at a temperature of 125° while operating for eight hours at a pressure of 250 p.s.i. or more. The amount of acid formed is satisfactory at pressures as low as 100 p.s.i. when operating at the higher temperatures. A large increase in temperature, pressure, and reaction time do not result in a significant increase in yield.

Based on further studies made along these lines several points of general interest may be noted:

(a) A 2:1 molar ratio of potassium carbonate/*p*-cresol gave yields of

product in general as high as did a ratio of 3:1. Reducing the ratio below this level usually served to decrease the yield.

(b) No *p*-cresotinic acid was formed when potassium carbonate was replaced by sodium carbonate, sodium bicarbonate, lithium carbonate, or the carbonates of magnesium or calcium. When potassium bicarbonate, cesium carbonate or rubidium carbonate was used the reaction proceeded normally except that yields were lower than with potassium carbonate (being of the order of 20%).

TABLE I

YIELD OF *p*-CRESOTINIC ACID UNDER VARIOUS REACTION CONDITIONS

RUN NO.	TEMP., °C.	TIME, HRS.	PRESSURE, P.S.I.	YIELD, %
		PART A—HIGH PRESSURES		
1	100	24	1420	0
2	110	8	1480	13
3	125	2	1240	40
4	125	4	1400	68
5	125	8	1310	84
6	175	4	1540	85
7	250	4	1580	82
		PART B—LOW PRESSURES		
8	125	8	250	79
9	125	8	100	43
10	125	8	15 (1 atm)	5
11	175	8	250	87
12	175	8	100	78
13	175	8	15 (1 atm)	29

(c) When *p*-cresol was mixed with potassium carbonate and heated to 250° for 24 hours without carbon dioxide no *p*-cresotinic acid was isolated. Negative results were also obtained when the reaction vessel was filled with nitrogen and heated under the same conditions at 1300 p.s.i.

(d) The addition of as little as one ml. of water to the reaction mixture may decrease the yield by as much as one-half.

(e) Attempts to prepare *p*-cresotinic acid by dissolving potassium carbonate in water, adding *p*-cresol, and refluxing the mixture in an atmosphere of carbon dioxide were unsuccessful. When glycerol was used instead of water yields of the order of 5% were secured.

(f) The reaction was also carried out in the traditional manner, that is, by heating the dry sodium, potassium or lithium cresoxides with carbon dioxide under pressure. The yield of *p*-cresotinic acid is lower when prepared from the metallic cresoxide by the traditional Kolbe-Schmitt procedure than when it is made by reacting *p*-cresol with potassium carbonate and carbon dioxide under pressure. Judging from our results there is nothing

to be gained by preparing the cresoxide from the metal rather than the metallic hydroxide. The yield of product is generally largest when prepared from sodium cresoxide, somewhat less when the potassium salt is used, and lowest by far with the lithium salt.

It should be stated at this point that the authors found the regular Kolbe-Schmitt procedure to be unpredictable as to yield of product. It was not uncommon to observe no product formation at all under conditions which on a previous run had led to a good yield. Apparently the preparation of the cresoxide is not always reproducible, in spite of observing every precaution in isolating and drying the compound.

EXPERIMENTAL

Apparatus. Any of the commercial pressure reactors designed for hydrogenation studies may be used for these carbonations. It was not necessary to employ agitation in any form. Temperatures were automatically controlled to within ±5°. It was necessary to replace gaskets and small connection tubes frequently. Gaskets formed from copper or aluminum were found to be satisfactory. Stainless steel valves and tubing are desirable but not essential.

Preparation of potassium carbonate/p-cresol mixtures. The anhydrous potassium carbonate (fine granular) and freshly distilled *p*-cresol were used in a molar ratio of 3:1 or 2:1. Practically all of the runs were made with 0.05 mole (5.1 g.) of the cresol, but satisfactory results were obtained when using amounts of cresol as small as 0.01 mole. About one-half of the carbonate was placed in a Pyrex test tube of suitable size (20 × 200 mm.), the cresol added, and then the remainder of the carbonate. The two compounds may be mixed thoroughly or not mixed at all with little difference in yield obtained. All reagents and apparatus should be thoroughly dry, but otherwise no special precautions need be observed.

Preparation of sodium, potassium, and lithium cresoxides. Method A. About 400 ml. of dried toluene was placed in a one-liter three-neck flask and 0.25 mole of the metal was added. When lithium cresoxide was prepared the metal was hammered into thin wafers and trimmed into small places before being placed in the reaction flask. The flask was fitted with a Herschberg stirrer (9), reflux condenser, and a dropping-funnel. The metal (except lithium) was melted by bringing the toluene to a gentle reflux under stirring, and *p*-cresol (0.25 mole dissolved in 100 ml. of toluene) was added over a period of thirty minutes. The material in the flask became very viscous as the reaction progressed, and stirring under reflux was continued for two to three hours after all the cresol had been added.

The product was allowed to cool and the metallic cresoxide separated from toluene by suction filtration. The cresoxide was dried in a casserole by careful warming on a hot-plate, powdered by grinding gently with a pestle, and finally heated in a vacuum-oven (10–15 mm.) at 60° overnight.

Method B. p-Cresol (0.25 mole) and the metallic hydroxide (0.25 mole) were mixed in a casserole with 100 ml. of water. The solution was stirred constantly as it was rapidly evaporated to dryness on a hot-plate. Constant stirring was necessary to avoid charring the cresoxide. When the product appeared to be dry it was powdered in the casserole and dried further under the same condition as employed in Method A above.

Reaction procedure. The Pyrex tube containing the material to be studied was placed in the pressure reactor and carbon dioxide admitted from a commercial cylinder with no purification, following which the reactor was heated to the desired temperature. When operating at low pressures it was advisable to determine by preliminary blank runs the proper starting pressure so that when the desired temperature was reached it would not be necessary to reduce the pressure by venting the reactor, since this would inevitably be accompanied by loss of cresol and a marked decrease in the yield of product. Minor variations

in pressure that appear in Table I were due to variations in the starting tank pressure. Best yields of product were secured when a considerable excess of carbon dioxide was used. At no point in any of our reactions were sudden increases in pressure noted that might constitute an explosion hazard.

At the end of the reaction the apparatus was allowed to cool, vented, and the tube removed. The reaction product was usually a hard cake having a light yellow to brown color. The cake was dissolved in hot water and filtered to remove tarry material. The filtrate was then extracted with ether to remove unreacted cresol, boiled with charcoal, cooled and filtered. No effort was made to recover any unreacted cresol. The filtrate was acidified with concentrated hydrochloric acid and the precipitated *p*-cresotinic acid was thoroughly dried in an oven at 60°. Melting points and neutral equivalents were determined on all products isolated in all of the runs.

All yields of *p*-cresotinic acid are reported on a crude basis. This is felt to be justified since the melting point of practically every product was 149 ±1° (uncorrected), as compared with that of 152° for a carefully purified sample. The neutral equivalent of the products was 152 ± 1; calculated value, 152.

Further studies being pursued related to the preparation of aromatic hydroxy acids by the carbonation of phenols are: the application of the reaction to amino- and nitro-phenols, and the effect of reaction conditions on the relative amounts of isomeric products formed.

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SUMMARY

The modification proposed by Marassé for the preparation of aromatic hydroxy acids was shown to be superior to the Kolbe-Schmitt procedure when *p*-cresol was used as a starting material. The variation in yield of product with changes in temperature, pressure, and reaction time is tabulated.

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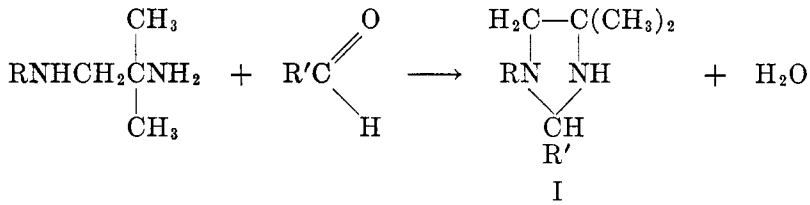
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

A STUDY OF THE REACTION PRODUCTS OF 1,2-DIAMINES WITH ALDEHYDES

J. L. RIEBSOMER

Received July 12, 1949

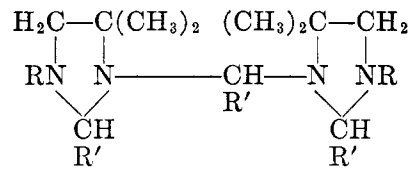
In view of the successful removal of water by heating 1,2-diamines with carboxylic acids to produce imidazolines (1), it seemed reasonable to anticipate that one might be able to split water from aldehydes or ketones and 1, 2-diamines to produce imidazolidines. This expectation was fulfilled in the case of aldehydes which react to give compounds of type I.



I

In the study reported here, R was isopropyl or phenyl and R′ was either hydrogen, methyl, *n*-propyl, phenyl or α-furyl. The experience thus gained would suggest that any 1,2-diamine and any aldehyde of the types indicated above would behave similarly. The literature reveals comparable results by other workers (2, 3, 4).

Previous experience with comparable compounds indicated that *bis*-methylene compounds of type II might be prepared by interacting 3 molar-equivalents of



II

the aldehyde with 2 molar-equivalents of the diamine. All attempts to do so resulted in failure.

The compounds of type I were colorless liquids or solids soluble in common organic solvents. When R (Formula I) was phenyl, they titrated potentiometrically as monoacid bases. When R was alkyl, the neutral equivalents were between the values for mono- and di-acid bases.

It seemed desirable to try to prepare derivatives of these compounds in order to have a more complete proof of their structures. All attempts to prepare the hydrochlorides or benzoyl derivatives by the usual procedures resulted in ring opening. While these results are in keeping with those of Rameau (5) they do not contribute greatly to the elucidation of the structures.

About the only reasonable alternative series of compounds which might have been formed would be the corresponding Schiff bases. Lob (6) has shown that imidazolidines are stable toward 10% sodium hydroxide or sodium ethoxide while Schiff bases are reduced by sodium and alcohol to form the corresponding amines. When the compound which is believed to be 1-phenyl-4,4-dimethylimidazolidine was treated with sodium and alcohol, it was recovered unchanged thus showing that a Schiff base was not involved.

Finally, two of the compounds in this series were carefully purified and their molar refractivities were observed. The observed values checked quite well with those calculated.

Bergmann and others (7) have shown recently that cyclohexanone will react with a 1,2-diamine to produce the corresponding imidazolidine. In the present work, several attempts were made to substitute ketones for aldehydes in these reactions, but in all instances only the starting materials were recovered.

EXPERIMENTAL

One example will suffice to illustrate the method of preparation of the compounds listed in Table I.

1-Phenyl-2-(2'-furyl)-4,4-dimethylimidazolidine (III). A mixture was prepared containing 82 g. (0.5 mole) of N-(2-aminoisobutyl)aniline and 48 g. (0.5 mole) of furfural. A small quantity of benzene was added and the mixture was heated under conditions to distill the benzene-water azeotropic mixture through a 4' packed-column. The column was fitted with a decanter stillhead so that the benzene was returned constantly to the reaction mixture. The temperature was increased slowly to a maximum of 110°. This five-hour period of heating caused the removal of 9 g. of water. The product was distilled at 151–159° at 4 mm. Upon redistillation, practically all the material distilled at 157–159° at 4 mm. Yield, 84.5 g. or 70%.

Anal. Calc'd for (III) $C_{15}H_{18}N_2O_4$: C, 74.35; H, 7.90; N, 11.57; Neut. equiv., 242.1. Found: C, 74.16; H, 7.47; N, 11.69; Neut. equiv., 236.6.

Attempted preparation of hydrochlorides of the imidazolidines. 1-Isopropyl-2,4,4-trimethylimidazolidine was dissolved in anhydrous ether and treated with dry hydrogen chloride gas. A white solid formed which sublimed above 200°.

Anal. Calc'd for N-(2-aminoisobutyl)isopropylamine·2 HCl, $C_7H_{20}Cl_2N_2$: N, 13.64; Cl, 34.97.

Found: N, 13.70; Cl, 35.30.

A similar experiment with 1-isopropyl-2-phenyl-4,4-dimethylimidazolidine gave the same dihydrochloride of N-(2-aminoisobutyl)isopropylamine.

Attempted preparation of benzoyl derivatives of the imidazolidines. 1-Isopropyl-2,4,4-trimethylimidazolidine was treated with benzoyl chloride under the usual conditions for benzoylating an amine. A white solid was isolated which melted at 144°.

Anal. Calc'd for the dibenzoyl derivative of N-(2-aminoisobutyl)isopropylamine, $C_{21}H_{26}N_2O_2$: N, 8.28. Found: N, 8.13.

An experiment similar to the one immediately above was carried out with 1-isopropyl-4,4-dimethylimidazolidine and benzoyl chloride. The product melted at 146–147°.

Anal. Calc'd for the dibenzoyl derivative of N-(2-aminoisobutyl)isopropylamine, $C_{21}H_{26}N_2O_2$: N, 8.28. Found: N, 8.40.

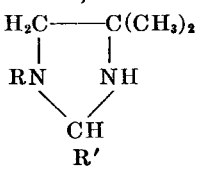
The *dibenzoyl derivative* of N-(2-aminoisobutyl)isopropylamine was prepared. It melted at 146–147°. A mixed melting point with the product above showed no depression.

ACKNOWLEDGMENT

The author is pleased to express his appreciation for the generous support given this study by the research laboratory of Commercial Solvents Corporation.

TABLE I

REACTION PRODUCTS OF 1,2-DIAMINES AND ALDEHYDES



ALDEHYDE USED	FORMULA OF PRODUCT	B.P., °C./MM.	YIELD, %	d_4^{20}	n_D^{20}	MOLECULAR REFRACTION		ANALYSIS							
								C		H		N		NEUT. EQUIV.[c]	
						Calc'd	Observed	Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Acetaldehyde[a]	$C_9H_{20}N_2$	72–75/24	20	0.8498	1.4440	49.12	48.84	69.17	69.01	12.98	12.92	17.95	17.70	156.1	92.6
Butyraldehyde[a]	$C_{11}H_{24}N_2$	93–94/18	60	.8522	1.4479	58.36	57.89	71.63	71.47	13.12	13.01	15.20	14.89	184.2	116.1
Benzaldehyde[a]	$C_{14}H_{22}N_2$	103–105/2	40	.9482	1.5088	—	—	76.99	76.97	10.16	10.03	12.87	12.69	218.1	210.8
Furfural[a]	$C_{12}H_{20}N_2O$	128–130/22	73	.9805	1.4863	—	—	69.23	68.64	9.61	9.53	13.45	13.11	208.1	117.0
Formaldehyde[b]	$C_{11}H_{16}N_2$	m.p. 73°	67	—	—	—	—	74.95	74.93	9.15	9.04	15.90	15.87	176.1	176.8
Acetaldehyde[b]	$C_{12}H_{18}N_2$	124–126/3	71	.9984	1.5510	—	—	75.74	75.74	9.54	9.54	14.72	14.74	190.1	188.4
Butyraldehyde[b]	$C_{14}H_{22}N_2$	134–135/3	71	—	—	—	—	76.58	76.20	10.16	10.27	12.83	12.27	218.1	219.1
Benzaldehyde[b]	$C_{17}H_{20}N_2$	m.p. 95–96°	79	—	—	—	—	80.91	80.95	7.99	7.90	11.10	10.99	252.2	252.9
Furfural[b]	$C_{15}H_{18}N_2O$	157–159/4	70	—	1.5764	—	—	74.35	74.16	7.90	7.47	11.57	11.69	242.1	236.6

[a] Amine used was N-(2-aminoisobutyl)isopropylamine. *R* = Isopropyl. [b] Amine used was N-(2-aminoisobutyl)aniline. R = Phenyl. [c] Calculated as monoacid bases. Potentiometric titrations.

SUMMARY

1. Nine new imidazolidines have been prepared by the interaction of aldehydes and 1,2-diamines. The type reaction seems to be general.

ALBUQUERQUE, N. M.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

THE PRODUCTS FORMED FROM THE REACTIONS OF 1,2-DIAMINES AND DIBASIC ACIDS

J. L. RIEBSOMER

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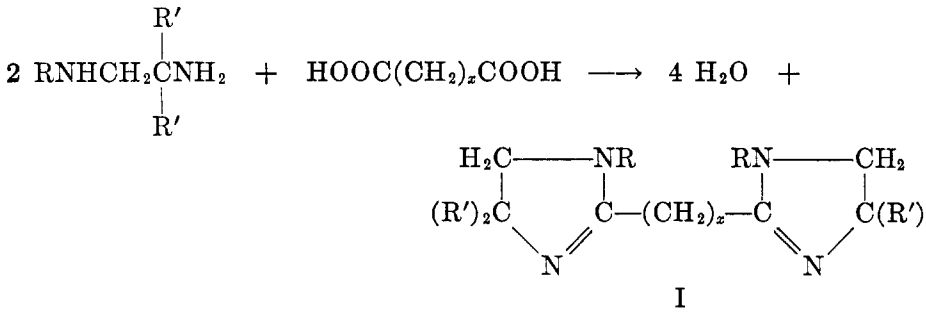
It has been shown previously (1, 2, 3, 4) that when 1,2-diamines are heated with carboxylic acids under conditions to remove water, imidazolines (or their complexes) may be produced in satisfactory yields. These reactions were especially satisfactory when there was one secondary- and one primary-amino group in the diamine.

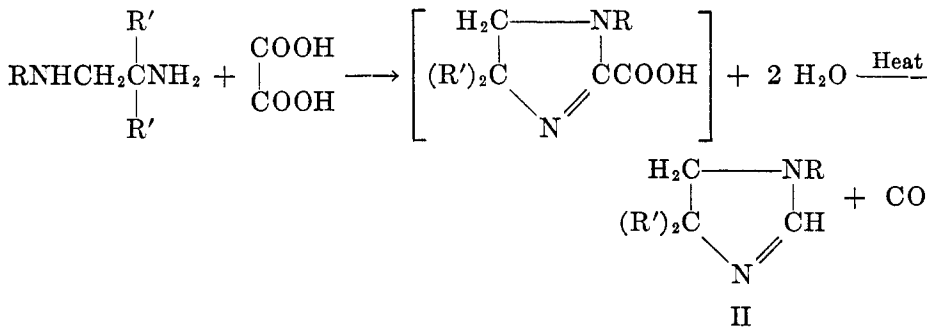
In view of the above, it seemed reasonable to anticipate that dibasic acids should react under similar conditions with two molar equivalents of typical 1,2-diamines to produce *bis*-imidazolines (I) in accordance with the equation below. It is assumed that the mechanism is similar to that previously suggested for monobasic acids.



I

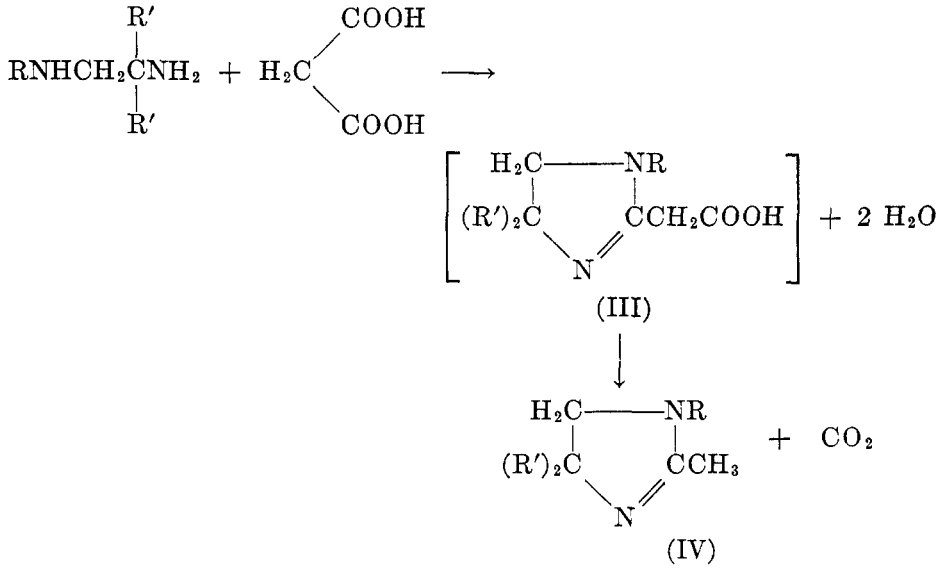
With the expected exceptions of oxalic and malonic acids, other dibasic acids have been found to behave as indicated above. When oxalic acid was allowed to react with a diamine, an imidazoline (II) was produced in low yield and was the same compound which one obtains with formic acid and the same diamine.

Thus, in the general case, oxalic acid appears to behave as follows:



II

Similarly, malonic acid with a typical diamine may proceed as indicated:



It is not possible to state with certainty whether the postulated imidazolinylacetic acid (III) formed as indicated, or the malonic acid first lost carbon dioxide to form acetic acid which in turn formed the imidazoline (IV). In any event, the effect was the same as if acetic acid had interacted with the diamine.

EXPERIMENTAL

N-(2-Aminoisobutyl)isopropylamine and oxalic acid. A mixture of 26 g. (0.2 mole) of N-(2-aminoisobutyl)isopropylamine and 25.2 g. (0.2 mole) of oxalic acid dihydrate was prepared. A little benzene was added and the mixture was heated under conditions to distill the benzene-water azeotropic mixture through a 4′ packed-column. The column was fitted with a decanter stillhead so that the benzene returned constantly to the reaction mixture. The temperature was increased to 100° at which temperature 6.5 g. of water collected. The temperature was then increased during a 3-hour period to 190°, thus removing 4.5 g. of water. Heating one more hour at 190° gave no more water. The product was transferred to a modified Claisen flask and the benzene was removed *in vacuo*. A mixture of solid and liquid remained. Ether was added and the insoluble solid was removed. Upon distillation, the ether extract boiled from 55–85° at 25 mm. and weighed 16.2 g. Upon redistillation, an 8.0-g. fraction was obtained, boiling from 55–80° at 25 mm.; this was mainly the original diamine. A second fraction weighing 6.0 g. boiled at 80–83° at 25 mm. This fraction was redistilled and a middle cut taken for analysis (1-isopropyl-4,4-dimethyl-2-imidazoline).

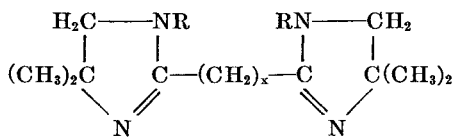
Anal. Calc'd for $C_8H_{16}N_2$: N, 19.98; Neutral equivalent, 140.1.
Found: N, 19.39; Neutral equivalent, 139.8.

N-(2-aminoisobutyl)isopropylamine and malonic acid. To a mixture of 26 g. (0.25 mole) of malonic acid and 65 g. (0.50 mole) of N-(2-aminoisobutyl)isopropylamine was added 150 ml. of benzene. The mixture was heated under the conditions described in the preceding experiment to remove water through a 4′ packed-column. The temperature was maintained at 180–200° for 7 hours. This procedure removed 6.4 g. of water. The temperature was increased to 220° during one hour, but no more water was removed.

Upon distillation at 23 mm., the first fraction boiled from 55–71°. It was mainly the original diamine and weighed 40.2 g. The second fraction boiled from 71–130° at the same pressure and weighed 9.0 g. About 5 g. of tar remained undistilled.

TABLE I

Bis-IMIDAZOLINES OF TYPE



ACID USED	FORMULA	B.P., °C. (MM.)	M.P., °C.	YIELD %	ANALYSES							
					C		H		N		Neut. Equiv.	
					Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
Succinic[a]	$C_{18}H_{34}N_4$	—	115–116	59	70.53	70.39	11.19	11.19	—	—	153.2	157.9
Glutaric[a]	$C_{19}H_{36}N_4$	170–174 (4)	—	33	—	—	—	—	17.48	16.91	160.1	175.3
Adipic[a]	$C_{20}H_{38}N_4$	—	84–85	26	71.76	71.23	11.46	11.30	16.75	16.38	167.1	174.5
Azelaic[a]	$C_{23}H_{44}N_4$	215–220 (4)	—	73	73.33	72.78	11.78	11.72	14.85	14.39	188.2	194.9
Sebacic[a]	$C_{24}H_{46}N_4$	210–215 (2)	—	70	73.77	73.00	11.87	11.65	14.34	13.96	189.2	199.0
Adipic[b]	$C_{26}H_{34}N_4$	235–237 (2)	—	64	—	—	—	—	13.94	13.44	201.2	227.9

[a] Amine used was N-(2-aminoisobutyl)isopropylamine; R = isopropyl. [b] Amine used was N-(2-aminoisobutyl) aniline; R = phenyl.

The 9.0-g. fraction was redistilled at 27 mm. and separated into two main fractions; the first, b.p. 87–90° and the second b.p. 130–132°. The lower-boiling fraction proved by analysis to be 1-isopropyl-2,4,4-trimethyl-2-imidazoline.

Anal. Calc'd for $C_9H_{18}N_2$: N, 18.15; Neutral equivalent, 154.15.
Found: N, 17.93; neutral equivalent, 157.8.

The higher-boiling fraction analyzed correctly for the *acetic acid complex* of *1-isopropyl-2,4,4-trimethyl-2-imidazoline.*

Anal. Calc'd for $C_{13}H_{26}N_2O_4$: N, 10.21. Found: N, 10.70.

Succinic, glutaric, adipic, azelaic, and sebacic acids were each reacted with N-(2-aminoisobutyl)isopropylamine. Also adipic acid was allowed to react with N-(2-aminoisobutyl)-aniline. Since the procedure was about the same for all these examples, only one will be described in detail.

Bis-1,4-(2',2"-diisopropyl-4',4"-tetramethyl)-2',2"-imidazolinylbutane (*V*). A mixture of 65 g. (0.5 mole) of N-(2-aminoisobutyl)isopropylamine, 36.5 g. (0.25 mole) of adipic acid, and benzene was heated under the conditions described in the preceding experiments to remove water. A total of 11 g. of water was removed by heating at 200–260° for 12 hours. The product distilled at 5 mm. using a modified Claisen flask. After a small forerun, 31 g. of distillate was collected at 175–185°. An undistilled residue of 7 g. remained. Yield of crude product, 40%. It solidified upon standing and was purified by crystallization from petroleum ether (26% yield of purified product). The purified material, m.p. 84–85°, analyzed correctly for (V).

Table I summarizes the data for the examples of this type.

Attempts were made to prepare the *hydrochlorides* of several of the above imidazolines, but in most instances non-crystallizable oils were obtained. In the case of the *bis*-imidazoline produced from N-(2-aminoisobutyl)isopropylamine and succinic acid, a solid hydrochloride was obtained.

Anal. Calc'd for the dihydrochloride: N, 14.77; Cl, 18.72.
Found: N, 14.31; Cl, 18.15.

Since the hydrochlorides were difficult to prepare and since the nitrogen analysis was poor for the product obtained from glutaric acid, the *dipicrate* was prepared from this compound.

Anal. Calc'd for the dipicrate: N, 17.98. Found: N, 18.29.

It is interesting to observe that the neutral equivalents reported are consistently higher than the calculated values. However, they are near enough to suggest that these compounds act as diacid bases.

ACKNOWLEDGMENT

The author is pleased to express his appreciation for the generous support given this study by the research laboratory of Commercial Solvents Corporation.

SUMMARY

1. It has been shown that dibasic acids above malonic react with 1,2-diamines to produce *bis*-imidazolines.

2. Six new compounds of this type have been reported. These compounds behave as diacid bases.

ALBUQUERQUE, N. M.

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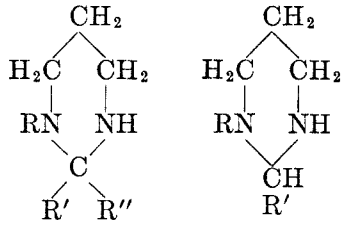
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

THE SYNTHESIS OF HEXAHYDROPYRIMIDINES FROM 1,3-DIAMINES AND KETONES OR ALDEHYDES

J. L. RIEBSOMER AND GLEN H. MOREY[1]

Received July 18, 1949

Previous workers (1, 2, 3, 4) have shown that 1,3-diamines will condense with aldehydes or ketones to produce hexahydropyrimidines. We have extended this earlier work by preparing a number of new compounds. Several ketones tried in this study have been found to produce good yields of the corresponding hexahydropyrimidines (I). When benzophenone, ethyl oxomalonate, quinone, and benzalacetone were substituted for the common ketones, none of the expected pyrimidines were obtained.

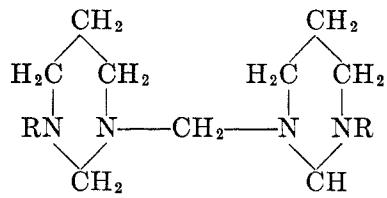


I II

In some instances aldehydes give a comparable reaction (producing compounds of type II) but for some unknown reason this type of reaction is less general and less satisfactory. Thus when acetaldehyde, butyraldehyde or benzaldehyde was interacted with N-isopropyl-1,3-propanediamine, none of the expected hexahydropyrimidines was isolated.

Also, it has been demonstrated that when the aldehyde is formaldehyde *bis*-compounds (III) may form.

$$2\ RNHCH_2CH_2CH_2NH_2 + 3\ HCHO \rightarrow 3H_2O +$$



III

It has not been found possible to cause other aldehydes (for example furfural) to behave in a similar manner. Presumably in these reactions the hexahydropyrimidine of type II is first formed followed by the interaction of 2 moles of the hexahydropyrimidine and 1 mole of formaldehyde with the loss of 1 mole of water.

[1] Present address: Glas-Col Apparatus Co., Inc., Terre Haute, Ind.

EXPERIMENTAL

A. KETONES AND 1,3-DIAMINES

A number of hexahydropyrimidines were prepared using the same general procedure, which was essentially that used by Bergmann, *et al.* (4). Only one needs to be given in detail. Table I summarizes the data.

1-Isopropyl-2-methyl-2-phenylhexahydropyrimidine. A mixture of 34.8 g. (0.3 mole) of N-isopropyl-1,3-propanediamine and 36 g. (0.3 mole) of acetophenone was prepared. A little benzene was added and the mixture was heated under conditions to distill the benzene-water azeotropic mixture through a 4′ packed-column. The column was fitted with a decanter stillhead so that the benzene returned constantly to the reaction mixture. The temperature was gradually increased from 120° to 180° during a 6-hour period, resulting in the removal of 5 g. of water. Upon distillation from a modified Claisen flask at 20 mm., the product was a colorless liquid which boiled at 173–175°. Yield, 37 g. (57%).

Anal. Calc'd for $C_{14}H_{22}N_2$: C, 76.96; H, 10.16; N, 12.82; Neut. equiv., 109.12.
Found: C, 77.03; H, 10.14; N, 12.80; Neut. equiv., 110.44.

B. ALDEHYDES AND 1,3-DIAMINES

Reaction of N-isopropyl-1,3-propanediamine and formaldehyde. In one experiment, a mixture of 58 g. (0.5 mole) of N-isopropyl-1,3-propanediamine and 63 g. (0.75 mole) of 40% aqueous formaldehyde was prepared and heated under the usual conditions to remove water by distilling the benzene-water azeotropic mixture through a 4′ packed-column. By heating for 3 hours from 90 to 110°, a total of 51 g. of water was removed. The residue was distilled and separated into two main fractions. The first fraction, b.p. 74–75° at 22 mm., analyzed correctly for N-isopropylhexahydropyrimidine; yield 30%.

Anal. Calc'd for $C_7H_{16}N_2$: N, 21.85; Neut. equiv., 64.1.
Found: N, 21.41; Neut. equiv., 65.8.

The second fraction, b.p. 140–142° at 3 mm., analyzed correctly for *bis*-(3-isopropyl-1,3-diazacyclohexyl)methane (Type III); yield, 24%.

Anal. Calc'd for $C_{15}H_{32}N_4$: N, 20.85; Neut. equiv., 67.06.
Found: N, 20.34; Neut. equiv., 70.46.

In a second experiment, equimolecular quantities of N-isopropyl-1,3-propanediamine and formaldehyde were allowed to react under the conditions of the preceding experiment. Apparently some of the expected N-isopropylhexahydropyrimidine formed, but it was not sufficiently pure to give a suitable analysis.

In a third experiment, 152 g. (1.31 moles) of N-isopropyl-1,3-propanediamine was dissolved in 100 ml. of methanol. Then 2.8 moles of 40% aqueous formaldehyde was added portionwise while stirring and cooling. The temperature was maintained at 30–40°. The mixture was finally heated to 60° on a steam-bath. The methanol and other volatile constituents were removed *in vacuo* by heating to a maximum temperature of 110°. The product was distilled at 2 mm.; yield, 91 g. (70%).

Anal. Calc'd for the *bis*-compound, $C_{15}H_{32}N_4$: N, 20.85; Molecular weight, 268.
Found: N, 21.14; Molecular weight, 264.

N-isopropyl-2-(2′-furyl)hexahydropyrimidine. A mixture was prepared containing 58 g. (0.5 mole) of N-isopropyl-1,3-propanediamine and 48 g. (0.5 mole) of furfural. Much heat was evolved and the mixture was cooled externally to prevent the temperature exceeding 50°. Benzene was added and the mixture was heated under the usual conditions to remove water. The temperature was increased during a 5-hour period to a maximum of 160°, thus removing 8.5 g. of water. The product which distilled at 122–123° at 5 mm. weighed 62 g. (64%).

Anal. Calc'd for $C_{11}H_{18}N_2O$: C, 67.98; H, 9.34; N, 14.42; Neut. equiv., 97.08.
Found: C, 67.98; H, 9.53; N, 14.23; Neut. equiv., 91.69.

N-(β-Hydroxyethyl)hexahydropyrimidine. To 206 g. (1.745 moles) of N-(β-hydroxyethyl)-1,3-propanediamine was added 100 ml. of methanol. To this mixture was added 1.7

TABLE I

HEXAHYDROPYRIMIDINES OF TYPE I FROM KETONES AND 1,3-DIAMINES

AMINE USED	KETONE USED	FORMULA	B.P., °C.	MM.	YIELD, %	ANALYSES							
						C		H		N		Neut. Equiv.	
						Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
N-Isopropyl-1,3-propanediamine	Acetophenone	$C_{14}H_{22}N_2$	173–175	20	57	76.96	77.03	10.16	10.14	12.82	12.80	109.12	110.44
N-Isopropyl-1,3-propanediamine	Ethyl methyl ketone	$C_{10}H_{22}N_2$	104–107	20	61	70.50	70.49	13.03	13.03	16.39	16.36	85.11	86.81
N-2-Ethylhexyl-1,3-propanediamine	Acetophenone	$C_{19}H_{32}N_2$	183–185	4	82	—	—	—	—	9.71	9.38	144.16	151.22
N-2-Ethylhexyl-1,3-propanediamine	Acetone	$C_{14}H_{30}N_2$	115–120	3	78	—	—	—	—	12.33	12.90	113.14	109.18
N,N-Dibutyl-4-aza-1,7-heptanediamine	Acetone	$C_{17}H_{37}N_3$	160–165	4	73	—	—	—	—	14.83	15.79	94.4	89.7
N,N-Dibutyl-4-aza-1,7-heptanediamine	Acetophenone	$C_{22}H_{39}N_3$	205–208	3	75	—	—	—	—	12.16	11.83	115.1	119.02

moles of 40% aqueous formaldehyde with stirring and cooling so that the temperature remained at 45–50°. This mixture was finally heated ½ hour on a steam-bath. The methanol and other volatile constituents were distilled *in vacuo* up to a pot temperature of 120°. The product which distilled at 137–140° at 17 mm. weighed 209 g. (92%).

Anal. Calc'd for $C_6H_{14}N_2O$: N, 21.43; Molecular weight, 130.1; Neut. equiv., 65.
Found: N, 21.23; Molecular weight, 113; Neut. equiv., 66.5.

When furfural was substituted for formaldehyde in the above reaction in an attempt to produce N-(β-hydroxyethyl-2-α-furyl)hexahydropyrimidine, only a black tar was formed.

N-(2-ethylhexyl)hexahydropyrimidine. To 233 g. (1.28 moles) of N-(2-ethylhexyl)propanediamine was added one mole of aqueous 40% formaldehyde with stirring and cooling so that the temperature was maintained at 45–50°. After the reaction was complete, the more volatile constituents were distilled *in vacuo* up to a pot temperature of 130°. The remainder of the product was fractionated at 10 mm. The main fraction boiled at 120–121° and weighed 194 g. (98%).

Anal. Calc'd for $C_{12}H_{26}N_2$: N, 14.40; Molecular weight, 198.
Found: N, 14.14; Molecular weight, 214.

Bis-3-(3'-dibutylaminopropyl)-1,3-diazacyclohexylmethane. To 243 g. (1.0 mole) of N,N-dibutyl-4-aza-1,7-heptanediamine was added 200 ml. of methanol. To this mixture was added portionwise 2 moles of aqueous 40% formaldehyde while stirring and cooling to maintain the temperature at 40–50°. After about 75% of the formaldehyde was added, two layers formed. The mixture was finally heated for a few minutes with steam. The methanol and other volatile constituents were removed *in vacuo* up to a pot temperature of 130°. Upon distillation, 230 g. (88%) of the expected product was obtained.

Anal. Calc'd for $C_{31}H_{66}N_6$: N, 16.09; Molecular weight, 522.
Found: N, 15.61; Molecular weight, 508.

A number of these new hexahydropyridmidines have been tested as insect repellents, but none have been found effective.

ACKNOWLEDGMENT

The authors are pleased to express their appreciation to the research laboratories of Commercial Solvents Corporation for generous support of this work.

SUMMARY

1. Ketones react with 1,3-diamines to give good yields of hexahydropyrimidines.

2. Some aldehydes likewise produce hexahydropyrimidines in good yields, but this type of reaction is less satisfactory.

3. In some instances, when formaldehyde reacts with 1,3-diamines, it has been shown that *bis*-1,3-diazacyclohexylmethanes may be produced.

ALBUQUERQUE, N. M.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

THE SYNTHESIS OF TRIMETHYLENE-1,2,4-THIADIAZINE-3,5-DIONE-1,1-DIOXIDE. A NEW MOLECULAR REARRANGEMENT

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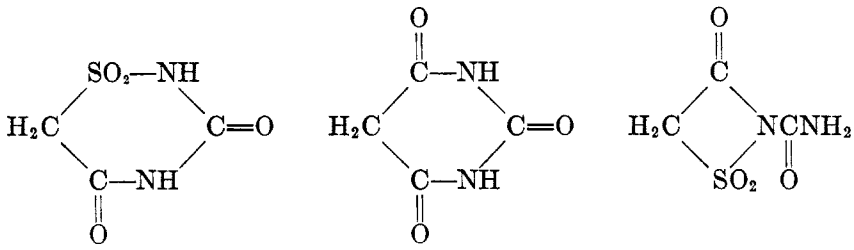
Received July 22, 1949

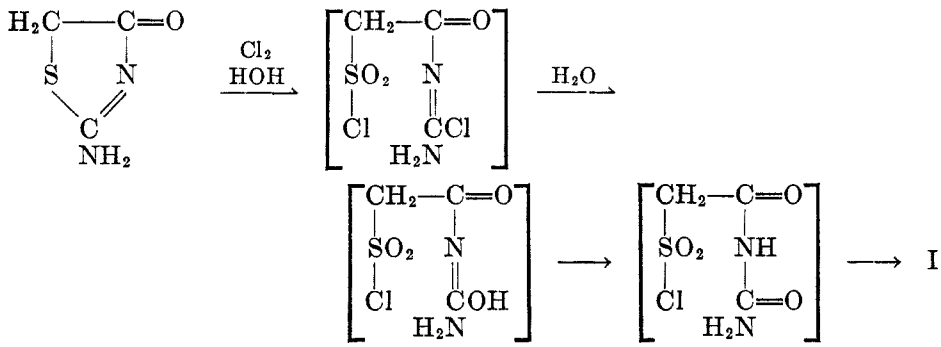
The close similarity of trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (I) to barbituric acid (II) is apparent by inspection of the following structures:



I II III

A comparison of the physiological activity of I and its 6-substituted derivatives with the corresponding barbituric acids seemed of interest. The ring system contained in I is unknown and previous attempts to prepare it or its 6-substituted derivatives met with failure (1).

Examination of the literature revealed that Kramp (2) in 1880 had investigated the reaction between chlorine gas and a dilute hydrochloric acid solution of 2-imino-4-thiazolidone. He reported only decomposition products when the reaction was carried out at room temperature. However, if the reaction was carried out at 0° a white, chlorine-free, precipitate formed to which he assigned the empirical formula, $C_3H_6N_2O_3S$. I required $C_3H_4N_2O_4S$ which however fits Kramp's analytical values very well. It is well known that certain S-alkylthiuronium salts will undergo cleavage with chlorine to give good yields of the alkylsulfonyl chloride (3). 2-Imino-4-thiazolidone hydrochloride may be considered a nitrogen-substituted S-alkylthiuronium salt which on chlorination might undergo a rearrangement similar to the following to give I.



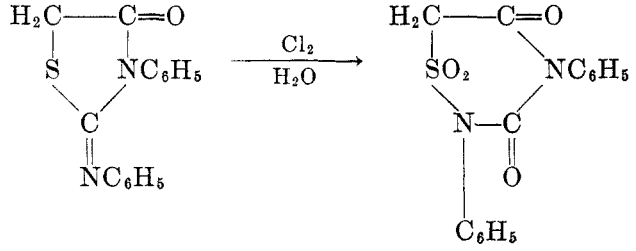
[1] From a thesis submitted by Paul N. Rylander to the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Doctor of Philosophy.

Kramp's work was, accordingly, repeated and a compound shown to be I was obtained in a maximum yield of 40%.

I was decomposed by boiling sodium bicarbonate solution into sulfoacetic acid. It dissolved easily in 10% potassium hydroxide but it was not reprecipitated by acidification of the solution with hydrochloric acid. Raney nickel desulfurized I to give a 79% yield of acetylurea, whereas degradation of 2-imino-4-thiazolidone with Raney nickel gave as the only isolated product N-formylacetamide. All of these facts taken together strongly indicate that I is the correct structure for the product obtained by the reaction of chlorine gas with a solution of 2-imino-4-thiazolidone.

Only one other structure (III) was given serious consideration. III, which is isomeric with I, could not be eliminated by any of the chemical evidence presented and no chemical test could be devised which would unequivocally distinguish between these possibilities. However, III was considered unlikely for it should be thermodynamically less stable than the strainless six-membered ring.

Direct proof that the six-membered ring can and does exist was made in the following reaction. N,N′-diphenyl-2-imino-4-thiazolidone (IV) was reacted with chlorine in dilute hydrochloric acid solution to give N,N′-diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (V).

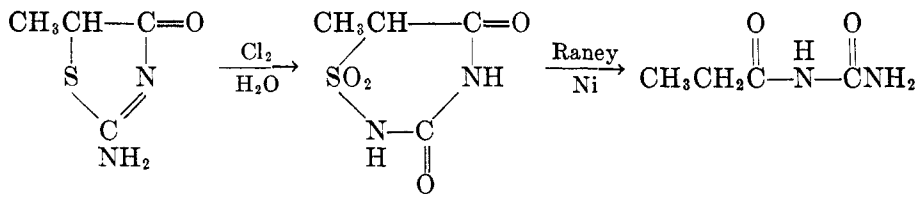


IV V

Formation of the four-membered ring was in this case impossible. V, like I, spontaneously lost sulfur dioxide. It was desulfurized with Raney nickel to give a solid which was a mixture of diphenylurea and N-acetyldiphenylurea. On repeated recrystallization of this mixture from dilute alcohol, the melting point rose until a mixed melting point with authentic diphenylurea showed no depression. Acetyldiphenylurea, the product expected in this degradation, is reported to be readily hydrolyzed to diphenylurea (4). Desulfurization of IV with Raney nickel gave aniline and acetanilide, probably due to the ease of hydrolysis of the expected N-acetyl-N,N′-diphenylformamidine.

The reaction of chlorine with 5-methyl-2-imino-4-thiazolidone (VI) produced as expected 6-methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (VII), which was subsequently desulfurized with Raney nickel to give propionylurea in good yield.[2]

[2] There was an annoying side reaction connected with this chlorination. Explosive by-products were formed which decomposed even when in water. This disturbing phenomenon was largely circumvented by using small quantities of pure starting materials, keeping the



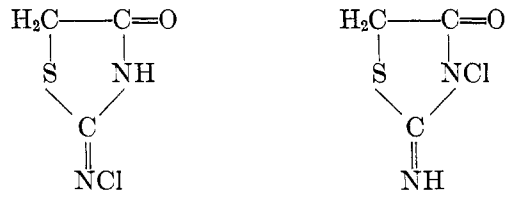
VI VII

To determine the influence of other substituents on the reaction, 5-carbethoxy-, 5-benzal-, 5-benzyl-, and the heretofore unknown 5-phenyl-, 5-carboxamido-, and 5,5-diphenyl-2-imino-4-thiazolidone were prepared and chlorinated. The main reaction in each case was oxidation of the sulfur to sulfate ion; there was no evidence of any rearrangement. It seems that those factors which might be expected to stabilize the rearranged product are the very ones which promote cleavage of the methylene carbon-sulfur bond in aqueous solution.

Chlorination of 5-ethyl-2-imino-4-thiazolidone proceeded in a manner entirely different from that of its two lower homologs. The precipitate formed was so unstable, disappearing at intervals in a puff of smoke, that it could not be purified for analysis. It contained chlorine, but this chlorine was not ionic, for a precipitate formed with silver nitrate only after shaking for several seconds. The precipitate oxidized iodide ion to iodine, indicating that a "positive" halogen was present. A compound of such marked instability probably has a nitrogen-chlorine linkage.

Chlorination of 5,5-dimethyl-2-imino-4-thiazolidone in ice-cold dilute hydrochloric acid gave a "positive" halogen compound of much greater stability than that derived from the 5-ethyl derivative. A sample was kept in the dry state for several months without apparent decomposition, but it too decomposed suddenly and unexpectedly. Analysis of the compound for chlorine showed slightly less than one chlorine per molecule.

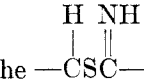
An attempt was made to obtain a possible intermediate, 3-chlorotrimethylene-1,2,4-thiadiazine-5-one, by chlorination of 2-imino-4-thiazolidone in the nonpolar solvent, chloroform. However, the product isolated contained a "positive" chlorine, indicating a nitrogen-chlorine linkage. Analysis for chlorine agreed well with the formula corresponding to the structure for VIII or IX.



VIII IX

solution below 5° at all times, and bubbling the chlorine gas in at a very slow rate. See reference (1), page 98.

This product is not an intermediate in the formation of I from 2-imino-4-thiazolidone for I was not formed when VIII or IX was dissolved in ice-cold, dilute hydrochloric acid, or when chlorine gas was bubbled through this solution.

Since the molecular rearrangement of 2-imino-4-thiazolidone is a new reaction, it was thought desirable to determine if the reaction was applicable to other compounds containing the  linkage. Accordingly, 2-iminothiazolidine, 2-aminothiazole, 2-amino-4-methylthiazole, and 2-amino-4-phenylthiazole were chlorinated under these conditions. No rearranged product was detected with any of these compounds.

From the reaction studied certain generalizations relating the structure of the 2-imino-4-thiazolidone to the course of the reaction can be made. Electron-releasing groups on the methylene carbon tend to promote substitution of the nitrogen atom by chlorine; electron-attracting groups cause cleavage of the carbon-sulfur bond. These statements apply to all cases studied in the 4-thiazolidone series. Substitution of the electron-attracting carbonyl group in 2-imino-4-thiazolidone by a methylene group to give 2-iminothiazolidine would be expected to increase the amount of nitrogen substitution. Experiment bore out this observation for a "positive" halogen compound seemed to be the only product produced by the chlorination of this thiazolidone. In the 2-amino-thiazole series the electron-releasing methyl group in the 4-position favored nitrogen substitution to such an extent that the product vigorously decomposed as fast as it was formed, a phenyl substituent in the 4-position caused cleavage of the sulfur to give sulfate ion, and as might be expected both of these effects occurred with the unsubstituted 2-aminothiazole. Therefore it seems that structural requirements are too exacting for the rearrangement reaction to have wide application.

EXPERIMENTAL

2-Imino-4-thiazolidones. All the compounds in this series were prepared in yields of 50 to 80% according to the procedure of *Organic Syntheses* (5) by the reaction of the appropriate alpha-haloacid or alpha-haloester with thiourea.

5,5-Diphenyl-2-imino-4-thiazolidone (IV). Ten grams of crude diphenylchloroacetic acid (6) was refluxed for two hours with 4 g. of thiourea, 1 g. of sodium acetate, and 75 ml. of ethanol. The solution was cooled and a 15% solution of sodium carbonate was added until basic. The precipitate was recrystallized twice from dilute alcohol; m.p. 270° with decomposition.

Anal. Calc'd for $C_{15}H_{12}N_2OS$: S, 11.92. Found: S, 12.10.

5-Phenyl-2-imino-4-thiazolidone was prepared from ethyl α-chlorophenyl acetate and thiourea in the manner just described; m.p. 234° with decomposition.

Anal. Calc'd for $C_9H_8N_2OS$: S, 16.67. Found: S, 16.89.

2-Imino-4-thiazolidone-5-carboxamide. Ten grams of 5-carbethoxy-2-imino-4-thiazolidone was suspended in 75 ml. of conc'd ammonia solution at room temperature for twelve days. By the third day small red crystals appeared in the flask and by the eighth day all the material had been converted to red crystals. These crystals were soluble in dilute hydrochloric acid but were not reprecipitated by the addition of base. The product was purified by dissolving in warm water, adding Norit, filtering, and cooling the filtrate in an ice-box. The compound had a slight reddish tinge; m.p. 219–221°.

Anal. Calc'd for $C_4H_5N_3O_2S$: S, 20.14. Found: S, 20.55.

Trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (I). All chlorinations carried out in aqueous solvents were run in the manner described below. Ten grams of 2-imino-4-thiazolidone hydrochloride was dissolved in 50 ml. of water, four drops of hydrochloric acid were added, the solution was cooled to 0–5°, and maintained at this temperature while chlorine gas was bubbled slowly through the mixture. In a short time a flocculent precipitate formed. The flow of gas was continued until no further precipitate formed. The precipitate was washed with water, alcohol, and ether. The yield of dry, snow-white product was 3.7 g., or 38%. The melting range of 110–120° varied greatly with the rate of heating. The compound was very slightly soluble in water, ethanol, ether, or dilute hydrochloric acid. It could be recrystallized from water with considerable loss, and reacted with nitrous acid at 0°, producing sulfur dioxide and nitrogen. The compound did not react with Fuchsin aldehyde reagent, Fehling's solution, nor 2,4-dinitrophenylhydrazine test reagent. It slowly lost sulfur dioxide, even in a vacuum desiccator over phosphorus pentoxide. No similar product was obtained when 2-imino-4-thiazolidone was treated with other oxidizing agents, such as hydrogen peroxide or potassium permanganate.

When samples were made for analyses, they were prepared from analytically pure starting material, washed with distilled water, alcohol, and ether, dried quickly under vacuum, and analyzed immediately.

Anal. Calc'd for $C_3H_4N_2O_4S$: S, 19.49. Found: S, 19.32.

6-Methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (VII). This compound was prepared by chlorination of 5-methyl-2-imino-4-thiazolidone hydrochloride in the manner just described. The yields varied from 0 to 30% depending on whether or not the reaction exploded. The melting point, about 140°, varied widely with the rate of heating.

Anal. Calc'd for $C_4H_6N_2O_4S$: S, 18.00. Found: S, 18.05.

N,N'Diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide (V). This substance was prepared by chlorinating N,N'-diphenyl-2-imino-4-thiazolidone in the manner described above. The compound lost sulfur dioxide so readily that analyses for sulfur were low and not reproducible.

Oxidation of other 5-substituted-2-imino-4-thiazolidones. Due to the explosive nature of the products obtained when hydrochloric acid suspensions of 5-carbethoxy-, 5-benzal-, 5-benzyl-, 5-phenyl-, 5,5-diphenyl-, and 5-carboxamido-2-imino-4-thiazolidones were treated with chlorine, these compounds were not studied after preliminary tests which showed in each case that a great deal of free sulfate ion was produced. In one quantitative estimation, using 5-phenyl-2-imino-4-thiazolidone, 66.4% of the sulfur was found as free sulfate. The main reactions were evidently cleavage of the carbon-sulfur bond to give sulfate, and formation of an unstable nitrogen-chlorine bond.

Chlorination of 2-imino-4-thiazolidone in chloroform. Two grams of finely ground 2-imino-4-thiazolidone was suspended in 40 ml. of chloroform at 25°. The mixture was stirred mechanically while chlorine gas was slowly bubbled in. The suspension soon became very flocculent and after twenty minutes it was filtered. The precipitate was dried by suction, m.p. 170–175° dec. A water suspension of the precipitate oxidized iodide ion to iodine, showing the presence of "positive" chlorine.

Anal. Calc'd for $C_3H_3ClN_2OS$: Cl, 23.53. Found: Cl, 23.27.

Desulfurization of trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. Two grams of this compound, 25 ml. of Raney nickel (7), and 130 ml. of 75% ethanol were refluxed for four hours. The hot solution was filtered and the Raney nickel was washed with 200 ml. of hot 95% ethanol. The alcohol was evaporated under vacuum and the residue was recrystallized from alcohol; yield 1.1 g. (79%), m.p. 215–216°. A mixture melting point with an authentic sample of *acetylurea* showed no depression.

Desulfurization of 6-methyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. This compound was degraded in the same manner as its lower homolog. The solid obtained by evaporation of the solvent alcohol was recrystallized from diluted alcohol, and melted at 209°. A mixture melting point with an authentic sample of *propionylurea* showed no depression.

Desulfurization of N,N'-diphenyltrimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. Two grams of this compound was desulfurized as above, and the residue, after evaporation of the solvent, was recrystallized from dilute alcohol. The product melted over the range 206–216°. Five recrystallizations were required to raise the melting range to 233–235°, and a mixture melting point determination with an authentic sample of *sym*-diphenylurea (8) m.p. 235°, showed no depression (233–235°).

Attempts to prepare N-acetyldiphenylurea from *sym*-diphenylurea and acetylchloride led to low-melting crude mixtures which on recrystallization from dilute alcohol, were gradually converted to diphenylurea again.

Desulfurization of N,N'-diphenyl-2-imino-4-thiazolidone. Two grams of this compound was refluxed with 25 ml. of Raney nickel suspension in 100 ml. of 70% ethanol for six hours. After filtering, the hot solution was evaporated to a small volume. The characteristic aniline odor was evident, so an aliquot portion was extracted with ether, dried, and precipitated with dry hydrogen chloride. The crystalline hydrochloride so obtained melted at 197°, and did not depress the melting point of an authentic sample of *aniline hydrochloride.* The remaining filtrate was evaporated to dryness and recrystallized from dilute acid and then water, giving white needles, m.p. 113–114°, which did not depress the melting point of an authentic sample of *acetanilide.*

Chlorination of 5-ethyl-2-imino-4-thiazolidone. When this compound was chlorinated in the manner described for its lower homologs, a sticky, light-brown precipitate formed which disappeared in a puff of smoke from time to time. It was soluble in alcohol and ether. Chlorination of the thiazolidone in concentrated hydrochloric acid gave the same results.

SUMMARY

Oxidative cleavage of 2-imino-4-thiazolidone with chlorine in dilute hydrochloric acid caused rearrangement to a six-membered ring, trimethylene-1,2,4-thiadiazine-3,5-dione-1,1-dioxide. 5-Methyl-2-imino-4-thiazolidone gave a similar rearrangement, but other substituents in the 5-position gave unstable products.

The properties of several new 1,2,4-thiadiazine-1,1-dioxides and thiazolidones are described.

BLOOMINGTON, INDIANA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, CLARK UNIVERSITY]

CARBOXYMETHYLATION OF AMINES. III. PREPARATION OF SUBSTITUTED GLYCINES[1]

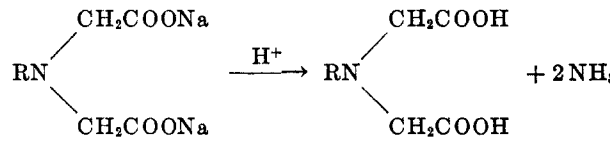
LEO W. ZIEMLAK,[2] JESSE L. BULLOCK, F. C. BERSWORTH, AND A. E. MARTELL

Received August 1, 1949

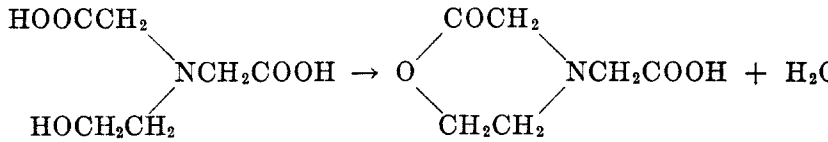
In previous publications the use of the carboxymethylation reaction for the preparation of ethylenediamine tetraacetic acid (1) and of triglycine (2) has been described. The purpose of the present paper is to demonstrate the usefulness of this reaction as a general method for the preparation of substituted α-amino acids by using benzylamine, *p*-aminobenzoic acid, isoamylamine, ethylamine, diethylamine, piperidine, and ethanolamine.

It was found that maximum yields of the substituted glycines were obtained when a dilute solution of formaldehyde was added slowly to an alkalized aqueous solution of the amine and sodium cyanide. The ammonia formed was completely removed by intermittent distillation under reduced pressure. The resulting solution was then neutralized or acidified, evaporated to dryness under reduced pressure, and the product separated from inorganic salts by extraction with organic solvents or by fractional crystallization. N-benzyliminodiacetic acid, N,N-*bis*-(carboxymethyl)anthranilic acid, and N-ethyliminodiacetic acid were separated in this manner. The general reaction may be represented by the equation:

$$RNH_2 + 2\,NaCN + 2\,CH_2O + 2\,H_2O \rightarrow$$



The lactone of N-(2-hydroxyethyl)iminodiacetic acid was obtained from the acidified reaction product resulting from dicarboxymethylation of ethanolamine:



Diethylglycine, piperidinoacetic acid, and N-isoamyliminodiacetic acid were not obtained in crystalline form from their respective reaction mixtures. These substances were isolated as the corresponding butyl esters by direct esterifica-

[1] Abstracted from a dissertation presented by Leo W. Ziemlak to the Faculty of Clark University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1947.

[2] Present address: Mellon Institute, Pittsburgh, Pa.

tion of the reaction mixture and by subsequent fractional distillation under reduced pressure. The esters were colorless liquids which darkened slowly on standing over a period of several weeks. The isoamyl derivative, however, seemed aprticularly unstable and darkened appreciably in the course of 24 hours.

The crystalline products were characterized by carbon, hydrogen, and nitrogen analyses, while the liquid esters were identified by nitrogen and molecular weight determinations. Insofar as it has been possible to ascertain, the substances reported, with the exception of N-ethyliminodiacetic acid prepared by Heintz (3) and of N,N-*bis*-(carboxymethyl)anthranilic acid prepared by Schwarzenbach, *et al.* (4), have not previously been described. On the other hand, diethylglycine has been prepared by Heintz (5) and piperidinoacetic acid has been reported by Kraut (6).

EXPERIMENTAL

N-Benzyliminodiacetic acid. A solution of 30.0 g. (0.75 mole) of sodium hydroxide' 58.8 g. (1.2 moles) of sodium cyanide, and 71.8 g. (0.5 mole) of benzylamine hydrochloride in 500 ml. of water was placed in a two-liter three-neck flask equipped with a stirrer, a dropping-funnel, and a reflux condenser. Then 81.8 g. of 37% formaldehyde solution was diluted to 500 ml., and 100 ml. of this solution was added, over a period of an hour, to the reaction flask with stirring at 75°. The addition was followed by the removal of 100 ml. of solvent under reduced pressure. The remainder of the formaldehyde was added in four successive batches at 80, 85, 90, and 95°, each addition requiring one hour. Each addition was followed by distillation of 100 ml. of solvent to insure complete removal of the ammonia. After the last distillation, the reaction mixture was neutralized with hydrochloric acid and evaporated to dryness under reduced pressure. The salt-like product was extracted with butyl alcohol in a Soxhlet apparatus for 6 hours. Upon cooling, crystals of *N*-benzyliminodiacetic acid precipitated from the alcoholic solution. An additional batch of crystals was obtained by a second extraction. Both batches proved to be free from sodium chloride and melted at 214° dec. The combined weight was 90 g. (84% yield).

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.3; H, 5.83; N, 6.27.
Found: C, 59.1; H, 5.29; N, 6.12.

N,N-bis-(carboxymethyl)anthranilic acid. The method of addition and the reaction conditions were the same as described for the previous preparation. The resulting reaction mixture was then refluxed for two hours. The product, slightly contaminated with *p*-aminobenzoic acid, was precipitated by cooling, acidifying to *p*H 4 with sulfuric acid, and washing with cold water. The unchanged *p*-aminobenzoic acid was removed by extraction with ethyl ether (Soxhlet). From 35.0 g. of *p*-aminobenzoic acid, 41 g. (65% yield) of pure material (m.p. 228° dec.) was obtained.

Anal. Calc'd for $C_{11}H_{11}NO_6$: C, 52.0; H, 4.33; N, 5.53.
Found: C, 51.8; H, 4.05; N, 5.25.

N-Ethyliminodiacetic acid. This substance was prepared by a method similar to that described for *N*-benzyliminodiacetic acid, but the temperature was maintained at 25° during the addition of sodium cyanide and formaldehyde. Upon cooling the butyl alcohol extracts, 148 g. of precipitate containing appreciable amounts of sodium chloride was obtained from 45.0 g. of ethylamine. Fractional crystallization from aqueous alcohol resulted in the isolation of the hydrochloride of N-ethyliminodiacetic acid, m.p. 185–190° dec.

Anal. Calc'd for $C_6H_{12}ClNO$: N, 7.08; HCl, 18.45.
Found: N, 6.99; HCl, 18.40.

N-(2-Hydroxyethyl)iminodiacetic acid lactone. A one-liter aqueous solution of 30.5 g. of ethanolamine, 3 g. of sodium hydroxide, and 58.5 g. of sodium cyanide was placed in an apparatus similar to that previously described and was treated in a similar manner with 100 g. of 37% formaldehyde solution diluted to 375 ml. The formaldehyde was added in five equal portions at temperatures of 25, 30, 35, 40, and 45°. After the last addition the mixture was distilled under reduced pressure to 250 ml. and acidified with sulfuric acid to *p*H 1.5. The resulting precipitate, which weighed about 108 g., was contaminated with about 30% sodium sulfate. The colorless crystalline product was purified of all traces of sulfate by two successive recrystallizations from hot concentrated aqueous solutions. The 75 g. of pure product (m.p. 185° dec.) obtained indicated nearly quantitative conversion to the lactone of N-(2-hydroxyethyl)iminodiacetic acid.

Anal. Calc'd for $C_6H_9NO_4$: C, 45.5; H, 5.90; N, 8.80.
Found: C, 45.3; H, 5.70; N, 8.80.

n-Butyl N,N-diethylglycinate. A solution of 36.6 g. of diethylamine, 5 g. of sodium hydroxide, and 30 g. of sodium cyanide dissolved in two liters of water was placed in an apparatus of 5-liter capacity similar to that used in the foregoing preparations. To this was added in 250-ml. portions (at the rate of 125 ml. per hour) 50 ml. of 37% formaldehyde diluted to one liter. The initial temperature of 20° was raised 5° during each subsequent addition. At the end of each addition the system was evacuated to 15 mm. for five minutes. After the last addition the temperature was maintained at 35° for four hours more. The solution was subsequently neutralized to *pH* 7 and evaporated at 15 mm. until no more solvent could be distilled. The residue was boiled with 500 ml. of butyl alcohol, filtered hot, cooled, and 30 ml. of conc'd sulfuric acid added; the solution was kept at 80° for 24 hours. A mixture of 500 ml. of butyl alcohol and 200 ml. of toluene was then added. The reaction flask was fitted with a thermometer, stirrer, and water separator, and the solution was refluxed gently for 12 hours, after which the amount of water being collected became negligible. The reaction mixture was distilled under reduced pressure to remove toluene and butyl alcohol, and the residue was then made alkaline with excess 20% sodium carbonate solution. The oil was removed with a separatory funnel, dried over calcium chloride, and finally distilled under reduced pressure. Yield, 54 g. of a clear colorless oily liquid boiling at 66°/1 or 55%. Index of refraction, 1.4270^{20}; density, 0.9091^{20} g./ml.

Anal. Calc'd for $C_{10}H_{21}NO_2$: N, 7.47; M.W., 187.
Found: N, 7.40; M.W., 180.

n-Butyl piperidinoacetate. By a method similar to that just described, piperidine was converted to a colorless liquid, b.p. 94–95°/1. Index of refraction, 1.4515^{20}; density, 0.9609^{20} g./ml.; Yield, 101 g. (50%).

Anal. Calc'd for $C_{11}H_{21}NO_2$: N, 7.07; M.W. 199.
Found: N, 6.98; M.W., 180.

Di-n-butyl N-isoamyliminodiacetate. Isoamylamine was carboxymethylated and esterified in a manner similar to that described for diethylamine. Upon distillation of the product, only 10 ml. of ester was collected at 49°/12 before extensive decomposition of the boiling liquid took place. The index of refraction of the clear colorless product was 1.420^{20}.

Anal. Calc'd for $C_{17}H_{33}NO_4$: N, 4.44; M.W., 315.
Found: N, 4.32; M.W., 298.

SUMMARY

The extension of the carboxymethylation reaction to benzylamine, *p*-aminobenzoic acid, isoamylamine, ethylamine, diethylamine, piperidine, and ethanolamine is described. The products which were prepared and characterized are: N-benzyliminodiacetic acid, N,N-*bis*-(carboxymethyl)anthranilic acid, N-ethyliminodiacetic acid, N-(2-hydroxyethyl)iminodiacetic acid lactone, butyl N,N-

diethylglycinate, butyl piperidinoacetate, and dibutyl N-isoamyliminodiacetic acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF PHARMACOLOGY, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY]

THE SYNTHESIS OF ETHYL-(1-METHYLBUTYL)- AND ETHYLISOAMYL-MALONURIC ACIDS[1]

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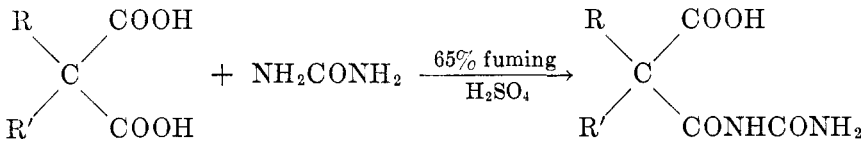
In connection with some studies on the metabolic fate of ethyl-(1-methylbutyl)barbituric acid (Pentobarbital) and ethylisoamylbarbituric acid (Amytal), it was necessary to prepare the corresponding malonuric acids for isotope dilution experiments. The only dialkylmalonuric acids with unsubstituted nitrogen atoms encountered in a literature survey were the diethyl and the di-*n*-propyl derivatives. Fischer and Dilthey (1) prepared these compounds by the reaction of the appropriate dialkylmalonic acids with urea in 70% fuming sulfuric acid. Diethylmalonuric acid was also synthesized by Einhorn (2) through the addition of diethylmalonyl chloride to a cold solution of urea in pyridine.

A modification of the procedure of Fischer and Dilthey proved to be satisfactory for the preparation of ethyl-(1-methylbutyl)malonuric acid. The product was obtained in 50% yield and consisted of only one of the two possible diastereoisomers. The identity of the malonuric acid was established by decarboxylation; a quantitative yield of the acetyl urea was obtained. The methyl ester and the methylammonium salts were prepared as further derivatives of the acid. Treatment of the methyl ester with alkali converted it to the corresponding barbituric acid.



The Fischer method was not as satisfactory for the synthesis of ethylisoamylmalonuric acid. It was possible on occasion to obtain the pure compound, but in low yield; at other times under the same conditions no malonuric acid could be isolated. A search for better experimental conditions was unsuccessful.

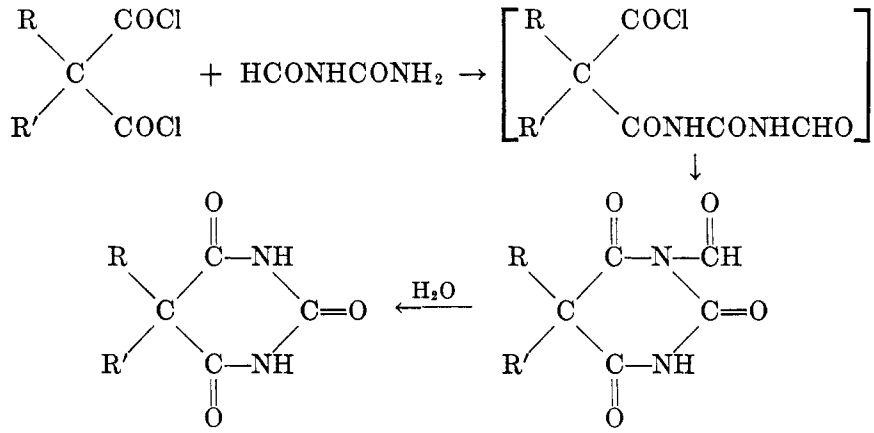
Fischer and Dilthey (1) found that their procedure could not be used for the synthesis of dimethylmalonuric acid. In fuming sulfuric acid, dimethylmalonic acid and urea react to form dimethylbarbituric acid. In the preparation of diethyl-, ethyl-(1-methylbutyl)-, and ethylisoamyl-malonuric acids in fuming sulfuric acid, no trace of the barbituric acids was encountered. In order to decide whether barbituric acids were formed from the malonic acids and urea and subsequently hydrolyzed to the malonuric acids during the isolation procedures, diethyl- and ethylisoamyl-barbituric acids were treated with fuming sulfuric acid. The only isolable products were the unchanged barbituric acids.

No success was achieved in attempts to prepare ethyl-(1-methylbutyl)- and ethylisoamyl-malonuric acids by the method of Einhorn (2). The reaction of the

[1] This work was supported by a grant from the United States Public Health Service.

malonyl chlorides with cold suspensions of urea in pyridine yielded only brown oils from which no crystalline compounds could be isolated. When the reaction mixtures were heated, the barbituric acids were obtained.

It was of interest to see whether the formation of the barbituric acid could be blocked by causing a malonyl chloride to react with an acyl urea instead of urea. Formylurea was considered attractive for this purpose because of the possibility that the formyl group could be removed later by oxidation or hydrolysis. Treatment of this compound with ethylisoamylmalonyl chloride yielded a product containing the barbituric acid ring. Under anhydrous conditions it was possible to isolate a chloride-free substance which was probably the formylbarbituric acid. It resisted purification but yielded pure ethylisoamylbarbituric acid when treated with water.



Experimental[2]

Ethyl-(1-methylbutyl)malonic acid. Dialkylmalonic esters are very resistant to hydrolysis. A mixture of 100 g. of ethyl-(1-methylbutyl)malonic ester,[3] 150 g. of potassium hydroxide, 140 ml. of water, and 80 ml. of ethanol was stirred and heated under reflux for fifteen hours. Water was added to dissolve crystals which separated upon cooling. The solution was extracted with ether to remove unchanged ester, made acid to Congo Red, and again extracted with ether. The ether solution was washed with a little water and dried with sodium sulfate. Evaporation of the solvent gave an oil which would not crystallize on long standing. Trituration of the oil with ligroin yielded 54 g. of a white crystalline solid, m.p. 107–109°. After recrystallization from water it melted at 118–119°.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.97; M. W., 202.
Found: C, 59.37; H, 8.86; M. W., 202.

The molecular weight was determined by titration of the acid as a monobasic acid with sodium hydroxide using a *p*H meter with a glass electrode.

Ethyl-(1-methylbutyl)malonuric acid. The procedure was similar to that used by Fischer and Dilthey (1) for diethylmalonuric acid. Four grams of ethyl-(1-methylbutyl)malonic acid and 2 g. of urea were ground together in a mortar and the mixture added in small portions with constant stirring over a period of 20–30 minutes to 5 ml. of 65% fuming sulfuric acid cooled to −10 to −15°. The thick brown mixture was kept in the ice-salt bath

[2] All melting points were taken with a Fisher-Johns apparatus.

[3] This compound was kindly supplied by Dr. D. L. Tabern of the Abbott Laboratories.

until all the ice had melted (if it was removed from the bath too soon, it decomposed spontaneously). It was then heated to 60–70° for ten minutes; during this period there was considerable evolution of gas. After cooling, the mixture was poured into 60 ml. of ice-water. A thick, brown oil separated. The mixture was extracted with ether; almost all of the color remained in the water phase. The ether was washed with a small amount of water and then extracted with 10% sodium carbonate solution. Neutralization of the alkaline extract yielded 2.6 g. of a white crystalline solid, m.p. 137–139° with evolution of carbon dioxide. The compound was purified by dissolving it in chloroform and precipitating with ligroin; m.p. 144–145° with evolution of carbon dioxide. The melting point depended very much on the rate of heating; rapid heating of an analytical sample gave much higher values (144–145°) than slow heating (127–128°).

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.47. Found: N, 11.54.

Evaporation of the ether extract gave 0.7 g. of a white crystalline solid, m.p. 77–88°. It was dissolved in ether and precipitated with ligroin to yield 0.3 g. of a compound melting at 91–92°; the melting point of a mixture with ethyl-(1-methylbutyl)acetamide[3] was 91–93°. From the filtrates a product melting at 60–75° was obtained; presumably this substance contained ethyl-(1-methylbutyl)acetylurea (*cf.* 1), but this compound could not be isolated from the mixture.

The preparation of the malonuric acid was repeated with consistent results. In one experiment carried out on a five-times larger scale the yield was 46%.

Decarboxylation of ethyl-(1-methylbutyl)malonuric acid. The malonuric acid (300 mg.) was heated in an oil-bath to 165°. After ten minutes the evolution of gas ceased. Upon cooling, the product crystallized. It was purified by precipitation from alcohol with water, m.p. 135–136°. It was shown to be ethyl-(1-methylbutyl)acetylurea by the melting point of a mixture with an authentic sample.[3] The yield was quantitative.

Methylammonium ethyl-(1-methylbutyl)malonurate. The malonuric acid (500 mg.) was dissolved in ether and treated with an ether solution of methylamine. The flask was scratched with a glass rod to start precipitation of the salt. Yield, 356 mg.; m.p. 133–136°.

Anal. Calc'd for $C_{12}H_{25}N_3O_4$: N, 15.27. Found: N, 15.37.

Methyl ethyl-(1-methylbutyl)malonurate. To a solution of diazomethane in ether was added 2 g. of the malonuric acid. As soon as the evolution of nitrogen ceased, the ether was evaporated in a stream of air to yield a faintly yellow solid. The ester was recrystallized from ligroin and from aqueous methanol; m.p. 109.5–110.5°.

Anal. Calc'd for $C_{12}H_{22}N_2O_4$: N, 10.85. Found: N, 10.85.

Equimolecular amounts of the ester and sodium hydroxide in aqueous alcoholic solution were heated under reflux for one day. The product consisted of ethyl-(1-methylbutyl)-barbituric acid and a small amount of unchanged ester. Other malonuric esters are reported to react in the same manner (3).

Ethylisoamylmalonic acid. The hydrolysis of ethylisoamylmalonic ester[4] was effected under the same conditions as those used for ethyl-(1-methylbutyl)malonic ester. Evaporation of the ether extract gave a 92% yield of the crystalline acid, m.p. 116–118°. After recrystallization from water it melted at 118–119°. Tiffeneau (4) reported m.p. 116–118°; a patent reference (5) gives 120–121°.

Anal. Calc'd for $C_{10}H_{18}O_4$: C, 59.37; H, 8.97; M. W. 202.
Found: C, 59.35; H, 8.63; M. W. 202.

Ethylisoamylmalonuric acid. A study of conditions for the synthesis of this compound did not indicate a change from those used for ethyl-(1-methylbutyl)malonuric acid. In the most successful experiment a yield of 19% of crude acid melting at 135–137° (with evolution of carbon dioxide) was obtained. When the strength of the fuming sulfuric acid was decreased, the only product was some unchanged malonic acid. In no experiment could the corresponding acetylurea or acetamide be isolated as a by-product. The crude

[4] This compound was kindly supplied by Dr. E. C. Kleiderer of the Lilly Research Laboratories.

malonuric acid was purified by dissolving it in chloroform and adding an equal volume of ligroin. The pure acid melted at 149–150° with evolution of carbon dioxide; the melting point did not appear to depend on the rate of heating.

Anal. Calc'd for $C_{11}H_{20}N_2O_4$: N, 11.47. Found: N, 11.50.

Decarboxylation of ethylisoamylmalonuric acid. The reaction was effected with a procedure identical with that for ethyl-(1-methylbutyl)malonuric acid. The product was identified as ethylisoamylacetylurea by the melting point of a mixture with an authentic sample.[4]

Methyl ethylisoamylmalonurate. This compound was prepared by the treatment of the malonuric acid with diazomethane; m.p. 74–75°.

Anal. Calc'd for $C_{12}H_{22}N_2O_4$: C, 55.79; H, 8.58.
Found: C, 55.82; H, 8.50.

Ethyl-(1-methylbutyl)- and ethylisoamyl-malonyl chlorides. These compounds were prepared by heating the malonic acids and a four-fold excess of thionyl chloride under reflux for two hours. Following the removal of excess thionyl chloride at atmospheric pressure, the malonyl chlorides were distilled *in vacuo*. No attempt was made to obtain analytically pure compounds.

Ethyl-(1-methylbutyl)malonamide.[5] This compound was obtained by adding a solution of the malonyl chloride in ether to an anhydrous, saturated solution of ammonia in ether at 4°. After two recrystallizations from water the product melted at 147–148°.

Anal. Calc'd for $C_{10}H_{20}N_2O_2$: N, 13.99. Found: N, 13.88.

Treatment of malonyl chlorides with urea in pyridine. Four grams of either ethylisoamyl- or ethyl-(1-methylbutyl)- malonyl chloride was added slowly with stirring to a mixture[6] of 1 g. of urea and 4 g. of dry pyridine at 0°. After two hours the mixture was acidified with hydrochloric acid and diluted with water. The product was a brown oil. When the procedure was conducted at room temperature, the product was also an oil. Heating the reaction mixtures under reflux gave the barbituric acids in good yield.

Formylurea. The procedure of Scheitz, *et al.* (6) was found to give yields of only 10% or less and called for anhydrous formic acid. A method was devised in which commercial formic acid could be used. In a flask attached to a reflux condenser *via* a moisture trap were placed 6 g. of urea, 10.5 g. of technical formic acid (88%), 25 ml. of benzene, and 2 drops of sulfuric acid. The mixture was heated in a water-bath for six hours; during this period 4 ml. of water was collected in the trap. The solution was allowed to stand overnight at room temperature. The white solid which separated was dried in a vacuum desiccator. After one recrystallization from 200 ml. of absolute alcohol the product melted at 166–167°. The yield was 2.8 g. (32% based on urea). Further recrystallization from alcohol raised the melting point to 168–169°; Scheitz reported the same values. Evaporation of the alcoholic filtrates yielded a mixture of urea and formylurea which could not be separated easily.

Anal. Calc'd for $C_2H_4N_2O_2$: N, 31.8. Found: N, 32.0.

In the procedure reported above a 100% excess of formic acid was employed. When only the theoretical amount of formic acid was used the yield was 16%.

Reaction of ethylisoamylmalonyl chloride with formylurea. (a) *In boiling dioxane.* To a suspension of 1.0 g. of formylurea in 25 ml. of purified dioxane (7) was added 3.6 g. of the acid chloride dissolved in 5 ml of dioxane. The solution was heated under reflux for four hours and then allowed to stand at room temperature overnight. Siuce no solid separated, the dioxane was evaporated to yield an orange, oily solid which was triturated with ligroin and filtered. Yield, 1.9 g.; m.p. 122–135°. The substance contained nitrogen but no chlorine. It was soluble in alcohols and acetone, only slightly soluble in chloroform, ether, and benzene and insoluble in ligroin. However, it was not possible to bring it to analytical

[5] This compound was prepared by Mr. E. F. Gurnee.

[6] Einhorn stated that he used a solution of 0.6 g. of urea in 2 g. of pyridine. It was found that at room temperature about 30 g. of pyridine was required to dissolve 0.6 g. of urea.

purity. Triturating with water or dissolving in sodium carbonate and acidifying yielded pure ethylisoamylbarbituric acid.

(b) *In dioxane at 60°.* A mixture of 4.3 g. of the acid chloride, 1.6 g. of formylurea, and 75 ml. of purified dioxane was stirred at room temperature for one day. Since none of the solid formylurea appeared to dissolve, the mixture was heated to 60° and stirred at this temperature for another day. All of the formylurea dissolved, and there was no precipitation on cooling. Water (2 ml.) was added and the solution stirred for two hours. Then 5 ml. of 40% sodium hydroxide was added; a white solid separated. The solvent was removed *in vacuo* and sufficient water added to dissolve the residue. The alkaline solution (*p*H 10) was extracted with ether to give 0.4 g. of oil which was not investigated further. It was then brought to *p*H 7.5. A white solid (1.1 g.) precipitated; it was identified as ethylisoamylbarbituric acid. Extraction of the filtrate yielded an additional 0.2 g. of the barbituric acid. The solution was then acidified (*p*H 3) and again extracted with ether; evaporation of the ether yielded 0.3 g. of ethylisoamylmalonic acid.

(c) *In benzene.* The conditions used by Stoughton (8) for the preparation of diacyl ureas were not satisfactory for the reaction of the malonyl chloride with formylurea or acetylurea. The acyl ureas would not dissolve and were recovered unchanged.

SUMMARY

Ethyl-(1-methylbutyl)- and ethylisoamyl-malonuric acids were synthesized by the reaction of the corresponding malonic acids with urea in fuming sulfuric acid. Attempts to prepare these compounds by other methods, both old and new, were unsuccessful.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. XI. NEW TRANSFORMATION PRODUCTS OF STROPHANTHIDIN: STUDIES ON ETHYL 3(β),5,19-TRIHYDROXYETIOCHOLANATE[1]

MAXIMILIAN EHRENSTEIN, ALDA RUTH JOHNSON, POLLY COMEGYS OLMSTED, VERA I. VIVIAN, AND MARY A. WAGNER[2]

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With the aim of preparing steroids structurally related to progesterone and the adrenal cortical hormones, strophanthidin (I) has been transformed into a number of new compounds which will serve as intermediates towards this goal. It is intended to prepare ultimately substances which are derived from progesterone, 11-desoxycorticosterone, and 17-hydroxy-11-desoxycorticosterone in that the angular carbon atom 19 between rings A and B is either missing (19-nor compounds) or is present in an oxygenated form, *e.g.* as a primary alcohol, aldehyde or carboxyl group. Not only compounds with "normal" configurations, but also those which possess "iso" configurations in particular at carbon atoms 14 and 17 will be included in our studies. The present investigation is dealing essentially with steroids possessing the "normal" configurations at these carbon atoms.

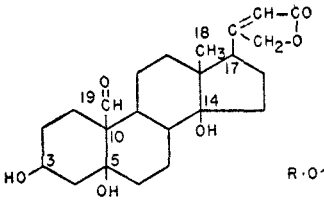
The previously (1) reported conversion of strophanthidin (I) into ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) and the corresponding free acid (IX) has been simplified and improved in a number of respects, details of which are given in the experimental section. The yield of crystalline ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate (VI) as obtained by direct crystallization is 33–35 per cent. In addition, there were isolated small amounts of a by-product, $C_{20}H_{28}O_4$, tentatively formulated as a lactone (1). The substance $C_{20}H_{28}O_4$ apparently does not arise from an impurity in 3(β),5,14,19-tetrahydroxy-14-isoetiocholanic acid (V)[3] since very pure samples of V also gave the so-called lactone. It is a rather labile substance and is altered on attempted recrystallization. On subjecting

[1] Aided by grants from Sharp & Dohme, Inc. in Philadelphia and from the American Cancer Society on the recommendation of the Committee on Growth of the National Research Council. Presented before the Division of Medicinal Chemistry at the 116th meeting of the American Chemical Society in Atlantic City, September 20, 1949. (*cf.* Ehrenstein and Wagner, Abstracts of Papers, 116th Meeting of the American Chemical Society, p. 12 L [1949]) and before the Physiological Society of Philadelphia, October 18, 1949 (Abstract *cf.* Ehrenstein and Wagner, The American Journal of the Medical Sciences, **218**, 716 [1949]).

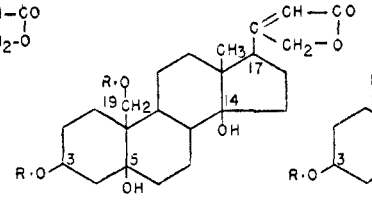
[2] Misses A. R. Johnson and V. I. Vivian as well as Mrs. P. Comegys Olmsted participated in particular in the preparation of larger quantities of ethyl 3(β),5,19-trihydroxyetiocholanate in accordance with an improved method. Miss M. A. Wagner was in charge of all experiments dealing with the products resulting from the Raney nickel dehydrogenation as well as the tritylation of ethyl 3(β),5,19-trihydroxyetiocholanate. Capable assistance was also rendered by Miss Mary G. Conroy.

[3] In our previous publication (1) compounds V and IV had been designated 3,5,14,19-tetrahydroxyetiocholanic acid and 3,19-diacetoxy-5,14-dihydroxyetiocholanic acid respectively. The new names are in stricter agreement with the nomenclature (2).

it to chromatographic purification it was recovered from the early eluates. A new substance melting at 167–168°, tentatively assigned the formula $C_{22}H_{32}O_5$, was found in some of the later eluates. Chromatography of the mother liquors from the crystallization of VI gave some ethyl 3(β),5,19-trihydroxy-$\Delta^{8,14}$-etio-

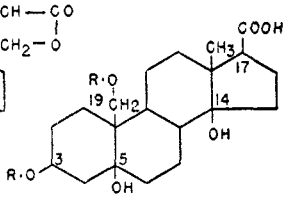


I. Strophanthidin



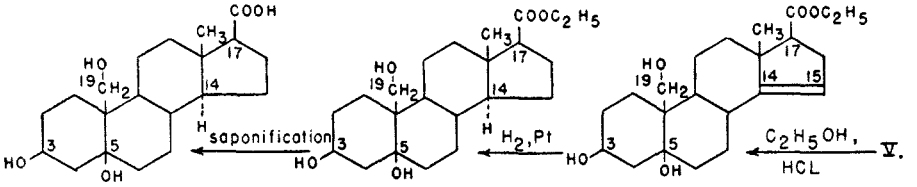
II. (R=H) Strophanthidol

III. (R=Ac) Strophanthidol 3,19-diacetate.



V. (R=H) 3(β),5,14,19-Tetrahydroxy-14-isoetiocholanic acid.

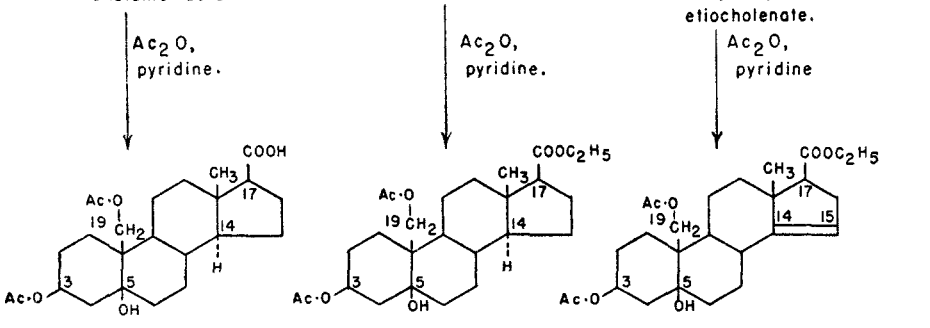
IV. (R=Ac) 3(β),19-Diacetoxy-5,14-dihydroxy-14-isoetiocholanic acid.



IX. 3(β),5,19-Trihydroxyetiocholanic acid.

VIII. Ethyl 3(β),5,19-trihydroxyetiocholanate.

VI. Ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate.



X. 3(β),19-Diacetoxy-5-hydroxyetiocholanic acid.

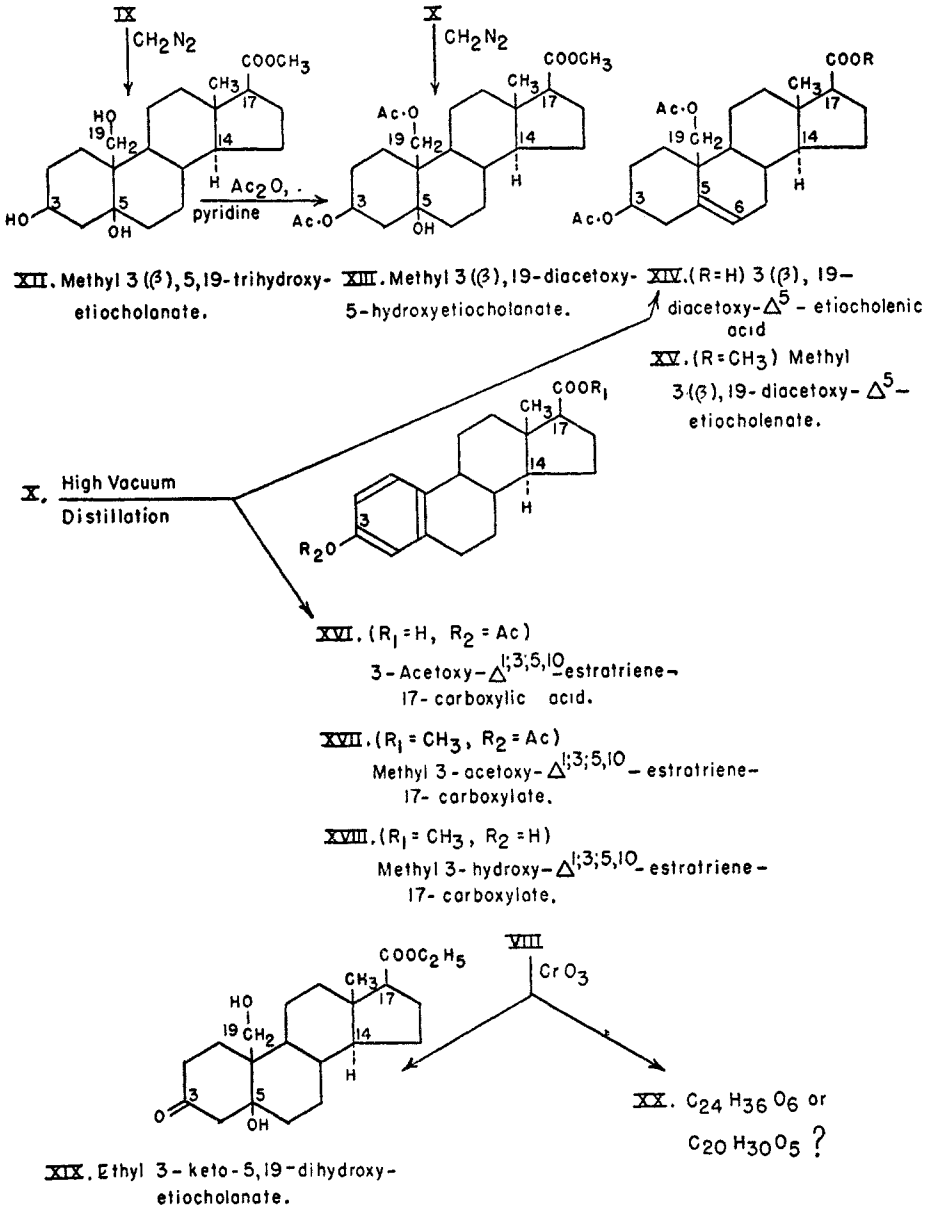
XI. Ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate

VII. Ethyl 3(β),19-diacetoxy-5-hydroxy-Δ^{14}-etiocholenate.

cholenate (*cf.* 1) and additional amounts of VI which was characterized as the diacetate (VII). Attempts to transform IV into VI by simultaneous dehydration and alcoholysis resulted in an impractically low yield.

Acetylation of 3(β),5,19-trihydroxyetiocholanic acid (IX) (1) gives the amorphous 3(β),19-diacetate (X). The latter yields with diazomethane the amor-

phous methyl ester (XIII) which can also be obtained by acetylation of crystalline XII (1). It may be noted that compounds analogous to X and XIII having



an additional hydroxyl group at carbon atom 14, *i.e.* IV and its methyl ester, are likewise amorphous (1, 2).

Ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate (XI) can be distilled in a high vacuum without decomposition. As reported earlier (1) it also remains un-

changed on treatment with pyridine-phosphorus oxychloride at room temperature. It was not attempted to enforce a dehydration at a higher temperature, because treatment of the methyl ester of IV with pyridine-phosphorus oxychloride at room temperature did not proceed in a uniform fashion (2).

Contrary to expectations based on previous experience (3) (4, p. 1048) distillation of 3(β),19-diacetoxy-5-hydroxyetiocholanic acid (X) led to a mixture of substances from which only a small amount of the anticipated 3(β),19-diacetoxy-Δ^5-etiocholenic acid (XIV) could be isolated as the methyl ester (XV). The major part of the material was the product of a more extensive decomposition. The portion which crystallized from ether was converted into the methyl ester. After purification by chromatography and deacetylation, methyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XVIII) was identified by comparison with a sample of the material recently synthesized from cholesterol by Djerassi and Scholz[5] (6, *cf.* also 7). The absorption spectrum of XVIII[4] showed a maximum at 281 mμ and a minimum at 249 mμ which is characteristic of natural estrogens in which ring A is benzenoid (5). It must have arisen from 3-acetoxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XVI) by way of methyl 3-acetoxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XVII).

It was attempted to subject ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) to selective oxidation either in position 3 or 19. Oxidation of VIII at room temperature with one equivalent of chromic acid yielded 80% of neutral material. Crystallization from ether gave a substance, probably $C_{22}H_{34}O_5$, which was characterized by its oxime. From its infrared spectrum (obtained through the courtesy of Drs. K. Dobriner and R. Norman Jones of the Sloan-Kettering Institute for Cancer Research in New York) the presence of a 3-keto group was indicated.[5a] The substance is tentatively designated as ethyl 3-keto-5,19-dihydroxyetiocholanate (XIX). From the lower-melting and resinous fractions resulting from the isolation of XIX another substance, possibly $C_{24}H_{36}O_6$ or $C_{20}H_{30}O_5$ (XX), was obtained after chromatography. It still awaits chemical identification.[5b] Attempts to prepare an oxime were of no avail.

An effort was made to dehydrogenate ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) according to the Oppenauer method. In general, the dehydrogenation of secondary alcohol groups in position 3 does not present any difficulties, and the participation in the reaction of the primary alcohol group in position 19 was not expected. As is known from the literature, primary alcohols will react only in case they contain an activated hydroxyl group (8, 9). On treating ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) in the usual fashion with acetone and aluminum *tert*-butoxide in benzene solution, there was an almost quantitative recovery

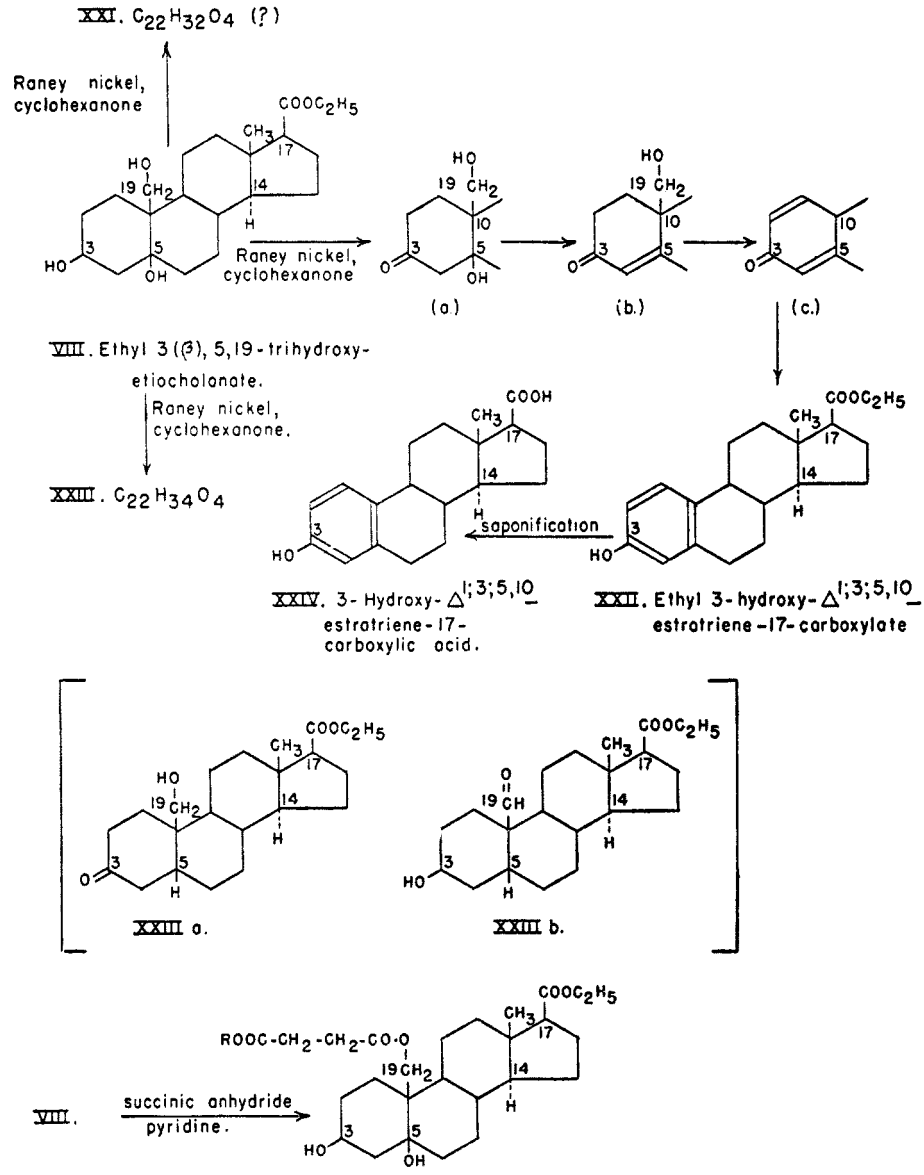
[4] Determination by Messrs. J. L. Ciminera and K. B. Streeter of the Sharp & Dohme Research Laboratories.

[5] Private communication; published while this paper was in press (6).

[5a] Position of bands ($CHCl_3$): 1723 cm.$^{-1}$ (probably $COOC_2H_5$); 1710 cm.$^{-1}$ (probably 3-ketone or possibly, but less likely an aldehyde).

[5b] Determination of the infrared spectrum at the Sloan-Kettering Institute gave the following bands ($CHCl_3$): 1723–1719 cm.$^{-1}$ (probably $COOC_2H_5$ and/or aldehyde); 1703 cm.$^{-1}$ (could be 3-ketone; too low for aldehyde).

of the starting material. Aluminum phenoxide has been used successfully for the dehydrogenation of secondary alcohol groups in position 3 of saturated



XXV. (R=H) Ethyl 19-hemisuccinyloxy-3(β),5-dihydroxyetiocholanate.

XXVI. ($R=CH_3$) Methyl ester of ethyl 19-hemisuccinyloxy-3(β),5-dihydroxyetiocholanate.

steroids, especially where aluminum *tert*-butoxide had failed (10, *cf.* also 11, 12). Substituting aluminum phenoxide for aluminum *tert*-butoxide with ethyl 3(β),5, 19-trihydroxyetiocholanate (VIII) did not produce any result; under these ex-

perimental conditions ketonic material failed to appear. It would be interesting to determine whether there is any definite group in the molecule which prevents the reaction from proceeding in the normal fashion. In particular, the hydroxyl group in position 5 should be considered. In the present instance the hydroxyl groups at carbon atoms 3 and 5 are in *cis*-position. The question arises, whether an intermediary aluminum complex is formed in which both of these hydroxyl groups are involved, and whether such a complex would block the normal course of the reaction. It is proposed therefore, to study the Oppenauer reaction with various 3,5-dihydroxy steroids. Compounds having these two hydroxyl groups in *cis*-position as well as those having them in *trans*-position should be included.

Kleiderer, *et al.* (13, 14) recently described the dehydrogenation with Raney nickel (15) of 3-hydroxy steroids to the corresponding 3-keto compounds in the presence of cyclohexanone as hydrogen acceptor. This reaction was applied to ethyl 3(β),5,19-trihydroxyetiocholanate (VIII). In this instance the possibility of the formation of an aldehyde group at carbon atom 10 had to be considered. This might be followed by subsequent condensation of the aldehyde group with cyclohexanone.[6] The experiment was performed under conditions similar to those of Kleiderer and Kornfeld (14). The reaction yielded three products on chromatography.

The least polar substance (XXI) may possess the formula $C_{22}H_{32}O_4$. It is probably saturated. The amount obtained did not permit further investigation.

The second substance, as isolated in the process of chromatographic separation, was identified as ethyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XXII). The melting point was 176–178° (remelting at 184–186°). It is to be noted that, though this substance is a phenol, it is not soluble in a solution of 2 *N* sodium hydroxide. The ultraviolet absorption curve, plotted as molecular extinction coefficients, is practically identical with that of a reference sample of estradiol (Figure 1). With tetranitromethane the substance gave an orange color. Saponification of this compound (XXII) yielded 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XXIV) with the melting point 266–270°. The identical acid has been prepared by Djerassi and Scholz[5] (6) from methyl 3-keto-$\Delta^{1;4}$-etiocholadienate which in turn has been synthesized from cholesterol (7). The mixed melting point of the samples prepared in the two laboratories did not show a depression. It appears noteworthy, especially from the viewpoint of stereochemical considerations, that an identical product has been obtained from strophanthidin and cholesterol.

Furthermore it should be pointed out that Djerassi and Scholz[5] (6) have transformed XXIV into 3-methoxy-17-(β-acetoxyacetyl)-$\Delta^{1;3;5,10}$-estratriene, a compound which they could also prepare from 17-ethinylestradiol which is accessible from estrone. Hence, a correlation between the cardiac aglycones and the hormones of the estrogen series, which had been attempted by Butenandt and Gallagher (17), has been established.

It is not intended to present a detailed discussion of the reaction mechanism of the conversion of VIII into XXII. It is reasonable to assume that first dehy-

[6] Lit. *cf.* (9, p. 1266); for additional example *cf.* (16).

drogenation occurs at carbon atom 3 leading to (a) which is easily dehydrated to (b). The mechanism of the loss of carbon atom 19 is not clear. It is uncertain whether one molecule of methanol is split off directly or whether there is first a dehydrogenation to an aldehyde group followed by the elimination of one molecule of formaldehyde. The intermediate (c), a dienone, will rearrange to the phenol XXII.

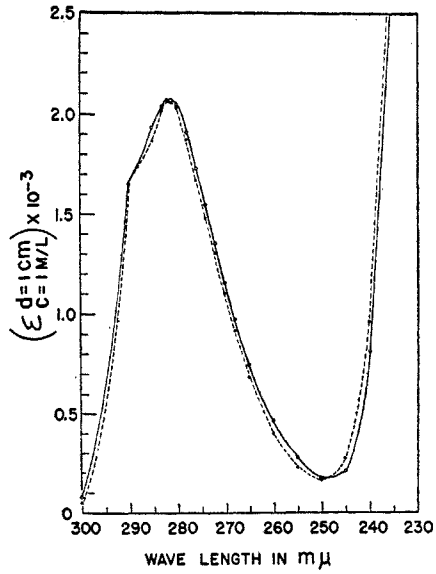


FIGURE 1.[7] BROKEN CURVE, *Estradiol*, U.S.P. Reference Standard, m.p. 174.5-176°; concentration of solution measured was 0.000437 *M* per liter (1.190 mg. per 10 cc. absolute alcohol). λ max. 282 mμ (ϵ = 2067); λ min. 250 mμ (ϵ = 171.5). SOLID CURVE, *Ethyl 3-hydroxy-*$\Delta^{1;3;5,10}$*-estratriene-17-carboxylate* (XXII), m.p. 176–178° (184–186°); concentration of solution measured was 0.000386 *M* per liter (1.270 mg. per 10 cc. absolute alcohol). λ max. 282 mμ (ϵ = 2075); λ min. 250 mμ (ϵ = 176.0).

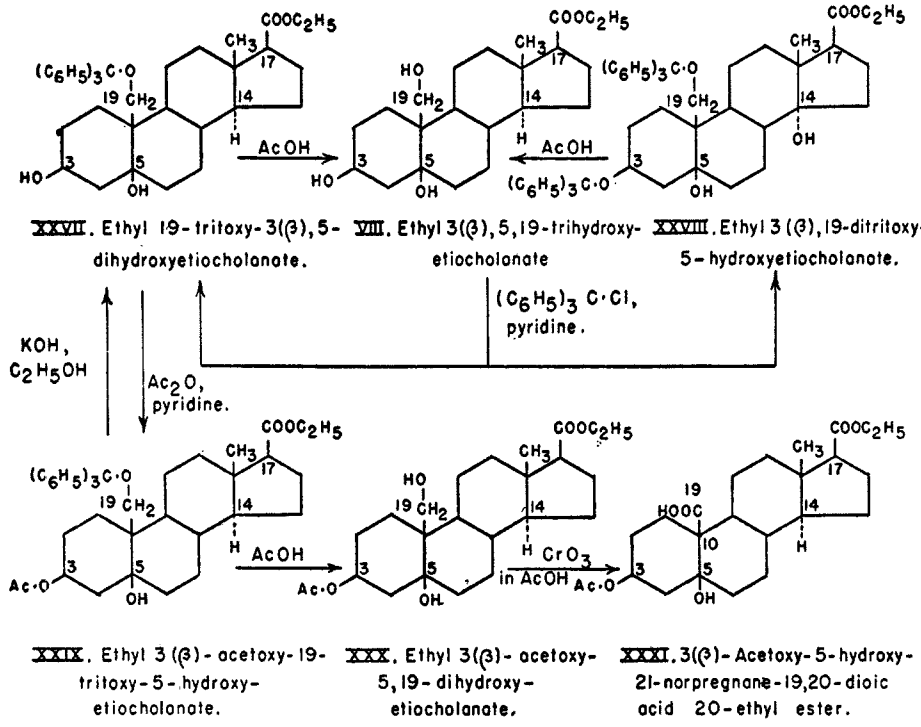
The ethyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XXII) and the 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XXIV) have been assayed for estrogenic activity through the courtesy of Drs. E. A. Doisy and S. A. Thayer at St. Louis University School of Medicine. The material was dissolved in water with the aid of a small amount of alcohol and injected into spayed mice according to a standard procedure, using estrone as the standard. Twenty mice were used at each dose level. The standard gave the usual 50% response at a level of 0.05 micrograms. Both XXII and XXIV were inactive at 0.05 micrograms and 10 micrograms. The ethyl ester (XXII) was also inactive at a level of 20 micrograms. The latter dosage represents the maximum solubility of this compound in water.

The third substance (XXIII) isolated from the chromatogram probably possesses the formula $C_{22}H_{34}O_4$ and, in view of its polarity, the structures XXIIIa or XXIIIb may be considered. It appears to be saturated and gives a resinous acetate from which the original material may be recovered by saponification.

[7] The absorption curves were kindly determined by Dr. D. L. Drabkin (Dept. of Physiological Chemistry, Graduate School of Medicine, University of Pennsylvania) with a Beckman DU Spectrophotometer with a 1 cm. depth silica cuvette.

Another approach to achieving partial oxidation of VIII would have consisted in performing a partial deacetylation of XI followed by oxidation of the resulting monoacetate. Various attempts to bring about such a partial deacetylation failed. Partial succinoylation (*cf. e.g.*, 18, 18a, 19, 20, 21, 21a) of VIII furnished a small yield of a resinous acid succinate interpreted to possess formula XXV. It was characterized as the crystalline methyl ester XXVI.

As is known from sugar chemistry, primary alcohol groups react much more rapidly with triphenylchloromethane than secondary ones. If one uses stoichiometric proportions the primary group or groups can be tritylated, whereas the



XXVII. Ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate. VIII. Ethyl 3(β),5,19-trihydroxy-etiocholanate XXVIII. Ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate.

XXIX. Ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxy-etiocholanate. XXX. Ethyl 3(β)-acetoxy-5,19-dihydroxy-etiocholanate. XXXI. 3(β)-Acetoxy-5-hydroxy-21-norpregnane-19,20-dioic acid 20-ethyl ester.

reaction with secondary alcohol groups is negligible. There are almost no instances of the use of this reagent in steroid chemistry (*cf.*, *e.g.* 22). Ethyl 3(β),5, 19-trihydroxyetiocholanate (VIII) represented a test case, in that it contains a primary alcohol group at carbon atom 19, and a secondary one at carbon atom 3. On treating it with one mole of triphenylchloromethane, ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) was obtained as main reaction product. It was accompanied by a small amount of ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate (XXVIII) and a fair quantity of unchanged starting material, (VIII). A regular by-product was triphenylcarbinol. These four components of the reaction mixture may be separated quantitatively by chromatography. Considering the fact that part of the triol VIII is recovered unchanged and that the ditrityl ether XXVIII can be smoothly hydrolyzed to the triol VIII, no steroid material is lost.

A complete cleavage of the 19-monotrityl ether XXVII to the triol VIII is best achieved by treating it at room temperature with slightly diluted acetic acid overnight. Attempts to prepare under similar conditions ethyl 3(β)-tritoxy-5,19-dihydroxyetiocholanate by partial hydrolysis of the ditrityl ether XXVIII failed. Only the triol VIII resulted.

On acetylating ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) in the usual fashion, the resinous ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate (XXIX) was obtained. The uniformity of this resinous substance was assured by chromatographic purification. On saponifying XXIX in an alkaline medium (KOH, absol. ethanol), ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) was recovered. On performing the hydrolysis of XXIX in slightly diluted acetic acid, cleavage of the ether linkage occurred leading to ethyl 3(β)-acetoxy-5,19-dihydroxyetiocholanate (XXX). This monoacetate could easily be subjected to an oxidation with chromic acid yielding the 20-ethyl ester of 3(β)-acetoxy-5-hydroxy-21-norpregnane-19,20-dioic acid (XXXI).[8] The dicarboxylic acid from which the latter ester (XXXI) is derived, *i.e.* 3(β),5-dihydroxy-21-norpregnane-19,20-dioic acid is a stereoisomer of a compound prepared in Butenandt's laboratory (17) and by Ehrenstein (3). The latter possesses the iso configurations at carbon atoms 14 and 17.

According to preliminary experiments XXVII can be oxidized to the corresponding 3-keto compound by N-bromoacetamide (25, 26, 27). Treatment of XXVII with chromium trioxide in acetic acid is connected with simultaneous cleavage of the ether linkage and, therefore, apparently a mixture of oxidation products results.

EXPERIMENTAL

The melting points were determined with the Fisher-Johns melting-point apparatus. The readings are sufficiently near the true melting points so that no corrections have been made. Unless stated otherwise the microanalyses were carried out by Mr. Joseph F. Alicino, Metuchen, N. J. (J.F.A.), Dr. E. W. D. Huffman, Denver 2, Colo. (E.W.D.H.), and Mr. James Rigas, Brooklyn 25, N. Y. (J.R.).

Further observations on the preparation of the starting material: Ethyl 3(β),5,19-trihydroxyetiocholanate (VIII)

a. *Strophanthidol* (II). The melting point of this substance, when crystallized from ethyl acetate, was usually between 216 and 222°.

b. *Strophanthidol 3,19-diacetate* (III). After the termination of the acetylation of strophanthidol (1), the reaction product is poured into water. The following day the crystalline material is washed with 0.5 *N* hydrochloric acid and with water. The subsequent treatment remains unchanged; recrystallization of the crude diacetate from acetone-petroleum ether or acetone-ether.

c. *3(β),19-Diacetoxy-5,14-dihydroxy-14-isoetiocholanic acid* (IV). Since publication of the earlier paper (1) the oxidation of a total of 494.03 g. of III yielded 206.64 g. (41.8% of the invested material) of acid-ether extract. Reoxidations of a total of 69.82 g. of neutral oxidation product gave 22.21 g. (31.8%) of acid-ether extract. On reoxidizing (ratio of $KMnO_4$ one-half that of an original oxidation) neutral material which had been oxidized twice, a yield of about 12% of acid-ether extract resulted. In any instance the subsequent

[8] This nomenclature is based on recent proposals by Reichstein (23). A different nomenclature has been suggested by Fieser (24, page 522; footnote 15).

extraction with ethyl acetate furnished additional acid fractions. However, on saponification of such material either no, or only small, amounts of V resulted.

d. *3(β),5,14,19-Tetrahydroxy-14-isoetiocholanic acid* (V). Since the last report (1) a total of 148.35 g. of acid-ether extract was converted into 63.60 g. of crystalline tetrahydroxy acid (V).[9] The resinous products (45.51 g.) still contain appreciable amounts of V (1). The saponification of acid-ether extracts originating from reoxidations of neutral material furnished considerably smaller yields of crystalline V.

e. *Dehydration of 3(β),5,14,19-tetrahydroxy-14-isoetiocholanic acid* (V): *Crystalline ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate* (VI) *and other products.* A solution of 3.5 g. of 3(β),5,14,19-tetrahydroxy-14-isoetiocholanic acid in 102 parts of approximately 0.1 *N* absolute alcoholic hydrogen chloride was kept just at the boiling point (bath temperature 81–87°) for a period of two hours. A slow distillation was subsequently performed under such conditions that within 1½ hours the solution was reduced to about ⅛ of its volume. Addition of water until the first appearance of turbidity and subsequent heating gave a clear solution. On standing overnight needles of the compound $C_{20}H_{28}O_4$, tentatively designated a lactone (1) separated. Any adhering resinous material may be removed by careful leaching with 50% alcohol or with ether. After removal of alcohol from the combined filtrates *in vacuo*, the mixture was extracted first with 245 cc. of ether and then with five portions of 122 cc. of ether. The combined ether extracts were washed with two 7-cc. portions of water, then extracted with 25.2 cc. and 12.6 cc. of a solution of 5% sodium carbonate and finally washed with seven 7-cc. portions of water. After drying with sodium sulfate, removal of the ether left a neutral residue. Crystallization of this from acetone gave successive crops (33–35% yield) of ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate. After further crystallization from acetone it melted at 187–191.5°. Analyses and optical rotation have been reported previously (1).

The combined carbonate extracts and aqueous washings were acidified with 6.3 cc. of conc'd hydrochloric acid and extracted with six portions of ether. After washing the ether extracts with water and drying with sodium sulfate, removal of the solvent left a resinous acid residue which has not been investigated in detail (*cf.* 1).

The combined acetone mother liquors were treated as previously described (1, footnote 5a).

From a total of 67.06 g. of 3(β),5,14,19-tetrahydroxy-14-isoetiocholanic acid in 25 experiments, 2.89 g. of the so-called lactone, 5.27 g. of resinous acid material, 32.94 g. of resinous neutral material, and 24.30 g. of VI were obtained.

When the resinous acid from the saponification of 3(β),19-diacetoxy-5,14-dihydroxy-14-isoetiocholanic acid was treated similarly, none of the lactone was obtained, and 7–14% of VI was isolated. A total of 57.18 g. of resinous acid yielded in 24 experiments 8.55 g. of resinous acid material, 5.26 g. of VI, and 35.62 g. of resinous neutral material.

The dehydration of resinous material which had been obtained by saponification of the acid ethyl acetate extracts resulting from the oxidation of strophanthidol diacetate (*vide supra*) did not yield any VI by direct crystallization.

f. *Dehydration of 3(β),19-diacetoxy-5,14-dihydroxy-14-isoetiocholanic acid* (IV). One gram of the crude 3(β),19-diacetoxy-5,14-dihydroxy-14-isoetiocholanic acid (*i.e.*, acid-ether extract from the oxidation of strophanthidol 3,19-diacetate) was treated exactly according to the procedure given above for the dehydration of the crystalline 3(β),5,14,19-tetrahydroxy-14-isoetiocholanic acid. This yielded 0.063 g. of the lactone (?) fraction; m.p. 75–77°. In addition 0.090 g. of resinous acid material and 0.626 g. of a resinous neutral fraction was

[9] In a recent comparison Dr. Helmut C. Neumann varied the saponification in carrying it out in a solution of methanol with three moles rather than ten moles of potassium hydroxide. In addition, the solution was not refluxed, but allowed to stand at room temperature (25–30°) for eighteen hours. The yield of the crystalline acid (V) as obtained from ethyl acetate was 44.4% rather than 39.6%. Also the purity was somewhat superior (m.p. 213–217° rather than 209–214°).

obtained. The latter did not crystallize when it was treated with acetone. The late eluates of a subsequent chromatographic purification produced some crystalline material, which by recrystallization from acetone yielded 0.032 g. of a compound melting at 189–191°. It gave no depression in melting point when mixed with an authentic sample of ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate.

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.27): C, 69.79; H, 9.06.
Found: C, 69.80; H, 8.93 (J.F.A.).

g. *Ethyl 3(β),5,19-trihydroxyetiocholanate* (VIII) *by hydrogenation of crystalline ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate* (VI). Reduction of 1.00 g. of VI in a total of 15 cc. of glacial acetic acid over 400 mg. of previously reduced platinum oxide (room temperature; atmospheric pressure) resulted in the uptake of one equivalent of hydrogen in 2½ hours. The solution was filtered from the platinum and quickly brought to dryness *in vacuo* (45°). The sirupy residue was repeatedly dissolved in a small volume of absolute alcohol and taken to dryness in order to remove the last traces of acetic acid. Recrystallization of the residue from acetone gave ethyl 3(β),5,19-trihydroxyetiocholanate as prisms. First crop: wt., 0.8231 g.; m.p. 187–188°, remelt. 190–191°; no depression of the m.p. when mixed with an authentic sample of VIII (1, page 842). Second crop: wt., 0.0858 g.; m.p. 178–181°. Third crop: wt., 0.0173 g.; m.p. 178–181°.

The mother liquors from the above gave low-melting or resinous material. A solution of 2.53 g. of this (from several runs) in 200 cc. of benzene was chromatographed over 65 g. of Brockmann aluminum oxide (Merck & Co., Rahway). A fraction resulting from a benzene-ether (1:1) eluate (0.2247 g.) yielded by repeated recrystallizations from acetone 0.0257 g. of a substance melting at 210–213°. It gave a depression of the melting point when mixed with a reference sample of ethyl 3(β),5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate. The analysis is in agreement with the formula $C_{20}H_{32}O_4$.

Anal. Calc'd for $C_{20}H_{32}O_4$ (336.25): C, 71.37; H, 9.59.
$C_{22}H_{36}O_4$ (364.28): C, 72.47; H, 9.96.
Found: C, 71.43, 71.78; H, 9.63, 9.50 (J.F.A.).

Elution with ether and ether-chloroform (3:1) gave 0.2665 g. of crystalline material which after crystallization from acetone yielded 0.0780 g. of ethyl 3(β),5,19-trihydroxy-$\Delta^{8,14}$-etiocholenate, m.p. 211–214°, which was identified by mixed m.p. with a known sample.

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.27): C, 69.79; H, 9.06.
Found: C, 69.56; H, 9.36 (J.F.A.).

Successive elution with a mixture of 198 c. of chloroform and 2 cc. of methanol and a mixture of 195 cc. of chloroform and 5 cc. of methanol gave 0.8575 g. of material from which, after recrystallization from acetone, 0.1887 g. of VIII was obtained.

Compound (Lactone?) $C_{20}H_{28}O_4$. Various attempts were made to purify and identify the compound tentatively (1) interpreted to be a lactone. The pooled material resulting from several dehydrogenation experiments (melting points between 90 and 100°) was purified by chromatographic adsorption on aluminum oxide. The major part was recovered from the early eluates (benzene and benzene-ether) which yielded crystalline residues. The crystalline residues (m.p. 103–104°)[9a] were analyzed as such as well as after washing them with a mixture of acetone and petroleum ether.

Anal. Calc'd for $C_{20}H_{28}O_4$ (332.22): C, 72.24; H, 8.49.
Found: C, 72.44, 71.57; H, 9.14, 8.82 (J.F.A.).

Treatment of the residues of some of the late eluates (ether-methanol) with acetone furnished material which was purified by crystallization from acetone; m.p. 167–168°. There was a pronounced depression (mixed m.p. 143–150°) of the melting point when mixed with ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate (m.p. 191–192°). In chloroform solution the substance gave a yellow color with tetranitromethane.

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.27): C, 69.79; H, 9.06.
$C_{22}H_{32}O_5$ (376.25): C, 70.17; H, 8.57.
Found: C, 70.24, 70.41; H, 8.70, 8.49 (J.F.A.).

[9a] Determination of the infrared spectrum at the Sloan-Kettering Institute gave a band (CS_2) at 1739 cm.$^{-1}$, probably indicating an alkyl ester or a δ-lactone.

The compound $C_{20}H_{28}O_4$ proved to be rather labile. In unsuccessful attempts at recrystallization it was treated with a number of solvents. When some of these solutions were brought to dryness, the previously crystalline material refused to crystallize. Renewed purification by chromatography proved that the major part of the material had become considerably more polar, since it was now eluted in the later fractions of the chromatogram. A crystalline sample of compound $C_{20}H_{28}O_4$ (m.p. 98–100°) was subjected to catalytic hydrogenation in the presence of platinum in a solution of glacial acetic acid. No crystalline hydrogenation product could be obtained.

Ethyl 3(β),19-diacetoxy-5-hydroxy-Δ^{14}-etiocholenate (VII). To a solution of 30 mg. of ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate (m.p. 191–192°) in 0.2 cc. of pyridine was added 0.2 cc. of acetic anhydride and the mixture allowed to stand at room temperature overnight. The solvents were removed *in vacuo* and the resinous residue taken up in 12.5 cc. of ether which was subsequently washed twice with 0.4-cc. portions of 2 *N* hydrochloric acid, twice with 0.2-cc. portions of *N* sodium carbonate, and finally five times with 0.1-cc. portions of water. After drying with sodium sulfate, the ether solution was concentrated. Crystalline material separated and, on further concentrating, another crystalline crop was obtained. First crop: wt., 18.5 mg.; m.p. 118–120°. Second crop: wt., 13.0 mg.; m.p. 112–113°. Resinous residue: wt., 5.5 mg. (Total: 37.0 mg.). Recrystallization of the first crop from ether yielded 11.6 mg., m.p. 115–117°.

Anal. Calc'd for $C_{26}H_{38}O_7$ (462.30): C, 67.49; H, 8.28.
Found: C, 67.17; H, 8.32 (J.F.A.).

3(β),19-Diacetoxy-5-hydroxyetiocholanic acid (X). To a solution of 0.307 g. of 3(β),5,19-trihydroxyetiocholanic acid (m.p. between 265 and 270°) in 1.5 cc. of pyridine was added 0.9 cc. of acetic anhydride and the mixture allowed to stand at room temperature for a period of about two days. After the addition of 0.9 cc. of water it was heated on the water-bath for 2½ hours and then concentrated to a syrupy consistency *in vacuo* (60°). The residue was taken up in 150 cc. of ether and this solution washed free of pyridine with 5 cc. of N hydrochloric acid (acid to Congo) and with three 1-cc. portions of water. The ether phase was extracted with five 3 cc.-portions of *N* sodium carbonate and subsequently washed three times with 1 cc. of water. After drying, the ether solution yielded 0.015 g. of resinous neutral material. The combined carbonate extracts and aqueous washings were cooled with ice, transferred into a separatory funnel, and made acid to Congo by the addition of 2 cc. of conc'd hydrochloric acid which produced a thick colorless precipitate. This was extracted with three 50-cc. portions of ether. The combined ether extracts were washed five times with 1 cc. of water, dried, and brought to dryness *in vacuo*. Since the sticky colorless residue contained some acetic acid, it was dried in a vacuum desiccator over pellets of potassium hydroxide, then taken up in acetone and again brought to dryness *in vacuo*, which yielded a colorless brittle foam. The treatment with acetone was repeated a few times and the foam eventually dried over potassium hydroxide. Constant weight: 0.368 g. (Calc'd 0.380 g.). This material resisted all attempts at crystallization. In chloroform solution no yellow color was obtained with tetranitromethane, indicating that no simultaneous dehydration had occurred. $[\alpha]_D^{26}$ +68.1° (20.0 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +1.03°).

Anal. Calc'd for $C_{24}H_{36}O_7$ (436.28): C, 66.01; H, 8.32.
Found[10]: C, 65.40, 65.20; H, 8.37, 8.22.

Methyl 3(β),19-diacetoxy-5-hydroxyetiocholanate (XIII). (a) *From 3(β),19-diacetoxy-5-hydroxyetiocholanic acid* (X). To a solution of 61 mg. of 3(β),19-diacetoxy-5-hydroxyetiocholanic acid in 5 cc. of ether was added at 0° a slight excess of an ethereal solution of diazomethane. The mixture was kept at 0° for 15 minutes and at room temperature for an additional 10 minutes. The excess diazomethane was boiled off on a water-bath. This yielded a colorless solution which was transferred into a separatory-funnel by means of 20 cc. of ether. After washing with 1.5 cc. of *N* hydrochloric acid, 1 cc. of water, 11.5 cc. of 5% sodium carbonate, and three times with 1 cc. of water, the solution was dried and subsequently brought to dryness. Yield, 54 mg. of a colorless glass which resisted all attempts at crystallization.

Anal. Calc'd for $C_{25}H_{38}O_7$ (450.30): C, 66.62; H, 8.50.
Found: C, 67.00, 66.93; H, 8.73, 8.67 (E.W.D.H.).

(b) *From methyl 3(β),5,19-trihydroxyetiocholanate* (XII). To a solution of 82 mg. of methyl 3(β),5,19-trihydroxyetiocholanate (m.p. 218°) in 0.35 cc. of pyridine was added 0.35 cc. of acetic anhydride and the mixture allowed to stand at room temperature overnight. It was then brought to dryness *in vacuo* (65°), the resinous residue taken up in 25 cc. of ether, and the latter solution washed with 2 cc. of *N* hydrochloric acid, 2 cc. of 5% sodium carbonate, and four times with 1-cc. portions of water. The ethereal solution was subsequently dried and brought to dryness. Yield, 90 mg. of a resin; attempts at crystallization were unsuccessful. The material was dissolved in a mixture of 5 cc. of benzene and 10 cc. of petroleum ether and chromatographed over 3.0 g. of aluminum oxide (diam. of column: 8 mm.). The adsorbate was successively eluted with 15-cc. portions of benzene-petroleum ether (benzene content gradually increasing), benzene, benzene-ether (ether content gradually increasing), ether, ether-acetone (acetone content gradually increasing), acetone, acetone-methanol (methanol content gradually increasing), and methanol. All residues obtained from these eluates were resinous. The main fraction (34 mg.) was obtained from the benzene phase. It resisted all attempts at crystallization.

Anal. Calc'd for $C_{25}H_{38}O_7$ (450.30): C, 66.62; H, 8.50.
Found: C, 66.75, 66.86; H, 8.71, 8.77 (E.W.D.H.).

Distillation in a high-vacuum of 3(β),19-diacetoxy-5-hydroxyetiocholanic acid (X). This is an abbreviated account of two experiments. First experiment: A total of 0.287 g. of dry 3(β),19-diacetoxy-5-hydroxyetiocholanic acid was heated in a vacuum (oil-pump) to 170° and the temperature gradually raised to 205°. During this time there was a persistent gas evolution in the retort. After this reaction had come to a standstill, the reaction product was distilled in a high-vacuum (oil and mercury vapor pumps combined) at a temperature of 240–265°. The distillate was a slightly greenish glass; wt., 0.234 g.; $[\alpha]_D^{26}$ +3.3° (20.0 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +0.05°). The residue in the retort was a light brown resin; wt., 0.005 g.

Total loss of weight: 0.048 g. (16.7%).

Calc'd loss of weight:

$$C_{24}H_{36}O_7\ (436.28) \xrightarrow{-H_2O} C_{24}H_{34}O_6\ (418.27): 4.1\%$$

$$C_{24}H_{36}O_7\ (436.28) \xrightarrow[-CH_3COOH]{-H_2O} C_{22}H_{30}O_4\ (358.23): 17.9\%$$

$$C_{24}H_{36}O_7\ (436.28) \xrightarrow[-CH_3COOCH_3]{-H_2O,\ -2\ H} C_{21}H_{26}O_4\ (342.20): 21.6\%$$

Anal.[10] Calc'd for $C_{24}H_{34}O_6$ (418.27); C, 68.86; H, 8.19.
$C_{22}H_{30}O_4$ (358.23): C, 73.69; H, 8.44.
$C_{21}H_{26}O_4$ (342.20): C, 73.64; H, 7.66.
Found: C, 71.17; H, 7.81.

The distillate resisted attempts at crystallization. A sample was subjected to a separation into acid and neutral material; only small amounts of neutral material were obtained. The distillate was transformed into the methyl ester with diazomethane; 0.215 g. of distillate yielded 0.225 g. of methyl ester. The latter was a colorless glass which was dissolved in a mixture of 25 cc. of benzene and 7.5 cc. of petroleum ether and chromatographed over 10.0 g. of aluminum oxide (diam. of column: 20 mm.). The adsorbate was successively eluted with 25-cc. portions of benzene-petroleum ether (benzene content gradually increasing), benzene, benzene-ether (ether content gradually increasing), ether, ether-methanol (methanol content gradually increasing). A substantial amount (0.052 g.) was recovered from the benzene-petroleum ether fractions. One of them (0.023 g.) was crystalline. Recrystallization from ether yielded several crystalline crops, totalling 12.4 mg. with melting points between 133 and 144°. The melting point of the purest fraction (4.9 mg.) was 143–144°. A solution in chloroform yielded a yellow color with tetranitromethane.

[10] Microanalysis by Mr. William Saschek, Department of Biochemistry, Columbia University, New York.

Anal.[11] Calc'd for $C_{25}H_{36}O_6$ (432.28): C, 69.40; H, 8.39.
[Methyl 3,19-diacetoxy-Δ^5-etiocholenate (XV)]
Found: C, 69.77; H, 8.98.

Second experiment:[12] A total of 0.657 g. of 3(β),19-diacetoxy-5-hydroxyetiocholanic acid was quickly heated in a high-vacuum (oil and mercury vapor pumps combined) to 153°, then slowly raised to 176°. After the gas evolution had ceased the material was distilled at about 250°. Total loss of weight, 0.124 g. (18.8%). The glassy distillate was recrystallized from ether. This furnished several crops of rosette arrangements of crystals totalling 0.138 g., m.p. between 144 and 150°. The weight of the non-crystalline part was 0.372 g. Recrystallization of the combined crystalline fractions from ether furnished several crops of crystals with varying melting points; wt. of the first crop, 0.041 g.; m.p. 158–161°.

Anal.[11] Calc'd for $C_{24}H_{34}O_6$ (418.27): C, 68.86; H, 8.19.
$C_{22}H_{30}O_4$ (358.23): C, 73.69; H, 8.44.
$C_{21}H_{26}O_4$ (342.20): C, 73.64; H, 7.66.
Found: C, 72.43; H, 8.75.

The further working up of this experiment was delayed for a period of more than one year. During the course of this time, there occurred a slight weight increase of the non-crystalline fraction. In addition, it had also become very sparingly soluble in ether (autoxidation?) Treatment with diazomethane yielded the methyl ester which was subsequently subjected to a chromatographic fractionation. No uniform material resulted from this treatment. The crystalline part which was still readily soluble in ether, was likewise transformed into the methyl ester. The resulting resinous product was purified by chromatographic fractionation. From a total of 100 mg. of crude methyl ester, about 36 mg. could be recovered from the early eluates (benzene-petroleum ether combinations). This material, which was resinous, was subjected to solvolysis with 0.5 equiv. of potassium hydroxide in methanol at room temperature, to transform any acetoxy groups into hydroxy groups. The resulting non-crystalline product was purified by chromatographic fractionation. As expected, it had become more polar. After first eluting with benzene-petroleum ether combinations and with benzene, approximately 11 mg. could be secured from the benzene-ether eluates. On recrystallizing from a mixture of acetone and petroleum ether 1.6 mg. of feather-shaped crystals (methyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate), m.p. 217–219° was obtained. A solution in chloroform gave with tetranitromethane a deep golden-yellow color. The ultraviolet absorption spectrum was determined[4] in the region between 200 and 300 mμ. There was a maximum at 281 mμ and a minimum at 249 mμ. There was no depression of the melting point when mixed with an authentic sample of methyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate which was kindly supplied by Drs. C. Djerassi and C. R. Scholz (6).

Partial oxidation of ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) *with chromic acid.* In a preliminary experiment oxidation of VIII with one equivalent of chromium trioxide and subsequent treatment of the neutral fraction with Girard's Reagent T resulted in a substantial loss of material, indicating the possible presence of an aldehydic substance. To avoid this loss, the use of this reagent was excluded in the main experiment.

To a solution of 0.9505 g. (2.5 millimoles) of VIII in 55 cc. of glacial acetic acid there was added at room temperature over a period of seven hours, a solution of 0.1853 g. (1.1 equivalent) of chromium trioxide in 55 cc. of 95% acetic acid. The following day 10 cc. of alcohol was added and the solution brought to dryness *in vacuo*. In order to remove the acetic acid completely the residue was repeatedly dissolved in 5-cc. portions of alcohol and taken to dryness. Thereafter 25 cc. of water was added and the material transferred into a separatory-funnel by means of 500 cc. of ether. The ether phase was washed with 30 cc. of *N* sulfuric acid and four 4-cc. portions of water. Some gummy, probably acid material remained undissolved, but went into the carbonate phase when the ether solution was subsequently extracted with three 10-cc. portions of *N* sodium carbonate. After washing the ether solution

[11] Microanalysis by Dr. Francine Schwarzkopf, Elmhurst, L. I.
[12] Partly with the assistance of Mr. Charles P. Balant.

four times with 5 cc. of water, it was dried and brought to dryness; wt. of neutral residue, 0.7722 g. The combined carbonate phases and aqueous washings were cooled with ice and acidified to Congo by the addition of an excess (20 cc.) of 4 *N* sulfuric acid. This was followed by thorough extraction with 500 cc. and 25 cc. of ether. The combined ether extracts were washed eight times with 5 cc. of water, dried, and brought to dryness. In order to remove traces of acetic acid, the resinous acid residue was dried overnight in a vacuum desiccator over potassium hydroxide; wt. of the acid material, 0.1013 g.; it has not yet been investigated.

To the neutral residue (0.7722 g.) was added some ether, which caused the separation of crystalline material (1st crop); after drying, 0.1110 g.; m.p. 155–165°. The filtrate was brought to dryness, the brittle foamy residue dissolved in a small amount of ether, and the solution allowed to stand in a refrigerator. This caused the separation of additional crystalline material (2nd crop); wt., 0.0484 g., m.p. 120–138°. The filtrate yielded 0.6135 g. of a resinous residue.

Ethyl 3-keto-5,19-dihydroxyetiocholanate (XIX)? It was possible to purify the first crop by repeated fractional crystallizations from ether. In each instance the material was dissolved in the required amount of ether and this solution concentrated to about one half of its volume. Transparent needles separated on standing in a refrigerator. Thus six fractions (A) were obtained, totalling 0.0326 g.; melting points between 199 and 203°. For additional material of this substance *vide infra*, $[\alpha]_D^{29.5}$ +76.2° (10.6 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +0.61°). For infrared spectrum see theoretical part.

Anal. Calc'd for $C_{22}H_{34}O_5$ (378.27): C, 69.63; H, 9.04.

Found: C, 69.05; H, 9.21 (J.F.A.); C, 69.04; H, 9.07 (E.W.D.H.).

Two other fractions (B), totalling 0.0216 g., represented the same substance, but were less pure. The melting points were between 181 and 186°. Two other fractions (C), totalling 0.0180 g., had melting points between 140 and 163°. They definitely represented mixtures. The combined resinous fractions (D) resulting from the recrystallizations of the first original crop, weighed 0.0460 g.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, G.	APPEARANCE OF RESIDUE
1	25 cc., benzene (original solution)	0.0037	Colorless resin
2	15 cc., benzene	.0015	Colorless resin
3	10 cc. of benzene + 5 cc. of ether	.0048	Yellow resin
4	5 cc. of benzene + 10 cc. of ether	.0037	Colorless resin
5	15 cc. of ether	.0156	Yellowish, crystalline
6	10 cc. of ether + 5 cc. of chloroform	.0061	White, crystalline
7	5 cc. of ether + 10 cc. of chloroform	.0030	White, crystalline
8	15 cc. of chloroform	.0035	Yellowish, crystalline
9	15 cc. of chloroform + 0.005 cc. of methanol	.0109	White, crystalline
10	15 cc. of chloroform + 0.01 cc. of methanol	.0117	White, crystalline
11	15 cc. of chloroform + 0.01 cc. of methanol	.0093	White, crystalline
12	15 cc. of chloroform + 0.02 cc. of methanol	.0077	White, crystalline
13	15 cc. of chloroform + 0.03 cc. of methanol	.0074	White, crystalline
14	15 cc. of chloroform + 0.04 cc. of methanol	.0072	White, crystalline
15	15 cc. of chloroform + 0.1 cc. of methanol	.0056	Partially crystalline
16	14.5 cc. of chloroform + 0.5 cc. of methanol	.0070	Colorless resin
17	10 cc. of chloroform + 5 cc. of methanol	.0017	Colorless resin
18	15 cc. of methanol	.0017	White, crystalline
Total		0.1021	

Recrystallization from ether of the second original crop of crystals (0.0484 g.) gave various fractions, melting over a wide range between 130 and 160°. This material was therefore combined with the above C-series (0.0180 g.) and the resinous D-series (0.0460 g.); total, 0.1124 g. This was subjected to a chromatographic separation by dissolving it in 25 cc. of benzene and passing this solution through a column (diam. 10 mm.) of 4 g. of alkali-free aluminum oxide[13] within a period of 75 minutes. The eluting was done at the rate of 15–20 minutes for each fraction.

No crystals were obtained from fractions 1 to 4. Fractions 5–7 furnished from ether eight crops of crystalline material, totalling 0.0146 g.; melting points between 180 and 199°. They obviously represented impure ethyl 3-keto-5,19-dihydroxyetiocholanate and were therefore pooled with the above B-series. Fraction 8 represented a mixture; only low-melting (between 144 and 164°) material was obtained.

Compound $C_{24}H_{36}O_6$ *or* $C_{20}H_{30}O_5$ (XX)? From fractions 9–15 there were secured twenty-five crops of crystalline material totalling 0.0332 g., range of melting points between 162 and 171°. The combined crops furnished from ether silky, felt-like needles, which sometimes had the appearance of long fibers, such as in asbestos. The melting point of the purest material (0.0170 g.) was 171–173°. For additional material of this substance *vide infra*. $[\alpha]_D^{29}$ −11.2° (9.5 mg. in 2.0 cc. of chloroform, l = 1.51 dm., α −0.08°). For infrared spectrum see theoretical part.

Anal. Calc'd for $C_{24}H_{36}O_6$ (420.28): C, 68.53; H, 8.63.
$C_{20}H_{30}O_5$ (350.23): C, 68.53; H, 8.63.
Found: C, 68.64, 69.06; H, 8.87, 8.91 (E.W.D.H.).[14]

An attempt to secure an oxime of this substance failed. The isolated reaction product contained no nitrogen and was apparently unchanged starting material. In an attempt to prepare an acetyl derivative the acetylation carried out in the usual fashion at room temperature yielded a resinous reaction product, which resisted attempts at crystallization. Seeding with ethyl 3,19-diacetoxy-5-hydroxyetiocholanate was of no avail. There was not enough material for a chromatographic purification.

The resinous residue (0.6135 g.), as obtained after the separation of the original crops of crystals, was chromatographed over 18 g. of alkali-free aluminum oxide.[13] The combination of eluants was similar to those of the chromatogram given above. There resulted a total of only 0.0712 g. of crystalline material. Of these crystalline fractions only 0.0067 g. were obtained from the benzene, benzene-ether, ether, ether-chloroform, and chloroform eluates. The eluate secured with a mixture of 50 cc. of benzene and 0.03 cc. of methanol yielded 0.0096 g. of crystalline material, m.p. 192–198°. There was no depression of the melting point when mixed with the substance believed to be ethyl 3-keto-5,19-dihydroxyetiocholanate. It was therefore pooled with the crystalline B-series mentioned above. The subsequent eluates, resulting from further chloroform-methanol combinations, yielded altogether 0.0549 g. of crystalline material melting between 140 and 176°.

The latter crystalline fractions, including the material contained in their respective mother liquors was pooled with fraction 8 of the chromatogram recorded above (total, 0.1821 g.). A renewed chromatographic separation yielded only impure, if any, of the ethyl 3-keto-5,19-dihydroxyetiocholanate; however, several crops, totalling 0.0325 g., of the pure compound $C_{24}H_{36}O_6$ (or $C_{20}H_{30}O_5$) were obtained; 0.0198 g. of somewhat less pure material of the same substance was identified.

The crystalline B series mentioned above and the material which had been pooled with it during the course of these purification procedures (total 0.0458 g.) was recrystallized from ether and furnished 0.0247 g. of practically pure ethyl 3-keto-5,19-dihydroxyetiocholanate (m.p. 196–198°).

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[13] One part of aluminum oxide (standardized acc. to Brockmann, Merck & Co., Rahway, N. J.) was placed in an adsorption column and slowly washed with two parts of a 9:1 mixture of methanol-glacial acetic acid. The material was subsequently washed acid free with methanol and dried in an oven at a temperature of 200° for four hours.

[14] Two different samples of the same degree of purity.

Summary: The total yield of pure ethyl 3-keto-5,19-dihydroxyetiocholanate was 0.0573 g., that of compound $C_{24}H_{36}O_6$ or $C_{24}H_{38}O_6$ (?) 0.0493 g.

Oxime of ethyl 3-keto-5,19-dihydroxyetiocholanate. To 10.1 mg. of ethyl 3-keto-5,19-dihydroxyetiocholanate dissolved in 1.7 cc. of absolute alcohol was added a mixture of 20 mg. of hydroxylamine hydrochloride and 30 mg. of sodium acetate in 0.15 cc. of water. After refluxing on a water-bath for a period of three hours an ample amount of water was added which caused the immediate precipitation of short white needles. They were filtered after some standing and washed with water; 1st crop: dry wt., 4.6 mg., m.p. 187–189°. It gave a depression of the melting point when mixed with the starting material. An additional crystalline separation was obtained by removing the alcohol *in vacuo*; 2nd crop: dry wt., 4.6 mg., m.p. 185–187°. The combined material was recrystallized from aqueous alcohol, yield 5.9 mg., m.p. 188–189°.

Anal. Calc'd for (monoöxime) $C_{22}H_{35}NO_5$ (393.25): N, 3.56. Found: N, 3.80 (J.F.A.).

Attempts to dehydrogenate ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) *according to the Oppenauer method. (a) With aluminum tert-butoxide and acetone.* To a solution of 200 mg. of aluminum *tert*-butoxide (Eastman Kodak) in 8 cc. of dry benzene was added 100 mg. of ethyl 3(β),5,19-trihydroxyetiocholanate dissolved in 4 cc. of acetone. This mixture was refluxed on a water-bath for a period of ten hours; after five hours 1 cc. of additional acetone was added. The working up in the usual fashion was followed by a separation with Girard's Reagent T. This furnished practically no ketonic fraction (3.8 mg.). Recrystallization of the non-ketonic fraction (90.8 mg.) furnished 80.2 mg. of pure starting material. (b) *With aluminum phenoxide*[15] *and acetone.* Aluminum phenoxide (800 mg.) was dissolved in 30 cc. of benzene by warming. A solution of 200 mg. of ethyl 3(β),5,19-trihydroxyetiocholanate in 12 cc. of dry acetone was added and the mixture refluxed for a period of 25 hours. It was taken up in 260 cc. of ether and this solution washed with 25 cc. of *N* sulfuric acid. The phenol was removed with three 8-cc. portions of *N* sodium hydroxide. The ether phase was washed neutral with water, dried, and brought to dryness; wt. of the crystalline residue, 206 mg. This was separated by means of Girard's Reagent T. Practically no ketonic material was obtained (2.3 mg.). The weight of the non-ketonic part was 188 mg., from which by recrystallization 169 mg. of pure starting material was secured.

Treatment of ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) *with Raney nickel in the presence of cyclohexanone.*[16] To a total of 0.503 g. of pure ethyl 3(β),5,19-trihydroxyetiocholanate (melting points between 185 and 187°), dissolved in 5 cc. of redistilled cyclohexanone (b.p. 148–150°), was added a suspension of approximately 2.12 g. of Raney nickel[17] in 20.5 cc. of toluene. This mixture was stirred and refluxed continuously for a period of 24 hours, bath temperature 128–132°. Because part of the solvent had evaporated, 5 cc. of toluene each was added after 18 and 22 hours respectively. After the termination of the reaction the solution was filtered from the Raney nickel and the latter washed with acetone. The filtrate was freed from solvents by first distilling it in an ordinary and finally in an oil-pump vacuum (bath temperature, 75°). The oily residue had a strong phenolic odor. The residue was dissolved in 200 cc. of redistilled ether and this solution washed with two 10-cc. portions of 2 *N* sodium hydroxide and six 5-cc. portions of water. After drying with sodium sulfate the ether solution was brought to dryness, eventually in an oil-pump vacuum. The residue was a slightly yellow clear resin which resisted attempts at crystallization, weight 0.498 g.

The residue was dissolved in a mixture of 20 cc. of benzene and 20 cc. of petroleum ether which was chromatographed over a column of 15 grams of alkali-free aluminum oxide[13] (diameter 2.5 cm.). The adsorbed material was eluted successively with 40-cc. portions of mixtures of benzene and petroleum ether (benzene content gradually increasing), benzene,

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[15] (11, page 523).

[16] The initial reaction was carried out by Miss V. I. Vivian.

[17] The Raney nickel was kindly supplied by Drs. E. C. Kleiderer and E. C. Kornfeld of the Eli Lilly & Co. Research Laboratories in Indianapolis. They had used it successfully to catalyze the conversion of dihydrocholesterol to cholestanone in the presence of cyclohexanone, (14). It was applied in our experiment about three weeks after its preparation.

mixtures of benzene and ether, (ether content gradually increasing), ether, mixtures of ether and chloroform (chloroform content gradually increasing), chloroform, mixtures of chloroform and methanol (methanol content gradually increasing), and finally methanol. A total of 0.495 g. was recovered. The major part of the material (0.430 g.) was contained in the eluates of benzene-petroleum ether, benzene, and benzene-ether. Though the residues were partly crystalline, apparently no efficient separation had been achieved. One of the chloroform-methanol (39:1) eluates furnished 7.1 mg. of a crystalline residue, which yielded needle-shaped crystals from acetone; m.p. 209–211°. They were not further investigated. The test with tetranitromethane yielded no yellow color. This substance gave a depression of the melting point when mixed with the compound interpreted to be ethyl 3-keto-5,19-dihydroxyetiocholanate (XIX).

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, G.	APPEARANCE OF RESIDUE
1	15 cc. of benzene + 25 cc. of petr. ether (original solution)	0.0047	Greasy
2	15 cc. of benzene + 25 cc. of petr. ether	.0361	Resinous
3	20 cc. of benzene + 20 cc. of petr. ether	.0601	Crystalline
4	20 cc. of benzene + 20 cc. of petr. ether	.0222	Crystalline
5	25 cc. of benzene + 15 cc. of petr. ether	.0207	Resinous
6	25 cc. of benzene + 15 cc. of petr. ether	.0295	Partly cryst., partly resinous
7	30 cc. of benzene + 10 cc. of petr. ether	.0361	Essentially crystalline
8	30 cc. of benzene + 10 cc. of petr. ether	.0204	Crystalline
9	35 cc. of benzene + 5 cc. of petr. ether	.0200	Essentially crystalline
10	35 cc. of benzene + 5 cc. of petr. ether	.0224	Few cryst. centers
11	40 cc. of benzene	.0104	Resinous
12	40 cc. of benzene	.0113	Resinous
13	38 cc. of benzene + 2 cc. of ether	.0166	Resinous
14	37 cc. of benzene + 3 cc. of ether	.0175	Partly cryst., partly resinous
15	36 cc. of benzene + 4 cc. of ether	.0147	Essentially crystalline
16	35 cc. of benzene + 5 cc. of ether	.0136	Partly cryst., partly resinous
17	34 cc. of benzene + 6 cc. of ether	.0132	Partly cryst., partly resinous
18	33 cc. of benzene + 7 cc. of ether	.0119	Partly cryst., partly resinous
19	32 cc. of benzene + 8 cc. of ether	.0106	Partly cryst., partly resinous
20	31 cc. of benzene + 9 cc. of ether	.0071	Partly cryst., partly resinous
21	30 cc. of benzene + 10 cc. of ether	.0053	Resinous
22–32	40 cc. of each of benzene-ether mixtures; ether content gradually increasing	.0160	Resinous
33	40 cc. of ether	.0023	Greasy
34–38	40 cc. of each of ether-methanol mixtures; methanol content gradually increasing	.0165	Resinous
39	40 cc. of methanol	.0090	Crystalline
Total		0.4482	

The major part of the material (0.430 g.) was subjected to a renewed chromatographic separation, for which it was dissolved in a mixture of 15 cc. of benzene and 25 cc. of petroleum ether. The solution was filtered through a column (diam. 25 mm.) of 14 g. of alkali-free aluminum oxide[13] within a period of 30 minutes. The eluates were passed through, each within about 15 minutes.

The chromatogram on page 281 suggested the presence of at least three different substances.

Compound $C_{22}H_{32}O_4$ (XXI)? Fractions 1 and 2 resisted attempts at crystallization. Fractions 3 and 4 were separately recrystallized by dissolving them in a small volume of ether to which petroleum ether was added. This caused the immediate separation of rosette arrangements of long, thin needles. Several crystalline fractions, totalling 30.6 mg., with melting points varying between 97 and 114°, were repeatedly recrystallized. Eventually five crystalline fractions resulted, totalling 17.6 mg. and melting between 111 and 116°. The determination of mixed melting points established the identity of these fractions and hence the combined material was subjected to a renewed recrystallization from equal amounts of ether and petroleum ether: 1st crop: wt., 10.6 mg., m.p. 115–116°. 2nd crop: wt., 1.3 mg., m.p. 111–113°. 3rd crop: wt., 0.9 mg., m.p. 114.5–115.5°. Total pure material, 12.8 mg. It is believed that the total yield may be somewhat increased by subjecting the mother liquors, including the chromatographic fractions 2 and 5, to a renewed chromatographic fractionation. The substance (1st crop) was transparent in the region between 200 and 300 mμ.[4] The test with tetranitromethane yielded no yellow color.

Anal. Calc'd for $C_{22}H_{32}O_4$ (360.25): C, 73.28; H, 8.95.
$C_{22}H_{34}O_4$ (362.27): C, 72.87; H, 9.46.
$C_{22}H_{36}O_4$ (364.28): C, 72.47; H, 9.96.
Found: C, 73.10; H, 8.98 (J.R.); C, 71.43; H, 8.72 (J.F.A.).

Molecular Weight (Cryoscopic):
Wt. of solvent (camphor): 4.080 mg., wt. of sample: 0.375 mg., K = 36.0°; Δt: 8.8°, mol. wt. 376 (J.R.).
Wt. of solvent (exaltone): 2.366 mg., wt. of sample: 0.184 mg., K = 21.0°; Δt: 4.8°, mol. wt. 340 (E.W.D.H.).
Wt. of solvent (exaltone): 1.045 mg., wt. of sample: 0.104 mg., K = 21.0°; Δt: 6.3°, mol. wt. 332 (E.W.D.H.).

Ethyl 3-hydroxy-$\Delta^{1;3;5;10}$*-estratriene-17-carboxylate* (XXII). The chromatographic fraction 5 resisted attempts at crystallization. Fractions 6 to 9 were separately recrystallized by dissolving them in a small amount of ether and adding about twice the volume of petroleum ether. This caused the separation of rosettes of stout needles. Eventually 10 crystalline fractions of identical material (mixed m.p.'s), totalling 48.9 mg. with melting points between 175 and 178° (solidification and remelting between 184 and 188°) were obtained. Recrystallization of 43.7 mg. of combined material from ether-petroleum ether furnished several fractions (total, 37.5 mg.) of clusters of stout rectangular crystals which melted between 176 and 178°, then solidified and remelted between 184 and 186°. A solution of the substance in chloroform yielded with tetranitromethane an orange color. For ultraviolet absorption spectrum see the theoretical part. $[\alpha]_D^{26.0}$ +97.0° (12.7 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +0.93°).

Anal. Calc'd for $C_{21}H_{28}O_3$ (328.22): C, 76.78; H, 8.60.
Found: C, 76.00; H, 8.38 (J.R.); C, 76.88; H, 8.33 (E.W.D.H.);
C, 76.71; H, 8.78 (J.F.A.).

Molecular Weight (Cryoscopic):
Wt. of solvent (camphor): 4.900 mg., wt. of sample: 0.453 mg., K = 36.0°; Δt = 10.0°, mol. wt. 332.8 (J.R.).
Wt. of solvent (exaltone): 1.910 mg., wt. of sample: 0.170 mg., K = 21.0°; Δt = 5.6°, mol. wt. 334 (E.W.D.H.).
Wt. of solvent (exaltone): 4.505 mg., wt. of sample: 0.414 mg., K = 21.0°; Δt = 5.9°, mol. wt. 327 (E.W.D.H.).

The mother liquors resulting from the purification of chromatographic fractions 6–9

were combined with fraction 10. On rechromatographing this material only an additional 2.6 mg. of pure ethyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate was obtained.

3-Hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XXIV). Ethyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (6 mg.), melting at 175–177° (184–188°), was dissolved in 0.6 cc. of 10% potassium hydroxide in methanol. After refluxing this mixture for four hours, 2 cc. of water was added, and the methanol removed *in vacuo*. The solution was thereafter acidified to Congo with conc'd hydrochloric acid, which produced a gelatinous precipitate. This was followed by extracting with four 5-cc. portions of ether and washing the combined ether extracts with 1 cc. of water, 2 cc. of *N* sodium carbonate, and two 1-cc. portions of water. After drying with sodium sulfate the ether phase yielded 0.9 mg. of neutral material. The carbonate phase including the aqueous washings was made acid to Congo with conc'd hydrochloric acid and the resulting precipitate brought into solution by extracting four times with 5 cc. of ether. The combined ether phases were washed three times with 1 cc. of water, dried with sodium sulfate, and brought to dryness. Thus 3.5 mg. of crystalline acid material resulted which was recrystallized from small amounts of ether; immediate crystallization of small cubes. First crop: 1.5 mg., m.p. 266–270° (turning dark brown). Second crop: 0.7 mg., m.p. 266–270° (turning dark brown). This substance did not give a depression of the melting point when it was mixed with another sample of 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid which was kindly furnished by Drs. C. Djerassi and C. R. Scholz (6).

Compound $C_{22}H_{34}O_4$ (XXIII). The chromatographic fractions 11 and 12 were not investigated; fraction 13 resisted attempts at crystallization. Fractions 14–20 yielded identical material which crystallized from ether in rosettes of long stout rectangular prisms. Eleven crystalline fractions, totalling 41.8 mg., had melting points between 134 and 137°. Six fractions, totalling 12.0 mg., yielded melting points between 128–133°. Renewed crystallization of either combined group raised the melting point to 136–137°. Rechromatographing of the combined mother liquors including the chromatographic fraction 13 will probably yield additional amounts of this material. The substance was transparent in the region between 200 and 300 mμ.[4] The test with tetranitromethane gave no yellow color. $[\alpha]_D^{26.6}$ +69.8° (7.4 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +0.39°)

Anal. Calc'd for $C_{22}H_{32}O_4$ (360.25): C, 73.28; H, 8.95.
$C_{22}H_{34}O_4$ (362.27): C, 72.87; H, 9.46.
$C_{22}H_{36}O_4$ (364.28): C, 72.47; H, 9.96.
Found: C, 73.38, H, 10.02 (J.F.A.); C, 72.67; H, 9.52 (J.R.); C, 72.93; H, 9.42 (E.W.D.H.).

Molecular Weight (Cryoscopic):
Wt. of solvent (camphor): 4.102 mg., wt. of sample: 0.385 mg., K = 36.0°; Δt = 10.9°, mol. wt. 310 (J.R.).
Wt. of solvent (exaltone): 2.414 mg., wt. of sample: 0.168 mg., K = 21.0°; Δt = 4.0°, mol. wt. 365 (E.W.D.H.).
Wt. of solvent (exaltone): 3.061 mg., wt. of sample: 0.391 mg., K = 21.0°; Δt = 7.6°, mol. wt. 353 (E.W.D.H.).

Acetylation: A solution of 8.6 mg. of the above substance in 0.25 cc. of pyridine and 0.25 cc. of acetic anhydride stood overnight at room temperature. After bringing it to dryness *in vacuo*, the ether solution of the residue was washed neutral with *N* hydrochloric acid and *N* sodium carbonate. After drying, the ether solution yielded 8.6 mg. of a resinous residue which resisted attempts at crystallization from various solvent combinations. To a solution of the residue in 1 cc. of ethanol was added 0.22 cc. of 0.1 *N* potassium hydroxide in ethanol (*i.e.* 1 equiv. KOH). After standing overnight at room temperature the mixture was made acid to litmus with glacial acetic acid. It was then brought to dryness *in vacuo*, the residue taken up in ether and washed neutral with *N* sodium carbonate. After drying, the ether solution yielded 7.3 mg. of a resinous residue which was recrystallized from ether, m.p. 134–136°; mixed m.p. with starting material, 136–137°.

Attempts at partial de-acetylation of ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate (XI).

(*a*) *Ethanolysis in the presence of 0.25 equiv. of potassium hydroxide.* To a solution of 116.1 mg. (0.25 millimole) of ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate in 10 cc. of absolute ethanol was added at 3° a total of 0.625 cc. of 0.1 *N* absol. alcoholic potassium hydroxide (0.0625 millimoles). After three-days standing at about 3°, the solution was made acid to litmus with acetic acid and then worked up in the customary fashion. Yield, 95.9 mg. (Calc'd for complete solvolysis, $C_{26}H_{40}O_7 \rightarrow C_{22}H_{36}O_5$: 95.1 mg.). Recrystallization furnished at least 88.5 mg. of pure ethyl 3(β),5,19-trihydroxyetiocholanate.

(*b*) *Ethanolysis in the presence of 1 equiv. of hydrogen chloride.* A solution of 92.9 mg. (0.2 millimole) of ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate in 2.0 cc. of 0.1 *N* absolute alcoholic hydrogen chloride (0.2 millimole) was prepared at room temperature and then allowed to stand in the refrigerator for 46 hours. The solution was quickly brought to dryness *in vacuo* (40°), the resinous residue taken up in ether, and the latter washed with sodium carbonate, and water. After drying and removal of the ether, 84.8 mg. of a glassy residue was obtained. (Calc'd for partial solvolysis: $C_{26}H_{40}O_7 \rightarrow C_{24}H_{38}O_6$: 84.4 mg.) When this material was chromatographed over aluminum oxide, two peaks of the chromatogram were observed. Approximately 36 mg. of crystalline material appeared in the earlier, *i.e.* less polar eluates. One fraction of the latter eluates (15 mg.) resisted all attempts at crystallization. The last eluates gave 29 mg. of crystalline residues. On purifying, the former crystalline material was identified as unchanged ethyl 3(β),19-diacetoxy-5-hydroxy-etiocholanate and the latter as ethyl 3(β),5,19-trihydroxyetiocholanate.

(*c*) *Hydrolysis in aqueous methanol in the presence of potassium bicarbonate.* To 100 mg. of ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate dissolved in 5 cc. of methanol was added a solution of 100 mg. of potassium bicarbonate in 2.5 cc. of water. After standing at room temperature (28.5°) for 21 hours, the mixture was concentrated to 1.2 cc. *in vacuo* and extracted with chloroform which was subsequently washed with water, dried, and evaporated. This furnished 84.6 mg. of a dry foam which yielded from acetone a total of 60.9 mg. of crystalline material, identified as ethyl 3(β),5,19-trihydroxyetiocholanate. The remaining 23.7 mg. of non-crystalline material furnished by chromatographic separation only 1.6 mg. of ethyl 3(β),5,19-trihydroxyetiocholanate and 1.8 mg. of a less polar, still impure, crystalline substance.

Ethyl 19-hemisuccinyloxy-3(β),5-dihydroxyetiocholanate (XXV) *and its methyl ester* (XXVI). To a solution of 250 mg. of succinic anhydride (Eastman Kodak, m.p. 118–119° in 1.35 cc. of pyridine was added 250 mg. of ethyl 3(β),5,19-trihydroxyetiocholanate. It was allowed to stand at room temperature (28°) for three hours, and was poured on ice, and the precipitate taken up in 50 cc. of ether which was washed with 20 cc. of cold 2 *N* hydrochloric acid, four portions of 1 cc. of water, 5 cc. of cold 10% potassium carbonate, and four times with 1 cc. of water. The ether was dried with sodium sulfate and brought to dryness; wt. of the crystalline residue 202.7 mg. (neutral). The carbonate extract including the subsequent aqueous washings were acidified with 4 cc. of cold 2 *N* hydrochloric acid. The turbid solution was extracted with three portions of 25 cc. of ether. The combined ether was washed five times with 1 cc. of water, dried, and evaporated to dryness; wt. 54.2 mg. (acid).

Recrystallization of the neutral part (202.7 mg.) gave 183.6 mg. of pure ethyl 3(β),5,19-trihydroxyetiocholanate. The acid fraction (54.2 mg.) was a brittle foam which resisted attempts at crystallization. It was transformed into the methyl ester by treating it with a slight excess of diazomethane; yield, 51.9 mg. of resinous methyl ester. It was chromatographed in a mixture of 3.5 cc. of benzene and 6.5 cc. of petroleum ether through a column of 2.0 g. of alkali-free aluminum oxide[13] (diam. 10 mm.). The eluting was done successively with 10-cc. portions of benzene-petroleum ether (benzene content gradually increasing) benzene, benzene-ether (ether content gradually increasing), ether, and ether-methanol (methanol content gradually increasing). The major part of the material (35.0 mg.) was eluted by solvent combinations containing 8 cc. of benzene + 2 cc. of ether and 6 cc. of benzene + 4 cc. of ether. Recrystallization of these fractions from a small volume of ether yielded 16.4 mg. of flat hexagonal crystals, m.p. 103°. The mother liquors were rechroma-

tographed and thus furnished an additional 3.1 mg. of material, m.p. 101.5–102.5° and 1.0 mg. of slightly less pure crystals, m.p. 99–100°. Total yield of pure crystalline ester, 20.5 mg. $[\alpha]_D^{24}$ +52.5° (5.3 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α +0.21°).

Anal. Calc'd for $C_{27}H_{42}O_8$ (494.33): C, 65.54; H, 8.56.
(Methyl ester of hemisuccinate)
$C_{32}H_{48}O_{11}$ (608.38): C, 63.12; H, 7.95.
(Dimethyl ester of dihemisuccinate)
Found: C, 65.94; H, 8.62 (E.W.D.H.).

Ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) *and ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate* (XXVIII).[18] A total of 760.6 mg. (2 millimoles) of ethyl 3(β),5,19-trihydroxyetiocholanate with melting points between 180 and 186° was dissolved in 8 cc. of anhydrous pyridine (distilled over BaO) to which was added 557.1 mg. (2 millimoles) of triphenylchloromethane (Eastman Kodak, m.p. 102–103°; checked by titration, 97.7% pure). The solution was heated on a steam-bath for 85 minutes and then allowed to stand at 23° for 16 hours. It was poured into 250 cc. of ice and water. After one hour, the white gummy precipitate was taken up in 100 cc. of ethyl acetate and the aqueous phase washed with eight portions of 25 cc. of ethyl acetate. The combined ethyl acetate extracts were successively washed with four portions of 25 cc. of *N* hydrochloric acid, two portions of 25 cc. of *N* sodium bicarbonate, and six portions of 3 cc. of water. After drying with sodium sulfate, the ethyl acetate was evaporated, the residue taken up in acetone and again brought to dryness *in vacuo*. In this fashion 1196 mg. of a brittle foam (theoretical, 1244 mg.) was obtained which was dissolved in a mixture of 10 cc. of ether and 10 cc. of petroleum ether. Overnight 59.9 mg. of clusters of crystals separated, m.p. 182–184°. There was no depression of the melting point when mixed with an authentic sample of ethyl 3(β),5,19-trihydroxyetiocholanate. The filtrate was brought to dryness *in vacuo* and thus yielded 1140 mg. of a white brittle foam. This residue was subjected to chromatographic adsorption in a mixture of 140 cc. of benzene and 60 cc. of petroleum ether. The solution was filtered through a column (diam. 22 mm.) of 45 g. of alkali-free aluminum oxide.[13] The original solution was passed through within 3½ hours, the following eluate within one hour, and all other eluates within about thirty minutes each.

The residue of fraction 1 yielded from ether mushroom-like arrangements of long thin needles, yield 80.0 mg., m.p. 155–166° (decomp.) (representing crude ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate; *vide infra*). An attempt was made to purify this substance further by subjecting the total of fraction 1 to a renewed chromatographic separation (*vide infra*).

Fraction 2 furnished from ether five crops of small cubic crystals; yield 80.6 mg., melting points between 154 and 162°. Fraction 3 gave only one crop of similar crystals; yield, 16.4 mg., m.p. 156–162°. All of these samples were identified as triphenylcarbinol. There was, however, a depression of the melting point, when triphenylcarbinol was mixed with the crystalline crop resulting from fraction 1. No crystalline material resulted from fraction 4.

Fractions 5 to 11 gave by separate treatment with ether thirteen crops of cubic or rectangular crystals; yield 416.3 mg., melting points between 177 and 183°. Mixed melting points within this whole series did not show a depression, (representing fairly pure ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate, *vide infra*). No crystals were secured from fractions 12–14.

By dissolving fractions 15–17 separately in acetone and concentrating to a small volume, six crops of prismatic crystals were obtained; yield 138.3 mg., melting points between 181 and 185°. There was no depression of the melting point of either crop with ethyl 3(β),5,19-trihydroxyetiocholanate.

Fractions 18–20 were not investigated. The following material was combined for a renewed chromatographic separation: the mother liquors of the various crystalline crops

[18] A preliminary tritylation experiment was carried out by Miss M. G. Conroy.

resulting from fractions 2–10 and fractions 15–17 and the residues of fractions 11–14; total 366.2 mg. The chromatographic scheme differed from the one given above in particular in that the number of the benzene-petroleum ether combinations was doubled. This was done with a view of obtaining additional amounts of the crystalline material which had resulted from the above chromatographic fractions 5–11 (*i.e.* ethyl 19-tritoxy-3 (β), 5-dihydroxyetiocholanate; *vide infra*). The renewed chromatographic treatment yielded only a trace of crystals identical with those which had been obtained from fraction 2 of the previous chromatogram. A total of 15.2 mg. was identified as pure triphenylcarbinol. Three crystalline crops, totalling 70.3 mg. were found identical with the material isolated from fractions 5–11 of the previous chromatogram (*i.e.* ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate; *vide infra*). Only 4.6 mg. of more ethyl 3(β),5,19-trihydroxyetiocholanate resulted from this renewed chromatographic separation.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE, MG.	APPEARANCE OF RESIDUE
1	140 cc. of benzene + 60 cc. of petr. ether (original solution)	88.9	Brittle foam
2	140 cc. of benzene + 60 cc. of petr. ether	143.4	Crystalline
3	160 cc. of benzene + 40 cc. of petr. ether	118.4	Brittle foam
4	170 cc. of benzene + 30 cc. of petr. ether	99.1	Brittle foam
5	180 cc. of benzene + 20 cc. of petr. ether	155.4	Partly cryst., partly foam
6	190 cc. of benzene + 10 cc. of petr. ether	127.4	Brittle foam
7	200 cc. of benzene	103.6	Brittle foam
8	200 cc. of benzene	74.8	Brittle foam
9	190 cc. of benzene + 10 cc. of ether	27.7	Brittle foam
10	175 cc. of benzene + 25 cc. of ether	14.6	Partly resin, partly foam
11	150 cc. of benzene + 50 cc. of ether	19.5	Partly resin, partly foam
12	100 cc. of benzene + 100 cc. of ether	5.9	Resinous
13	50 cc. of benzene + 150 cc. of ether	5.1	Resinous
14	200 cc. of ether	4.0	Resinous
15	200 cc. of ether + 1 cc. of methanol	17.2	Partly resin, partly cryst.
16	195 cc. of ether + 5 cc. of methanol	133.0	Crystalline
17	190 cc. of ether + 10 cc. of methanol	19.8	Crystalline
18	175 cc. of ether + 25 cc. of methanol	4.5	Partly resin, partly cryst.
19	150 cc. of ether + 50 cc. of methanol	3.0	Crystalline
20	200 cc. of methanol	29.1	Crystalline
Total		1194.4	

The total yields of the various groups of crystalline materials, as obtained from both chromatograms, were therefore as follows: (a) material later identified as ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate, 80.0 mg.; (b) triphenylcarbinol, 112.2 mg.; (c) material later identified as ethyl 19-tritoxy-3(β), 5-dihydroxyetiocholanate, 486.6 mg.; (d) ethyl 3(β),5,19-trihydroxyetiocholanate, 142.9 mg. (The total of the latter substance recovered was 202.8 mg.; *cf.* the material isolated before chromatography.).

Ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII). The combined crystalline material referred to under (c) was recrystallized once more from ether. The first crop represented 391.0 mg. of rectangular crystals, m.p. 179–183°. In addition 56.4 mg. of crystalline material, m.p. 176–179°, was obtained. $[\alpha]_D^{21.5}$ −16.0° (19.6 mg. in 2.0 cc. of chloroform; l = 1.51 dm., α −0.24°).

Anal. Calc'd for $C_{41}H_{50}O_5$ (622.39): C, 79.05; H, 8.10.

Found: C, 78.99, 79.10; H, 8.09, 8.03 (E.W.D.H.); C, 78.91; H, 8.05 (J.R.).

Ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate (XXVIII). With a view of purifying the material referred to under (a) the total of fraction 1 (88.9 mg.) of the above chromatogram was subjected to another chromatographic adsorption. To obtain an efficient separation, the number of the benzene-petroleum ether combinations was raised to twenty-one. The bulk of the material (67.2 mg.) came out in three adjoining eluates (3 cc. of benzene +12 cc. of petr. ether; 3 cc. of benzene + 12 cc. of petr. ether; 4 cc. of benzene + 11 cc. of petr. ether). Separate recrystallization of these three fractions from ether furnished four crops of crystals (total 55.5 mg.), mushroom-like arrangements of long thin needles. They were combined and again recrystallized from ether. First crop, 31.2 mg., m.p. 153–164° (decomp.). Second crop, 6.3 mg., m.p. 153–162° (decomp.). $[\alpha]_D^{23.5}$ +28.0° (20.8 mg. in 2.0 cc. of chloroform, l = 1.51 dm.; α +0.44°).

Anal. Calc'd for $C_{60}H_{64}O_5$ (864.50): C, 83.29; H, 7.46.

Found: C, 82.67; H, 7.77 (E.W.D.H.).

The above preparation of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate and ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate has been repeated with similar results on a somewhat larger scale (starting material, 1.39 g. of ethyl 3(β),5,19-trihydroxyetiocholanate).

Oxidation of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) *with chromic acid in glacial acetic acid.* A total of 62.2 mg. (0.1 millimole) of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate was dissolved in 2 cc. of glacial acetic acid. Immediately thereafter 5.5 cc. (the equiv. of 1.1 atoms of oxygen) of a solution of 133.4 mg. of chromium trioxide in 100 cc. of 95% acetic acid was added over a period of 75 minutes at room temperature. After standing overnight, 0.4 cc. of absolute ethanol was added and the solution brought to dryness *in vacuo*. In order to remove the acetic acid completely, the residue was taken up in absol. ethanol and this solution again brought to dryness. To the residue was added 2 cc. of water and 25 cc. of ether. The solution was washed with 2 cc. of *N* sulfuric acid, three times with small amounts of water, once with 1 cc. of *N* sodium carbonate, and four times with 1 cc. of water. After drying and evaporating the ether 53.4 mg. of a neutral residue was obtained. After the addition of some ice, the carbonate phase and the subsequent aqueous washings were acidified with 0.6 cc. of 4 *N* sulfuric acid and extracted four times with 15 cc. of ether. The combined ether extracts were washed with water, dried, and evaporated to dryness. Only a trace of acid material (4.3 mg.) was obtained. The neutral phase was purified by chromatography. From the early eluates (benzene-petr. ether) triphenylcarbinol was isolated. From the later eluates (benzene-ether) several crystalline, but non-identical fractions resulted. One of them had the melting point 202–210°; it did not show a depression of the m.p. when mixed with the compound interpreted to be ethyl 3-keto-5,19-dihydroxyetiocholanate which had been obtained by the partial oxidation of ethyl 3(β),5,19-trihydroxyetiocholanate with chromic acid (*vide supra*).

Cleavage of the ether linkage of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII). To a solution of 31.1 mg. (0.05 millimole) of the 19-trityl ether in 1 cc. of glacial acetic acid was added 2.75 cc. of 95% acetic acid and the mixture allowed to stand at 27° for 24 hours (1st experiment) and one hour (2nd experiment) respectively. The solution was quickly brought to dryness *in vacuo* (50°), the residue taken up in ethanol, and this solution again evaporated *in vacuo*. This treatment was repeated until the odor of acetic acid had disappeared. The crystalline residue was dissolved in 15 cc. of ether and this solution successively washed once with 1 cc. of *N* sulfuric acid, four times with 0.5 cc. of *N* sodium carbonate, and four times with 0.5 cc. of water. After drying with sodium sulfate the ether solu-

tion was evaporated to dryness. The residue, weighing 28.4 mg. (1st expt.) and 29.5 mg. (2nd expt.) respectively, was recrystallized from a small amount of ether which furnished 8.5 mg. (1st expt.) and 9.4 mg. (2nd expt.) of not quite pure ethyl 3(β),5,19-trihydroxyetiocholanate. The remainder in each experiment was subjected to chromatographic adsorption. The scheme of the chromatogram was analogous to the one given in the preparation of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (*vide supra*). In either experiment only triphenylcarbinol and additional amounts of ethyl 3(β),5,19-trihydroxyetiocholanate resulted. No unchanged ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate was isolated.

Cleavage of the ether linkages of ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate (XXVIII). To a solution of 171.6 mg. (~0.2 millimole) of fairly pure 3(β),19-dityityl ether in 5.5 cc. of glacial acetic acid was added 15.1 cc. of 95% acetic acid. After standing at room temperature (30°) for a period of seven hours, the mixture was quickly brought to dryness *in vacuo*. The residue was dissolved in ethanol and evaporated *in vacuo*. This treatment was repeated several times until no more odor of acetic acid was noticeable. The residue was taken up with 5 cc. of water and 75 cc. of ether. The ether was washed with 6 cc. of *N* sulfuric acid, 4 cc. of *N* sodium carbonate, and four portions of 2 cc. of water, dried with sodium sulfate, and evaporated to dryness; wt. of the crystalline residue 156.1 mg. The chromatographic purification (*vide supra*) yielded from the early eluates (benzene-petroleum ether) triphenylcarbinol and from the late eluates (benzene-ether and ether-methanol) ethyl 3(β),5,19-trihydroxyetiocholanate. There was no indication of the presence of any other substance.

Ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate (XXIX). To a solution of 62.2 mg. (0.1 millimole) of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate in 1 cc. of pyridine was added 1 cc. of acetic anhydride and the mixture allowed to stand at room temperature (27°) for about 22 hours. It was brought to dryness *in vacuo*, the resinous residue dissolved in 75 cc. of ether and washed twice with 2 cc. of *N* hydrochloric acid, four times with 1 cc. of *N* sodium carbonate, and five times with 3 cc. of water. After drying with sodium sulfate and evaporating the ether 65.0 mg. of a brittle foam was obtained which resisted attempts at crystallization. In order to assure the uniformity of this material, 26.5 milligrams was chromatographed through 1 gram of alkali-free aluminum oxide[13] (diam. of column 10 mm.). The major part of the material (24.6 mg.) was recovered from the earliest eluates, varying from 2 cc. of benzene + 8 cc. of petr. ether to 3.5 cc. of benzene + 6.5 cc. of petr. ether. The chromatogram demonstrated, therefore, that in accordance with expectation, the acetylation had resulted in a decrease of polarity. The residues isolated from these early eluates still resisted attempts at crystallization. They were eventually combined. It is realized that the figures recorded for the optical rotation are of limited value. $[\alpha]_D^{23}$ +20.2° (19.8 mg. in 2.0 cc. of chloroform, l = 1.51 dm., α +0.30°).

Anal. Calc'd for $C_{43}H_{52}O_6$ (664.41): C, 77.66; H, 7.89.
Found: C, 76.27; H, 8.13 (J.R.).

Deacetylation of ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate (XXIX). To a solution of 10.2 mg. of 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate in 10 cc. of absol. ethanol was added 0.16 cc. of an absolute alcoholic solution of 0.1 *N* potassium hydroxide (1 equiv. of KOH). The mixture was allowed to stand at room temperature for 23 hours. The still alkaline solution was made slightly acid with one droplet of glacial acetic acid and then brought to dryness *in vacuo*. The residue was taken up in 30 cc. of ether and washed once with 0.5 cc. of *N* sodium carbonate and with six 0.5-cc. portions of water. After drying with sodium sulfate the ether phase was evaporated. On recrystallizing the residue from ether, 6.2 mg. of crystalline material was obtained, m.p. 177–179°; no depression of m.p. with ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate.

Ethyl 3(β)-acetoxy-5,19-dihydroxyetiocholanate (XXX) *by cleavage of the ether linkage of ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate* (XXIX). To a solution of 65.0 mg. of ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate in 2.0 cc. of glacial acetic acid was added 5.5 cc. of 95% acetic acid and the mixture allowed to stand at room temperature (29°) for two hours. It was brought to dryness *in vacuo* (50–55°) and the residue taken up in ethanol which was subsequently evaporated. This treatment was repeated several

times in order to remove all traces of acetic acid. The residue was taken up in 25 cc. of ether and washed with 2 cc. of *N* sulfuric acid, with four 1-cc. portions of *N* sodium carbonate, and with four 1-cc. portions of water. After drying and evaporating the ether, 61.0 mg. of a residue was obtained. No attempt at fractional crystallization was undertaken. This material was chromatographed in a mixture of 5 cc. of benzene and 20 cc. of petroleum ether through a column (diam. 10 mm.) of 4.0 g. of alkali-free aluminum oxide[13] within a period of about one hour. The eluants (25 cc. each) were passed through at the rate of approx. fifteen minutes. A substantial amount of material (21.3 mg.) was obtained from the second and third eluate (ratio, 10 cc. of benzene + 15 cc. of petr. ether). After recrystallization it was identified as triphenylcarbinol. Only traces of residues were secured from the eluates 4–7. Substantial quantities (total 34.2 mg.) were isolated from the eluates 8–14 (ratios, 20 cc. of benzene + 5 cc. of petr. ether; 25 cc. of benzene; 20 cc. of benzene + 5 cc. of ether; and 15 cc. of benzene + 10 cc. of ether). These residues were first separately recrystallized from ether. This furnished 25 crops of long thin rectangular crystals; total 29.2 mg., melting points between 150 and 153°. There were no depressions of the melting points within this whole series. All crystalline crops were therefore combined and recrystallized once more from ether; rosettes of short fine needles, wt. of first crop 14.0 mg., m.p. 149–152°. Additional crystalline crops of identical material were secured from the mother liquor. $[\alpha]_D^{20}$ +50.7° (12.8 mg. in 2.0 cc. of chloroform, l = 1.51 dm., α +0.49°).

Anal. Calc'd for $C_{24}H_{38}O_6$ (422.30): C, 68.20; H, 9.07.
Found: C, 68.30; H, 9.01 (E.W.D.H.).

In another experiment, carried out in the same fashion, the cleavage of the trityl ether linkage did not go to completion. In order to be safe, it is recommended, therefore, to perform the cleavage over 24 hours rather than two hours as stated above.[19]

3(β)-Acetoxy-5-hydroxy-21-norpregnane-19,20-dioic acid 20-ethyl ester,[8] (XXXI) *by oxidation with chromic acid of ethyl 3(β)-acetoxy-5,19-dihydroxyetiocholanate* (XXX). To a solution of 35.2 mg. of ethyl 3(β)-acetoxy-5,19-dihydroxyetiocholanate in 2.0 cc. of glacial acetic acid was added at room temperature within a period of 20 minutes, a total of 2.5 cc. (the equiv. of 2.2 atoms of oxygen) of a solution of 136 mg. of chromium trioxide in 25 cc. of 95% acetic acid. The mixture appeared green after the addition of 2.0 cc. of the chromium trioxide solution, but stayed brown after the total of 2.5 cc. had been added. After standing overnight 0.5 cc. of ethanol was added and the mixture brought to dryness *in vacuo.* In order to remove the last traces of acetic acid the residue was repeatedly taken up in ethanol and brought to dryness. Finally 2 cc. of water was added and the resulting precipitate taken up in 25 cc. of ether. The ether was washed successively with 2 cc. of *N* sulfuric acid, small amounts of water, 1 cc. of *N* sodium carbonate, and four 1-cc. portions of water. After drying and evaporating the ether, 14.1 mg. of a resinous neutral residue was obtained. In contradistinction to the starting material it did not crystallize from ether. The carbonate phase, including the subsequent aqueous washings, was cooled with ice, acidified with 1 cc. of 4 *N* sulfuric acid, and extracted with four 15-cc. portions of ether. The combined ether extracts were washed with eight 1-cc. portions of water, dried, and evaporated *in vacuo*; wt. of the acid residue 15.2 mg. On adding ether immediate crystallization of clusters of small rectangles occurred. First crop: wt. 2.2 mg., m.p. 206–212° (decomp.). Second crop: wt. 4.3 mg., m.p. 207.5–209° (decomp.). Third crop: wt. 2.2 mg., m.p. 203–204° (decomp.). These three crystalline fractions were combined and recrystallized once more from ether; rosettes of long thin needles, wt. 6.3 mg., m.p. 206–210° (decomp.). $[\alpha]_D^{24.5}$ +65.7° (22.45 mg. in 2.0 cc. of chloroform, l = 1.51 dm., α +1.11°).

Anal. Calc'd for $C_{24}H_{36}O_7$ (436.28): C, 66.01; H, 8.32.
Found: C, 66.14; H, 8.28 (E.W.D.H.).

A reoxidation of the neutral fraction (14.1 mg.) under analogous conditions yielded 8.0 mg. of neutral and 2.8 mg. of acid material. Both residues refused to crystallize.

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[19] In an additional experiment hydrolysis (20 hours) of 499.4 mg. of XXIX gave 269.5 mg. (85.0%) of pure XXX; m.p. 154–156° (decomp.)

SUMMARY

1. The process of making ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) from strophanthidin (I) has been revised and simplified. A detailed description of the preparation of the crystalline intermediate ethyl 3(β),5,19-trihydroxy-Δ^{14}-etiocholenate (VI) and its diacetyl derivative (VII) is given.

2. Ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate (XI) can be distilled in a high-vacuum without decomposition. On subjecting the corresponding free acid, 3(β),19-diacetoxy-5-hydroxyetiocholanic acid (X), to the same treatment, a mixture of substances resulted in which probably 3(β),19-diacetoxy-Δ^{5}-etiocholenic acid (XIV) is present. It was characterized by the crystalline methyl ester XV. Part of the material (X) is probably aromatized to 3-acetoxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XVI). This was characterized by transforming it into the methyl ester XVII which was hydrolyzed to methyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XVIII). The latter was compared with an authentic sample (6).

3 A partial oxidation of ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) with chromic acid in a solution of acetic acid led to a mixture of substances from which two compounds have been isolated in a pure crystalline form. One of them is probably ethyl 3-keto-5,19-dihydroxyetiocholanate (XIX).[20]

4. Contrary to expectations ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) could not be made to undergo the Oppenauer reaction.

5. On treating ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) with Raney nickel and cyclohexanone under mild conditions, a mixture of substances resulted from which three different compounds were isolated in a pure crystalline form. One of them was found to be ethyl 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylate (XXII). It was saponified to 3-hydroxy-$\Delta^{1;3;5,10}$-estratriene-17-carboxylic acid (XXIV). The latter was compared with a sample of the same substance as prepared from cholesterol (6). A correlation has been established between the cardiac aglycones and the estrogenic hormones. Both, XXII and XXIV possess no significant estrogenic activity.

6. Attempts to subject ethyl 3(β),19-diacetoxy-5-hydroxyetiocholanate (XI) to a partial deacetylation failed.

7. A partial succinylation of ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) yielded the monohemisuccinate XXV which was characterized by the crystalline methyl ester XXVI.

8. By tritylation, ethyl 3(β),5,19-trihydroxyetiocholanate (VIII) was converted into ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) as main product and ethyl 3(β),19-ditritoxy-5-hydroxyetiocholanate (XXVIII) as by-product. In an acid medium both of these trityl ethers are easily hydrolyzed to VIII. Acetylation of ethyl 19-tritoxy-3(β),5-dihydroxyetiocholanate (XXVII) yielded the resinous ethyl 3(β)-acetoxy-19-tritoxy-5-hydroxyetiocholanate (XX-

[20] (Addition to proof, February 10, 1950). Recent experiments by Mary A. Wagner indicate that the compound to which was assigned the structure of ethyl 3-keto-5,19-dihydroxyetiocholanate (XIX) is actually ethyl 19-oxo-3(β),5-dihydroxyetiocholanate. Details will be published shortly.

IX) which by alkaline solvolysis was reconverted into XXVII. Acid hydrolysis of XXIX gave ethyl 3(β)-acetoxy-5,19-dihydroxyetiocholanate (XXX). The latter was oxidized with chromic acid to 3(β)-acetoxy-5-hydroxy-21-norpregnane-19,20-dioic acid 20-ethyl ester (XXXI).[8]

PHILADELPHIA 4, PA.

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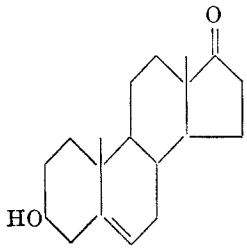
[CONTRIBUTION FROM THE CHEMICAL RESEARCH DIVISION OF SCHERING CORPORATION]

SYNTHESIS OF ESTRONE FROM ANDROSTADIENEDIONE

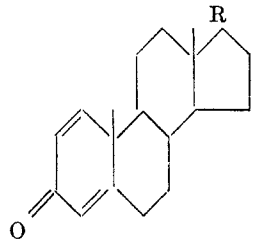
E. B. HERSHBERG, MARTIN RUBIN[1], AND ERWIN SCHWENK

Received August 11, 1949

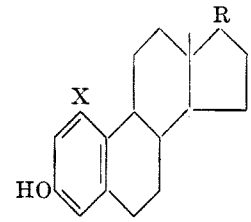
Inhoffen (1) was the first to convert the A-ring of the sterol skeleton into an aromatic structure. He developed methods (2, 3, 4, 5, 6, 7, 8) for obtaining the quinonoid structure II from a steroid I, and showed that it can be converted by pyrolysis or by rearrangement under the influence of sulfuric acid into the aromatic structure III.



I



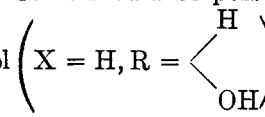
II



III

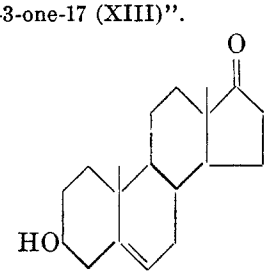
X = H, CH_3

R = O,  , 

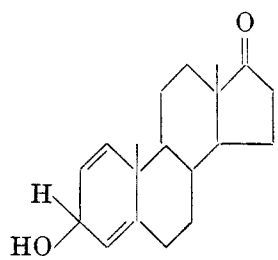
By appropriate choice of the starting material it should be possible to obtain either estrone, (X = H, R = O), or estradiol  It is therefore significant that the preparation of estrone is not described in either the scientific or patent literature on the aromatization process.[2]

[1] Present Address: Georgetown University, Department of Pathology, Washington, D. C.

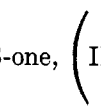
[2] Considerable amounts of estrone are said to have been made on a commercial scale by a process outlined in a report (8) by Allied investigators of German industry. This report is obviously incorrect in some of its statements. For example, it is stated that "dehydroisoandrosterone (I) is monobrominated and hydrogen bromide removed to yield $\Delta^{1,4}$-androstadiene-ol-3-one-17 (XIII)".



I

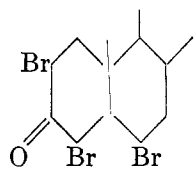


XIII

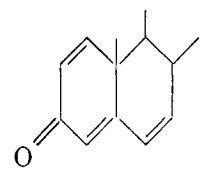
The conversion of dehydroepiandrosterone[3] (I) into estradiol through $\Delta^{1,4}$-androstadien-17-ol-3-one, (II, R = ), is reported by Inhoffen and Zuehlsdorff (7) and their findings have been confirmed by Wilds and Djerassi (14). From $\Delta^{1,4}$-androstadiene-3,17-dione, (II, R = O), Inhoffen (1) obtained instead of estrone a new compound which he characterised as an isoequilin by its analysis and its absorption in the ultraviolet region. The experiments reported in this paper, on the contrary, gave a good yield of estrone from this same starting material.

When the experiment described by Inhoffen (15) was repeated with only two deviations from his procedure no isoequilin was obtained, but instead a mixture of estrone and 1-methylestrone. The differences were that purified $\Delta^{1,4}$-androstadiene-3,17-dione was used as a starting material instead of the crude bromine-containing preparation used by Inhoffen, and the total crude phenolic fraction was benzoylated and submitted to a chromatographic separation instead of relying on crystallization alone for purification of the reaction product. Inhoffen's isoequilin may have been derived from one or the other of the impurities in his starting material.

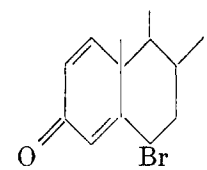
Djerassi and Scholz (18) have found that tribromides are formed in the dibromination of androstan-3,17-dione. Thus, 2,4,6-tribromoandrostan-3,17-dione, (IV), one possible isomer, would lead to a triene, (V), or to a monobromodiene, (VI), upon dehydrobromination, and either of these might form isoequilin upon aromatization.



IV



V



VI

$\Delta^{1,4}$-Androstadiene-3,17-dione, the starting material for the estrone preparation, was made by Inhoffen, Zuehlsdorff, and Huang-Minlon (5) by the Oppenauer oxidation of $\Delta^{1,4}$-androstadiene-17-ol-3-one, and they reported a melting point of 139–140°. The substance with a melting point of 168° assigned the same structure by Fujii and Matsukawa (16) has been found by repetition of

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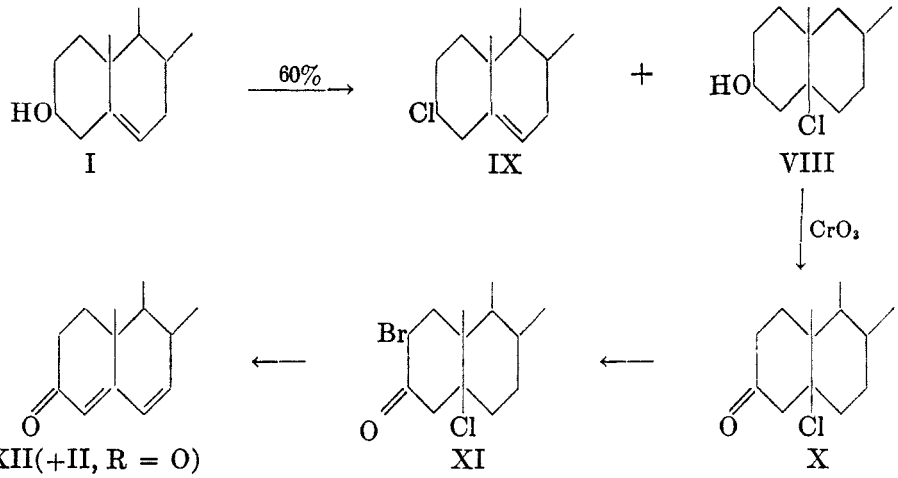
This unlikely monobromination reaction has not been described elsewhere in the chemical literature. [Compare, however, (10) page 77, paragraphs 4 and 5 which may be the source of the above mentioned report]. In neither of his two reviews on the subject (11, 12) does Inhoffen mention the use of this dieneolone to obtain estrone. Compound XIII is described (13) in a U. S. patent, granted to Schoeller, Serini, and Inhoffen. In his second review, Inhoffen reported that estrone was obtained as a by-product in the preparation of estradiol, without, however, giving any experimental details. Compare also Ref. (7), footnote 5, page 1914.

[3] We are here following the new nomenclature adopted by Professor and Mrs. Fieser in their monograph (23).

their experiments to be a mixture of dienediones containing only about half of the desired isomer.

When hydrogen chloride was added to the double bond of dehydroepiandrosterone, (I), only about 60% of the desired addition product 5-chloroandrostan-3-ol-17-one, (VIII), was obtained. From the mother liquors were isolated both unchanged starting material and 3-chloro-Δ^5-androsten-17-one (IX). Upon chromic acid oxidation, VIII was converted into 5-chloroandrostan-3,17-dione, (X), which was unstable when heated in solution. The bromination of X introduced one bromine atom and gave an equally unstable chlorobromandrostan-3,17-dione whose probable structure is XI. Dehydrohalogenation of this compound with collidine eliminated both the chlorine and the bromine and gave a mixture of $\Delta^{1,4}$- and $\Delta^{4,6}$-androstadiene-3,17-diones (II, R = O and XII), which could not be separated by crystallization. The ultraviolet spectrum of this mixture showed maxima at wavelengths characteristic for the two unsaturated ketones, and from the extinction coefficients it was estimated that each component formed about half of the mixture.



A quantity of $\Delta^{1,4}$-androstadiene-3,17-dione was prepared by the method first outlined by Inhoffen (1, 17) and described in greater detail by Djerassi and Scholz (18).

Several methods have been used to carry out the aromatization reaction such as heating the androstadienedione in a carbon dioxide atmosphere (15), heating in an evacuated tube with or without solvent (7, 19), and continuous flow through a heated tube in the presence of a solvent with and without a catalyst (10, 17). Both cyclohexane (17) and tetralin (10, p. 79) have been used as carrier-solvents. In the experiments reported here the $\Delta^{1,4}$-androstadienedione was dissolved in mineral oil and the contact time in the furnace was adjusted to the optimum value by changes in the concentration of this solution. Estrone was obtained in yields of 15–20 per cent by carrying out the aromatization in an electrically-heated glass tube filled with glass beads.

The standards of purity for estrone prescribed by the United States Pharmacopeia are based upon material obtained from natural sources. Estrone obtained from equine urine is accompanied by varying amounts of equilin $[\alpha]_D$ +308°, and equilenin $[\alpha]_D$ +87°, both of which are difficult to eliminate from the finished product. Substantial amounts of these closely related estrogens may be present in commercial estrone and the product will still meet the U.S.P. specifications for optical rotation, since the high rotation of the former will offset the low rotation of the latter. In order to determine the physical constants of estrone free from these impurities, a sample of the synthetic material was crystallized to constant rotation. The melting point was still broad due to the polymorphism of estrone (22).

ACKNOWLEDGEMENT

We are glad to acknowledge the skillful assistance of Miss Jean Scholler and Mr. John Mentha. For microanalyses, optical rotations, and the measurement of absorption spectra we are indebted to Mr. Edwin Conner, Miss Betty Blasko, and Mrs. Alice Barrella of the Micro Analytical Department of this laboratory.

EXPERIMENTAL[4]

Addition of hydrogen chloride to dehydroepiandrosterone. 5-Chloroandrostan-3-ol-17-one was prepared by dissolving 12 g. of dehydroepiandrosterone in chloroform and saturating the solution with hydrogen chloride while cooling in a Dry Ice-acetone bath. Upon standing 48 hours at 25°, a crystalline solid separated. When collected, washed with chloroform saturated with hydrogen chloride, and dried *in vacuo* over barium oxide, it weighed 6.9 g. A second crop of 1.45 g. was collected after the mother liquor had stood at room temperature for another 48-hour period (total 8.3 g., 60%). The crude product thus obtained from the solution was a loose solvate with chloroform and possibly with hydrogen chloride (1.65 g. lost 0.45 g. upon 5-hours drying in a vacuum). Recrystallization of 6.9 g. of crude chloro compound from chloroform-hexane resulted in some initial loss of hydrogen chloride and gave two crops totaling 5.5 g., m.p. 170–172.5°. A sample recrystallized several times from ether melted at 171.5–172.5° dec. $[\alpha]_D$ +62.4°. Fujii and Matsukawa (16) report the melting point 160° with decomposition, while Ruzicka, Fischer, and Megu (20) report 156–157°:

Anal. Calc'd for $C_{19}H_{29}ClO_2$: Cl, 10.9. Found: Cl, 11.1.

The material in the chloroform mother liquor was chromatographed on alumina (Brockmann) and gave two principal fractions upon elution with successive portions of petroleum ether, ether, ether-benzene (1:1), and benzene. The ether extract gave a product m.p. 135–145° which after three crystallizations from acetone melted at 155.5–156.5°, $[\alpha]_D$ +13.5°.

Anal. Calc'd for $C_{19}H_{27}ClO$: C, 74.36; H, 8.87; Cl, 11.56.
Found: C, 74.72; H, 8.89; Cl, 11.18.

Dr. Oliveto of this laboratory compared this compound by mixture melting point with 3-chloro-Δ^5-androsten-17-one prepared by the action of phosphorus pentachloride on dehydroepiandrosterone and found the two substances to be identical.

The ether-benzene extract gave dehydroepiandrosterone, m.p. 145.5–147.5° identified by mixture melting point with authentic material.

Oxidation of 5-chloroandrostan-3-ol-17-one to 5-chloroandrostan-3,17-dione. A solution of 2.38 g. of 5-chloroandrostan-3-ol-17-one was prepared by warming with 15 ml. of ethylene

[4] All melting points were determined on Anschütz thermometers using total thread immersion. Unless otherwise noted the rotations were determined in dioxane solution with a 1-dcm., 1-ml. capacity tube with 25.0° thermostatically controlled water flowing through the jacket of the tube. The probable precision is approximately ±1° unless specified otherwise.

chloride to 40–50°, then cooling to room temperature and diluting with 20 ml. of acetic acid. To this was added dropwise and with shaking over a 30-min. period a solution of 0.54 g. of chromic acid dissolved in 1 ml. of water and diluted with 30 ml. of acetic acid. The deep reddish-purple solution stood for 2.5 hours and to it was added slowly and with shaking 25 ml. of water. The ethylene chloride was removed at the water pump without applying heat and crystals of the ketone separated. More water was added slowly until, when a total of 50 ml. had been added, most of the ketone had crystallized. After drying at room temperature there was obtained 2.19 g. (92%) of 5-chloroandrostanedione. Apparently unnoticed by Fujii and Matsukawa (16), the compound melted with decomposition considerably below the melting point they reported. When immersed in a rapidly heated melting point bath (10°/min.) it melted with evolution of gas at 102–104° (inserted at 98°) then solidified and remelted at 155–166°.

The decomposition was very rapid and the upper melting point in the case of purified material approached that of Δ^4-androstene-3,17-dione (m.p. 173°). The initial decomposition point was dependent upon the temperature at immersion. For example, when the sample was immersed at 90°, it melted at 99–100°, while upon immersion at 110° it melted at 112°. A small portion was recrystallized by dissolving it in a minimum volume of chloroform at room temperature, adding pentane, and cooling in the refrigerator. It crystallized in clusters of flat needles which melted with gas evolution at 99–102°, solidified and then remelted at 160–167°. Fujii and Matsukawa (16) give the melting point 179° with decomposition. The chloroketone was extremely unstable and decomposed readily in warm solutions. Even at room temperature a chloroform solution instantly evolved hydrogen chloride upon treatment with Darco decolorizing charcoal.

Anal. Calc'd for $C_{19}H_{27}ClO_2$: Cl, 10.98. Found: Cl, 10.68, 10.85.

Bromination of 5-chloroandrostane-3,17-dione and dehydrohalogenation of the product. To a solution of 0.83 g. of chloroketone dissolved in 10 ml. of chloroform was added dropwise 0.44 g. of bromine dissolved in 15 ml. of chloroform. After a short induction period the bromine color was instantaneously discharged. The chloroform solution was concentrated to a small volume and 3 ml. of 2,4,6-collidine was added. All of the chloroform was distilled and the collidine solution was refluxed for 1 hr. The solution was cooled, diluted with ether, and extracted with dilute sulfuric acid and with sodium carbonate solution. Evaporation of the dried ethereal solution left a crystalline residue which after four recrystallizations from acetone-ligroin and from ether gave pale yellow prisms which melted at 161–163°. A solution of 2.106 mg. of this product dissolved in 100 cc. of isoöctane showed two absorption maxima in the ultraviolet region. One at 231 mμ, ϵ = 8700, was at the same wavelength as that of $\Delta^{1,4}$-androstadiene-3,17-dione, while the other at 269 mμ, ϵ = 10,300, coincided with that of $\Delta^{4,6}$-androstadiene-3,17-dione. From these data it would appear that each was present in approximately equimolecular amounts since the molar extinction coefficients, ϵ, are 15,600 and 26,200 respectively.

Abnormal dehydrobromination of 2,4-dibromoandrostan-3,17-dione in the presence of sodium iodide and butanol. At one time it was believed that the dehydrobromination of 2,4-dibromoandrostandione with γ-collidine could be aided by the addition of sodium iodide and butanol in order to first effect an exchange of the bromine atoms by iodine. The product obtained from this reaction was a mixture from which only androstan-3,17-dione and Δ^4-androsten-3,17-dione were isolated. A similar replacement of bromine by hydrogen has been observed by Schwenk and Whitman (21) but it appears that the sodium iodide increases the reducing effect to a considerable degree.

To a hot solution of 4 g. of sodium iodide in 15 ml. of 2,4,6-collidine and 1.5 ml. of butanol was added 3 g. of purified dibromoandrostandione (m.p. 194–200° dec., inserted at 190° and heated 4°/min.). The temperature of the solution was held at 130° for one hour whereupon collidine hydrobromide separated. After cooling and adding ether the collidine was extracted with dilute sulfuric acid and the neutral ethereal solution was dried over sodium sulfate and evaporated to dryness. A dark brown resin (1.8 to 2 g.) remained which usually crystallized upon short standing. Upon recrystallization from ether there was obtained a

yellow crystalline product melting at 156–168°. The melting point of this material was sharply depressed upon admixture with $\Delta^{1,4}$-androstadiene-3,17-dione. Its absorption in the ultraviolet in isoöctane solution showed a strong peak at 230–232 mμ characteristic of $\Delta^{1,4}$-androstadiene-3,17-dione or of Δ^{4}-androstene-3,17-dione and a weak band at 269–273 mμ.

The products from several such runs totaling 8.15 g. were combined and chromatographed upon alumina using (A) petroleum ether; (B) petroleum ether-benzene (75/25); (C) petroleum ether-benzene (50/50); (D) petroleum ether-benzene (25/75); (E) benzene; and (F) benzene-ether (75/25).

The product split into two principal fractions, A and CD. From a 1.5-g. portion of (2.74 g.) fraction A, there was obtained after three crystallizations from ether 0.71 g. of colorless flat blades of androstan-3,17-dione, m.p. 133.3–133.9°.

Anal. Calc'd for $C_{19}H_{28}O_2$: C, 79.12; H, 9.78.
Found: C, 78.97; H, 10.01.

Mixture melting point with authentic material was unchanged. Fractions C and D (1.07 g.) were combined and recrystallized from ether (Darco) and gave 0.49 g. of yellow prisms. After three more recrystallizations from ether there were obtained cream-colored prisms of androstene-3,17-dione, m.p. 170.0–171.4°, unchanged upon admixture with authentic material.

Anal. Calc'd for $C_{19}H_{26}O_2$: C, 79.61; H, 9.09.
Found: C, 79.39; H, 9.23.

Pyrolysis of $\Delta^{1,4}$-androstadiene-3,17-dione by the procedure of Inhoffen (15). Two 5-g. portions of androstadienedione, m.p. 138–140° were separately heated in a flask immersed in a molten metal-bath. Carbon dioxide gas was passed through the flask during the pyrolysis and the gaseous products of the thermal cracking were collected over 50% potassium hydroxide solution. At 300–310°, the temperature used by Inhoffen, the decomposition was very slow. With increasing temperature it accelerated until at 340–350° it was complete in 15–20 min. Each portion produced about 85 cc. of gas.

The resinous product remaining in the flask from each of the two pyrolyses was dissolved in a small volume of acetone and then extracted with ether. This reprecipitated much of the resin. After three such treatments with acetone followed by ether extraction the ether solutions were combined and exhaustively extracted with 5% sodium hydroxide solution until upon acidification of the last alkaline extract with dilute hydrochloric acid no further precipitate of acidic material was obtained.

The acidic product which precipitated was allowed to stand for several hours to coagulate and then collected and dried. It weighed 2.5 g. and was dark brown and amorphous in appearance. This product was then benzoylated in 15 cc. of pyridine with 3 cc. of benzoyl chloride by warming to 70° for three hours. After pouring onto ice the mixture was allowed to remain overnight to decompose the benzoyl chloride, and the aqueous layer was decanted from the dark brown resin which was then washed with water by decantation. The resin was taken up in ether, extracted with sodium carbonate solution and the dried ethereal solution adsorbed upon a chromatographic column consisting of 150 g. of a mixture of magnesium silicate and Celite (2:1) topped with a layer of sand. Development of the column gave two principal fractions with ether. Upon evaporation of the first fraction a resinous residue remained which formed a cheeselike solid after standing overnight with a little ether. By triturating with ether, filtering and washing with ether, there was obtained 0.75 g. of white solid, m.p. 165–175°. As described below, this mixture was eventually separated into two products, *estrone benzoate*, and *1-methylestrone benzoate*, while the second principal fraction (0.3 g. of resin) upon sublimation gave only benzoic acid as an identifiable product.

Rechromatography of the first mixture did not effect a further separation and it was found that the mixture was better separated by fractional crystallization. The less soluble component, (0.26 g., m.p. 210–218.5°) identified as estrone benzoate gave after four recrystallizations from acetone 90 mg. of thick, colorless prisms, m.p. 218.5–222°, $[\alpha]_{646}$ + 131.4°, $[\alpha]_{589}$ + 111.3°, $[\alpha]_{643}$ + 80.6° (14.42 mg./ml.).

A mixture melting point with an authentic sample of estrone benzoate (m.p. 218.4-

222.5°) was unchanged. The rotation of this sample of estrone benzoate at the same three wavelengths and concentration was: $[\alpha]_{546}$ + 133.0°, $[\alpha]_{589}$ + 112.1°, $[\alpha]_{643}$ + 80.3° (14.38 mg./ml.).

From the mother liquors left after the crystallization of the estrone benzoate there was obtained 40 mg. of pearly white leaflets after two crystallizations from acetone and two from hexane-acetone. M.p. 236–238.5°, $[\alpha]_{546}$ + 213.8°, $[\alpha]_{589}$ + 180.3, and $[\alpha]_{643}$ + 142.0°, (5.940 mg./ml.).

In order to compare this compound with 1-methylestrone the latter was synthesized according to the directions of Djerassi and Scholz (18) by the rearrangement of $\Delta^{1,4}$-androstan-3,17-dione with concentrated sulfuric acid in acetic anhydride. It was obtained as white needles from methanol, m.p. 251–253°, $[\alpha]_{546}$ + 348.4°, $[\alpha]_{589}$ + 292.4°, $[\alpha]_{643}$ + 227.5°, (11.20 mg./ml.). The above authors report m.p. 249–251°, $[\alpha]_D$ +271.6°.

A 0.30-g. portion of 1-methylestrone was dissolved in 3 ml. of pyridine and warmed for ¾ hr. at 90° with 0.5 ml. of benzoyl chloride. After dilution with hot water this gave 0.40 g. of crude product, m.p. 233–237°. Thick prisms were obtained upon recrystallization from acetone but the melting point range remained broad and unchanged. Upon further recrystallization from hexane-acetone, characteristic glistening pearly leaflets of 1-methylestrone benzoate separated, similar to those obtained by chromatographic separation of the batch pyrolysis product of $\Delta^{1,4}$-androstadiene-3,17-dione; m.p. 237.5–238.7°. The rotation was: $[\alpha]_{546}$ + 212.3°, $[\alpha]_{589}$ + 180.1°, and $[\alpha]_{643}$ + 145.1° (8.453 mg./ml.).

Anal. Calc'd for $C_{26}H_{28}O_3$: C, 80.37; H, 7.26.

Found: (Sample sublimed under high vacuum): C, 80.27; H, 7.35.

The mixture melting point with the product obtained from the pyrolysis experiment described above was unchanged.

Pyrolysis of $\Delta^{1,4}$-androstadiene-3,17-dione to estrone. $\Delta^{1,4}$-androstadiene-3,17-dione was prepared in substantially the same way as described by Djerassi and Scholz (18) except that purified 2,4-dibromoandrostan-3,17-dione was used. Upon dehydrobromination with 2,4,6-collidine this gave crystalline $\Delta^{1,4}$-androstadiene-3,17-dione, m.p. 130–135° from an ether solution without need for chromatography. Repeated recrystallization from ether gave androstadienedione in the form of square prisms, m.p. 140.9–142.1°, $[\alpha]_D$ +103.4°. Inhoffen (5), m.p. 139–140°, $[\alpha]_D$ +115.8° (chloroform). Djerassi and Scholz (18), m.p. 140–141°, $[\alpha]_D$ +118.8° (chloroform). In isoöctane solution its molecular extinction coefficient, ϵ was 15,600 at 230–232 mμ.

A solution of 6 g. of $\Delta^{1,4}$-androstadiene-3,17-dione in 300 ml. of mineral oil (b.p. 310–405°) was added dropwise over a ½ hour-period into a glass tube 1.25 in. in diameter and 12 in. long filled with glass beads and heated to 525–535° in an electric furnace. The vapor of the mineral oil condensed together with the estrone in the receiver. A small amount of low-boiling hydrocarbons which formed were condensed in a trap and the gaseous products were passed into an exhaust line. Upon dilution of the mineral oil with ether and extraction with 5% alkali there was obtained an aqueous solution of the crude acidic compounds. This solution was acidified with dilute hydrochloric acid and the precipitated estrone was collected, washed, and dried. There was obtained 3.2 g. of a yellow solid, m.p. 235–250°. After two recrystallizations from methanol or from acetone this gave 1.2 g. (21%) of colorless prisms m.p. 256–260°, $[\alpha]_D$ +160° to + 162°. A mixed melting point with U.S.P. Reference Standard material (m.p. 255–260°) was unchanged.

A sample of this estrone was recrystallized nine times alternating every three times between methanol and acetone as a solvent, whereupon the melting point determined by the capillary tube method rose to a constant figure of 257.8–260.6° (colorless to pale brown melt) from acetone and then dropped to about 257–260.6° upon shifting to methanol (Darco). This observation corresponds with the report on the crystalline modifications of estrone by Kofler and Hauschild (22) who found that crystallization from methanol gave only crystals of the rhombic metastable form with a hot-stage melting point of 256°. From acetone, however, we obtained the monoclinic-metastable crystalline platelets which we found melted somewhat higher. In any case, the melting point will be broad due to the equilibria

between the above two crystalline forms and the stable rhombic form, and only the endpoint of the melt will be sharp and unequivocal.

The rotation of the purified estrone at the sixth (acetone) and ninth (methanol) recrystallization stage was determined in dioxane solution at three different wavelengths using a monochromator and a sodium vapor lamp. The mean values of several determinations at from 20° to 25° are as follows:

$[\alpha]_{546}$ 199.6° ±1.6°; $[\alpha]_{589}$ 162.9° ±0.9°; $[\alpha]_D$ 163.5° ±0.7°; $[\alpha]_{643}$ 126.4° ±0.8°.

The synthetic estrone was indistinguishable from the natural product in biological activity. From it were prepared the benzoate, acetate, semicarbazone, and estradiol, which were likewise indistinguishable from similar derivatives of natural estrone. The product also showed the known color reactions of estrone.

SUMMARY

1. Repetition of the aromatization experiments of Inhoffen (15) by which he obtained "isoequilin" from $\Delta^{1,4}$-androstadiene-3,17-dione gave a mixture of estrone and 1-methylestrone.

2. In our hands the procedure of Fujii and Matsukawa for the preparation of $\Delta^{1,4}$-androstadiene-3,17-dione (16) gave a mixture of this and the corresponding $\Delta^{4,6}$ compound. Some of the intermediates in their synthesis differ in properties from those described in this paper.

3. In the case of 2,4-dibromoandrostan-3,17-dione, the addition of an iodide to the *s*-collidine dehydrobromination has been shown to give a mixture of reduction products.

4. A continuous-flow process is described for the formation of estrone by the aromatization of $\Delta^{1,4}$-androstadiene-3,17-dione in a furnace.

5. The physical constants of highly purified synthetic estrone have been determined.

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[CONTRIBUTION NO. 185 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

RANEY NICKEL AS HYDROGENATION CATALYST IN ACID SOLUTIONS. PREPARATION OF AMINO ALCOHOLS FROM MANNICH BASES

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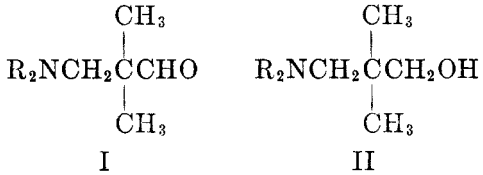
The selection of a suitable catalyst for catalytic hydrogenations is determined by several factors, one of the most important being the *p*H of the solutions to be hydrogenated. Adkins (1) states: "Acids may not be used with base metal catalysts". Therefore, noble metals exclusively are used as catalysts in acid solutions. This paper reports the use of Raney nickel for catalytic hydrogenations in distinctly acid solutions of *p*H 3–6. In the case of the reduction in acid solutions of Mannich bases of formula I (3) to the corresponding alcohols of formula II Raney nickel not only was found to be an efficient hydrogenation catalyst, but it proved even to be superior to noble metal catalysts.



I II

Mannich (3) reduced the free bases of formula I with sodium amalgam in poor yields. He found activated aluminum (2) and catalytic hydrogenation methods (2, 4) unsatisfactory for these compounds. Large amounts of palladium were required, the hydrogenations proceeded very slowly, and for unknown reasons did not always stop at the desired alcohol stage. Tuda, *et al.* (5) likewise report difficulties in the hydrogenation of similarly constituted amines.

When the hydrochlorides of amines of type I were hydrogenated with noble metal catalysts, only poor yields of the alcohols resulted. In all cases the amine portion was partly split out of the molecule. Hydrogenation of the *free* amines was even less satisfactory, no matter whether palladium charcoal, any other noble metal catalyst, or nickel were used.

However, the hydrogenations proceed smoothly and with high yields when the hydrochlorides of the amines of type I are hydrogenated *with Raney nickel* in aqueous solution. The *p*H of the hydrochlorides in aqueous solutions varies from about 3.5 to 5.5. Strongly acid solutions containing a considerable amount of free mineral acid can, of course, not be used. However, down to a *p*H of approximately 3 the hydrogenations take place readily even at temperatures as low as 40–50°, and practically no side reactions occur.

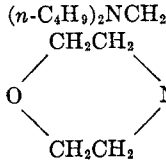
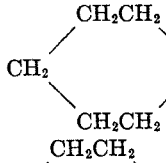
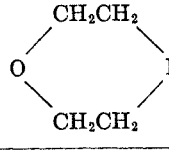
The amino alcohols prepared in this manner are listed in Table I. Since they are liquid and do not differ greatly in physical constants from the starting carbonyl compounds, they were characterized by their *p*-nitrobenzoates, a type of derivative which the carbonyl compounds cannot form.

Some of the amino alcohols have been prepared previously by Mannich (3). The present method makes them readily accessible.

The importance of the results consists in the fact that they prove that Raney nickel may be used as an efficient hydrogenation catalyst in distinctly acid solutions. The method may prove useful for similar reductions.

TABLE I

MANNICH BASES AND THEIR REDUCTION PRODUCTS

FORMULA	STRUCTURAL FORMULA	B.P., °C./MM.	M.P., °C.		LIT. REFERENCE
			Hydrochloride	Hydrochloride of *p*-Nitrobenzoate	
III	$(n\text{-}C_4H_9)_2NCH_2C(CH_3)_2CHO$	105–110/10	—	—	-
IV		92– 95/10	166	—	—
V	$(CH_3)_2NCH_2C(CH_3)_2CH_2OH$	34– 36/10	118–120	181–183	3
VI	$(C_2H_5)_2NCH_2C(CH_3)_2CH_2OH$	84– 88/10–11	—	157–159	3
VII	$(n\text{-}C_4H_9)_2NCH_2C(CH_3)_2CH_2OH$	113–117/10	—	136–139	—
VIII		93– 94/10	200–203	138–140	3
IX		—	146–148	192–194	—

EXPERIMENTAL

The melting points are uncorrected.

A. AMINO ALDEHYDES

In addition to the bases reported by Mannich, Lesser, and Silten (3) the following new members of this class of compounds were made:

1. *α-(Di-n-butylaminomethyl)isobutyraldehyde* (III). Di-*n*-butylamine (129 g.) is added to a cold mixture of concentrated sulfuric acid (60 g.) and alcohol (75 cc.). To the solution freshly distilled isobutyraldehyde (76 g.) and paraformaldehyde (73 g.) are added. The mixture is stirred and refluxed for four hours. After cooling, sodium sulfite (100 g.), water (500 cc.), and an excess of sodium hydroxide are added. The crude amino aldehyde separates as an oil and is fractionated *in vacuo*. Pure α-(di-*n*-butylaminomethyl)isobutyraldehyde (120 g.) is obtained as a colorless oil, $b.p._{10}$ 105–110°. The hydrochloride does not crystallize.

2. *α-(4-Morpholinylmethyl)isobutyraldehyde* (IV). In a cold mixture of concentrated sulfuric acid (60 g.) and alcohol (60 g.), morpholine (85 g.) is dissolved. Isobutyraldehyde (76 g.) and paraformaldehyde (73 g.) are added, and the mixture is refluxed and stirred for about three hours. After cooling, a solution of sodium sulfite (100 g.) in water (800 cc.) is added. The free base is then precipitated by an excess of sodium hydroxide solution. The

crude oil is fractionated *in vacuo*, yielding 120 g. of pure α-(4-morpholinylmethyl)isobutyraldehyde, b.p.$_{10}$ 92–95°. The hydrochloride melts at 166°.

B. AMINO ALCOHOLS

1. *γ-Dimethylaminomethyl-β,β-dimethylpropanol* (V). α-Dimethylaminomethylisobutyraldehyde (3) (20 g.) is dissolved in 60 cc. of 3 *N* hydrochloric acid. The acidity of the solution is adjusted to *p*H 3.5–4. Three grams of Raney nickel are added, and the mixture is hydrogenated at 40–50° and 600 lbs. pressure for about three hours. The catalyst is filtered, and the solution is distilled to dryness *in vacuo*. The hydrochloride of γ-dimethylaminomethyl-β,β-dimethylpropanol crystallizes. It is stirred up with acetone and filtered. Yield, 20 g.; m.p. 118–120° [Mannich (3) had m.p. 136°]. Since the free base is soluble to about 15% in water at room temperature, the base has to be made in concentrated aqueous solution with strong alkalies and must be salted out by saturation with potassium carbonate; it distills at 34–36°/10 mm.

The *methiodide* melted at 225° [Mannich (3) gives m.p. 222°]. It crystallizes from alcohol with one-half mole of alcohol.

Anal. Calc'd for $C_8H_{20}INO \cdot 1/2\ C_2H_6O$: C, 36.50; H, 7.82; N, 4.73.
Found: C, 36.47; H, 7.47; N, 5.00.

p-Nitrobenzoate. The free amino alcohol prepared from 3.4 g. of the hydrochloride is reacted with 4 g. of *p*-nitrobenzoylchloride in 60 cc. of benzene. The crude compound is crystallized from alcohol, yielding 6 g. of the pure hydrochloride of the nitrobenzoate; m.p. 181–183° [Mannich (3) gives m.p. 160°].

Anal. Calc'd for $C_{14}H_{20}N_2O_4 \cdot HCl$: C, 53.07; H, 6.68; N, 8.84.
Found: C, 52.82; H, 6.46; N, 9.04.

2. *γ-Diethylamino-β,β-dimethylpropanol* (VI). Distilled α-diethylaminomethylisobutyraldehyde (3) (100 g.) is slowly added to a cooled and stirred solution of 230 cc. of 10% hydrochloric acid. The resulting solution is acid to Congo paper. α-Diethylaminomethylisobutyraldehyde is added in small amounts until it is no longer dissolved. The solution then shows *p*H 4–4.5. The undissolved oil is removed by gravity filtration. The clear filtrate is hydrogenated at 150 lbs. pressure and about 79–80° with 5 g. of Raney nickel. At 50° the uptake of hydrogen becomes rapid. After two hours the solution is filtered. Generally it is pale green indicating the presence of dissolved nickel. Ammonia or sodium hydroxide is added in excess whereupon about 65 g. of crude amino alcohol separates. The aqueous layer is extracted twice with about 100 cc. of benzene. The combined benzene extracts are evaporated leaving about 30 g. of additional crude amino alcohol. Fractionation of the combined crude products *in vacuo* yields 80–90 g. of pure γ-diethylamino-β,β-dimethylpropanol b.p.$_{10}$ 84–88° [Mannich (3) had b.p.$_{12}$ 90–91°].

p-Nitrobenzoate. The distilled amino alcohol (5 g.) is dissolved in 50 cc. of benzene. A filtered solution of 6.5 g. of *p*-nitrobenzoylchloride in 50 cc. of benzene is added slowly with shaking. The mixture warms up, and an oil precipitates which soon solidifies. It is filtered after several hours, washed with benzene and ether, and dried; m.p. 146° or higher. Recrystallization from alcohol gives the pure *hydrochloride* of the *p-nitrobenzoate*, m.p. 157–159° [Mannich (3) gives m.p. 160°].

3. *γ-Di-n-butylamino-β,β-dimethylpropanol* (VII). α-(Di-n-butylaminomethyl)isobutyraldehyde (18.5 g.) (Exp. A2) is dissolved in 3 *N* hydrochloric acid. By the addition of ammonia the *p*H is adjusted to 4–5.5. Hydrogenation with 3 g. of Raney nickel at 60–70° and 400 lbs. pressure is complete after about two hours. The filtered solution is made alkaline with sodium hydroxide. The liberated crude amino alcohol is fractionated *in vacuo* yielding 12–13 g. of pure γ-di-*n*-butylamino-β,β-dimethylpropanol, b.p.$_{10}$ 113–117°.

Anal. Calc'd for $C_{13}H_{29}NO$: C, 72.50; H, 13.37; N, 6.50.
Found: C, 72.79, 72.74; H, 13.16, 13.22; N, 6.76.

p-Nitrobenzoate. The base (3.1 g.) is reacted with 3 g. of *p*-nitrobenzoyl chloride in 60 cc. of benzene. The ester hydrochloride separates slowly. After standing overnight it is filtered and washed with benzene. Yield 5 g., m.p. 135–139°.

Anal. Calc'd for $C_{20}H_{32}N_2O_4 \cdot HCl$: C, 59.91; H, 8.30; N, 6.99.
Found: C, 59.73; H, 7.71; N, 6.71.

4. *γ-(1-Piperidyl)-β,β-dimethylpropanol* (VIII). α-(1-Piperidylmethyl)isobutyraldehyde (3) (34 g.) is dissolved in dilute hydrochloric acid. The *p*H is adjusted to 4–5 by means of sodium carbonate. After addition of 2 g. of Raney nickel, the solution is hydrogenated at 60° and 300 lbs. pressure for about two hours. The filtered solution is evaporated, yielding the crystallized hydrochloride. It is washed with acetone and dried, m.p. 200–203°. The free base liberated from the hydrochloride with sodium hydroxide is distilled *in vacuo*. The pure compound boils at 93–94°/10 mm. [Mannich (3) gives b.p.$_{39}$ 140°]. Yield 22 g.

Anal. Calc'd for $C_{10}H_{21}NO$: C, 70.12; H, 12.36.
Found: C, 69.92; H, 12.10.

p-Nitrobenzoate. The base (3 g.) is reacted with 3.5 g. of *p*-nitrobenzoylchloride in 80 cc. of benzene, yielding 6 g. of the hydrochloride of the nitrobenzoate, m.p. 138–140° [Mannich (3) gives m.p. 162–163°].

Anal. Calc'd for $C_{17}H_{24}N_2O_4 \cdot HCl$: C, 57.21; H, 7.06; N, 7.85.
Found: C, 57.16; H, 6.86; N, 7.82.

5. *γ-(4-morpholinyl)-β,β-dimethylpropanol* (IX). α-(4-Morpholinylmethyl)isobutyraldehyde (Exp. A3) (21 g.) is dissolved in an equivalent amount of 10% hydrochloric acid. Water is added to bring the volume to 100 cc. The *p*H is adjusted to 4–5 by means of ammonia. After the addition of 2 g. of Raney nickel, the mixture is hydrogenated for about 3–4 hours at 50–60° and 600 lbs. pressure. The solution is filtered and evaporated. The crystallized crude hydrochloride is recrystallized from alcohol, yielding 15 g. of the pure hydrochloride, m.p. 146–148°. It contains one-half mole of alcohol.

Anal. Calc'd for $C_9H_{19}NO_2 \cdot HCl \cdot 1/2\ C_2H_6O$: C, 51.60; H, 9.96; N, 6.02.
Found: C, 51.37; H, 9.42; N, 5.88, 5.86.

p-Nitrobenzoate. The hydrochloride (4 g.) is converted into the free base with sodium hydroxide. The free amino alcohol is extracted with 30 cc. of benzene, the solution dried and 3.6 g. of *p*-nitrobenzoylchloride dissolved in 50 cc. benzene added. The *p*-nitrobenzoate separates soon. Recrystallization from alcohol gives 4 g. of the pure hydrochloride of the nitrobenzoate, m.p. 192–194°.

Anal. Calc'd for $C_{15}H_{22}N_2O_4 \cdot HCl$: C, 53.25; H, 6.98; N, 7.77.
Found: C, 53.48; H, 6.43; N, 7.73.

Acknowledgment. I am indebted to Dr. Al Steyermark of our Microchemical Laboratory for the microanalyses reported in this paper.

SUMMARY

Hydrogenations of Mannich bases of the type $R_2NCH_2C(CH_3)_2CHO$ proceed with high yields when their hydrochlorides are hydrogenated with Raney nickel in acid solution of *p*H 3–6.

NUTLEY 10, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

THE REACTION OF GRIGNARD REAGENTS WITH 3,4-EPOXY-1-BUTENE. I. 1-NAPTHYLMAGNESIUM BROMIDE

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INTRODUCTION

The addition of Grignard reagents to 3,4-epoxy-1-butene is of interest because the unsaturated alcohols formed in the reaction are promising intermediates. For example, dehydration would lead to substituted butadienes. Semeniuk and Jenkins have reported the reaction of 3,4-epoxy-1-butene with the methyl Grignard (1). From the acidic hydrolysis of the adduct of 3,4-epoxy-1-butene with methylmagnesium iodide, they obtained 2-penten-1-ol. The structure was assumed on evidence of the boiling point only. Based upon this result, they advanced analogous structures for the reaction products with cyclohexylmagnesium chloride, phenylmagnesium bromide, 1-naphthylmagnesium bromide, and *o*-ethoxyphenylmagnesium chloride. They further advanced reasons ". . .to explain the fact that alcohols of but one isomeric form could be isolated". Work in progress in our laboratories with methylmagnesium bromide indicates that a mixture of alcohols is obtained, rather than an ". . . alcohol of one isomeric form". Thus far, three different isomeric alcohols have been isolated and characterized (to be reported later).

Upon reviewing the literature concerning the reactions of the oxirane ring with Grignard reagents, it was found that a variety of courses had been observed. These are briefly reviewed here.

Ethylene oxide reacts with a Grignard reagent to form an adduct, which, upon hydrolysis, yields mainly a primary alcohol (2, 3) and a small quantity of secondary alcohol (4). The course of the reaction is set forth as proceeding through a complex which rearranges to give (upon hydrolysis) the alcohol. The rearrangement occurs when the ether, in which the reaction is run, is removed; the increased temperature effects the rearrangement.

Substitution in the oxirane ring causes the reaction to proceed differently. With 1,2-epoxypropane, ring cleavage occurs with formation of a secondary alcohol (5). Replacing a hydrogen of the methyl group of 1,2-epoxypropane with chlorine or with a methoxy group or a phenoxy group leads to the same result, namely, the secondary alcohol (6, 7, 8, 9). Substitution of an ethyl group on the oxirane ring also gives the secondary alcohol; Levene and Walti obtained 3-heptanol from *n*-propylmagnesium bromide and 1,2-epoxybutane and analogous products from isopropyl and phenyl Grignard reagents (10).

Disubstitution on the oxirane ring results in the formation of products which are dependent upon the location of the substitents. Thus, 1,2-epoxy-2-methyl-

[1] Taken from the thesis submitted by N. G. Gaylord in partial fulfillment of the requirements for the M.S. degree, Polytechnic Institute of Brooklyn, June 1949.

propane (isobutylene oxide) gives 3-methyl-2-butanol which appears to have resulted from initial isomerization of the oxide to an aldehyde followed by normal addition (12, 13).

Disubstitution involving both carbons of the oxirane ring results in apparent isomerization to a ketone. Thus, with 2,3-epoxybutane, methylmagnesium bromide gives 2-methyl-2-butanol (14). Henry also found that 2,3-epoxy-2-methylbutane gives 2,3-dimethyl-2-butanol with the methyl Grignard reagent (11). That this is a case of initial isomerization to the ketone followed by addition and not due to a normal ring cleavage was demonstrated by Norton and Hass when they obtained 2,3-dimethyl-3-pentanol from the oxide and the ethyl Grignard (15). The ethyl Grignard and 2,3-dimethyl-2,3-epoxybutane also react through isomerization to the ketone to give 2,2,3-trimethyl-3-pentanol (15).

Another epoxide which has been investigated extensively is 1-phenyl-1,2-epoxyethane (styrene oxide). Tiffeneau and Fourneau found that organomagnesium compounds gave the product resulting from addition to phenylacetaldehyde, presumably formed by initial isomerization of styrene oxide (16). Kharasch and Clapp, however, found that the order of addition of reagents determines the products formed in the reaction with aryl Grignards. Thus, from styrene oxide and phenylmagnesium bromide, addition of the oxide to the Grignard gave 2,2-diphenylethanol (no isomerization), while addition of the Grignard to the oxide gave 1,2-diphenylethanol (initial isomerization to phenylacetaldehyde) (17). Similar results were obtained with *p*-anisylmagnesium bromide. Golumbic and Cottle found that this same oxide gave 1-phenyl-2-propanol with methylmagnesium iodide, the result of apparent initial isomerization to the aldehyde (18).

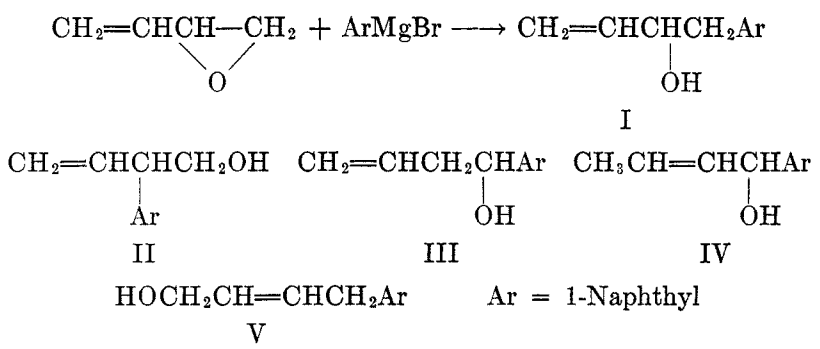
Tiffeneau observed that 1,2-epoxy-2-phenylpropane gives a secondary alcohol with phenylmagnesium bromide (apparent isomerization) (19). This same phenomenon was observed by Khaletzkii using the Grignard reagent from *tert*-butyl chloride (20).

It has been observed generally that the reaction of epoxides with dialkyl- or diaryl-magnesium compounds gives products resulting only from normal opening of the ring without attendant isomerization (15, 18, 21).

RESULTS AND DISCUSSION

The addition of 1-naphthylmagnesium bromide to 3,4-epoxy-1-butene or butadiene monoxide, in diethyl ether, followed by hydrolysis of the adduct gave a viscous, colorless liquid product (I) (assumed at this point), b.p. 147.5–153°/0.2 mm., in 55–58% yield. This compound slowly decolorized bromine in carbon tetrachloride and rapidly reduced potassium permanganate in acetone. It gave a 1-naphthylurethan (VI), m.p. 103–104.5°, and a xanthate (VII), m.p. 180.5–181.8° (dec.). It did not form an acid phthalate. Its analysis for carbon and hydrogen was in accord with one of the isomeric carbinols expected.

From the Introduction it is seen that several structures are feasible for this carbinol:



I and II would result from cleavage of the oxirane ring without attendant isomerization. III would result from initial isomerization to an aldehyde with subsequent normal Grignard addition. IV would result from isomerization to the aldehyde, as in III, followed by an allylic shift of the double bond with subsequent normal Grignard addition. This does not seem unlikely, since isocrotonaldehyde is not known; syntheses leading to it result in crotonaldehyde (22). V would result from formation of I followed by an allylic shift of the hydroxyl group or by an attack of the negative aryl group at the 1-position followed by shift of the double bond and opening of the oxirane ring to give the primary alcohol.

Since neither the isolated carbinol nor its isomers had been reported in the literature, experiments were undertaken to determine the position of the hydroxyl and 1-naphthyl groups by degradation and synthesis.

Hydrogenation of the carbinol was carried out over palladium on charcoal. The product (VIII) gave a xanthate (IX), m.p. 175–176° (dec.), which depressed the melting point, 180.5–181.8° (dec.), of the xanthate (VII) prepared from the unsaturated carbinol.

An Oppenauer oxidation was performed on VIII. A product (X) was obtained in 52.5% yield. It gave no 2,4-dinitrophenylhydrazone. However, it did give a positive von Bitto test (an alkaline nitroprusside solution) indicating the presence of the carbonyl group. Negative fuchsin and Tollens tests indicated that the compound was probably a ketone. A semicarbazone (XI) was obtained, m.p. 165–167°, with some difficulty.

The probable presence of a keto group eliminated structures II and V from consideration since oxidation of these carbinols would result in the formation of aldehydes. To confirm elimination of II, the compound (X) was subjected to a Clemmensen reduction. The product (XII) gave a picrate (XIII), m.p. 104°, which corresponds with that of 1-*n*-butylnaphthalene (104–106°) (23). The melting point of 1-(1-methylpropyl)naphthalene picrate is 76° (24).

The synthesis of the carbinol III was carried out in 94% yield from allylmagnesium chloride and 1-naphthaldehyde. The carbinol gave a xanthate (XIV), m.p. 163.8–165° (dec.), which depressed the melting point of the xanthate (VII), m.p. 180.5–181.8° (dec.), and a 1-naphthylurethan (XV), m.p. 115.5–117°, which depressed the melting point of the urethan (VI), m.p. 103–104.5°.

Therefore, structure III involving isomerization to vinylacetaldehyde followed by normal addition is eliminated. A further consideration in the elimination of III is the relative stability of the known carbinol as compared with the product from the Grignard reaction with the epoxide (see Experimental).

IV was synthesized by the addition of 1-naphthylmagnesium bromide to crotonaldehyde. The structure of the product was assumed, in view of the work of Stevens (25, 26) which demonstrated that phenylmagnesium bromide adds 1,2 to the α,β-unsaturated system in crotonaldehyde. All attempts to prepare the 1-naphthylurethan, acid phthalate, and potassium xanthate failed. Wherever the application of heat was necessary, the product was converted to a polymeric mass. None of the oily residues crystallized after standing two years. The ease with which this carbinol dehydrates upon heating and the inability to prepare derivatives of it, contrasts markedly with the behavior of the unknown carbinol.

Synthesis of I did not appear feasible since the Grignard reagent prepared from 1-chloromethylnaphthalene added to acrolein would not give an unambiguous reaction product. Delaby reported that the analogous reaction between acrolein and benzylmagnesium chloride gave only 5% of the carbinol expected by 1,2-addition (27). Thus, the synthesis of 1-(1-naphthyl)-2-butanone (X) was attempted since the ketone derived from I had given a semicarbazone.

1-(1-Naphthyl)-2-butanone was synthesized by adding ethylmagnesium bromide to 1-naphthaleneacetonitrile. This ketone gave a semicarbazone (XVI) m.p. 166–167.5°, which did not depress the melting point of the semicarbazone XI.

Therefore, the major product resulting from the reaction of 3,4-epoxy-1-butene with 1-naphthylmagnesium bromide is the carbinol, 1-(1-naphthyl)-3-buten-2-ol (I).

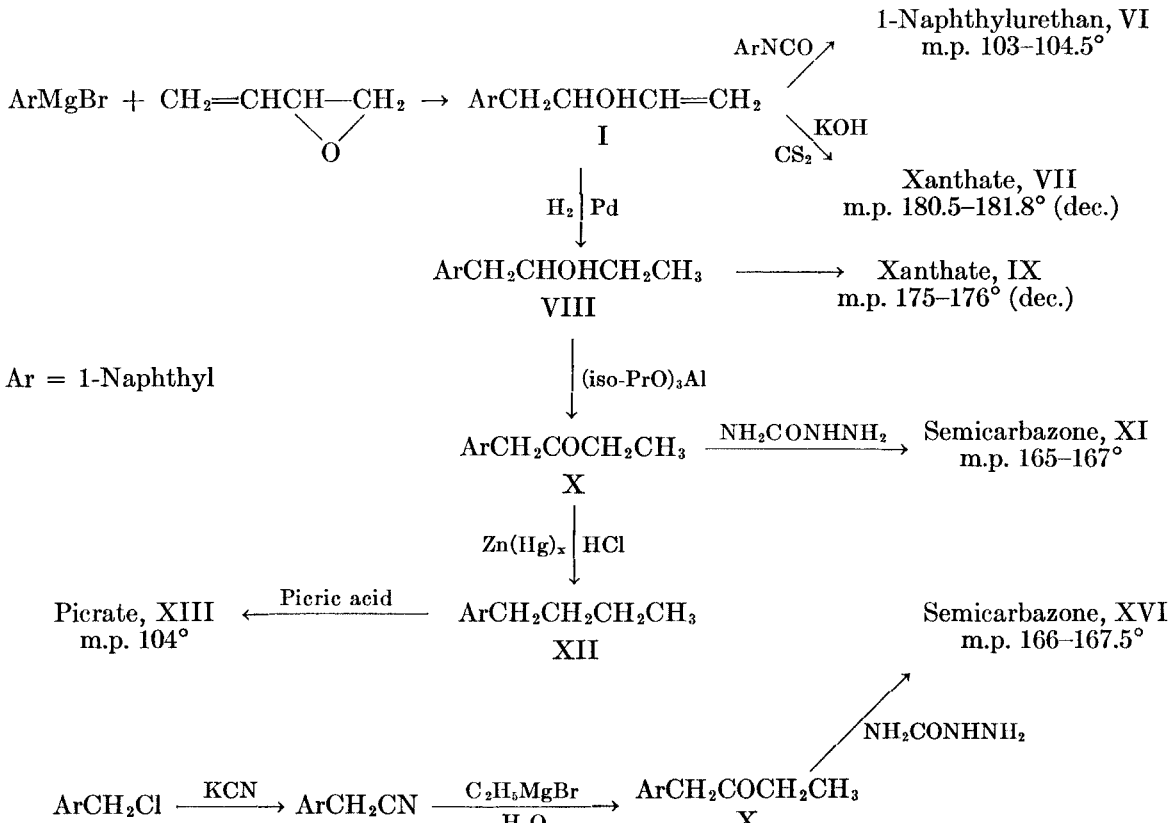
The steps leading to this conclusion are outlined in Chart I.

MECHANISM

The opening of an unsymmetrically substituted oxirane ring by means of the Grignard reagent, in general, takes place at the terminal carbon atom leading to a secondary alcohol. Thus, the addition of the Grignard reagent to 1,2-epoxypropane (10, 13, 15, 28–31), epichlorohydrin (7, 8, 32–42), 1,2-epoxy-3-methoxypropane (6, 9), and 1,2-epoxybutane (10) all give secondary alcohols. Only in the one instance, in which styrene oxide was added to the Grignard reagent, was the ring opened to give a primary alcohol (17).

Since the Grignard reagent is a strong base, other base-catalyzed reactions should be analogous. Kadesch has observed that the sodium methoxide-catalyzed methanolysis of 3,4-epoxy-1-butene results in the secondary alcohol (43). In the hands of Bartlett and Ross this result was verified, although a small quantity of the isomeric product was obtained (44). More recently, Swern and co-workers have reported similar results with allyl alcohol (45). Russell and Vander Werf have shown that the same ring opening is noticed with 3,4-epoxy-1-butene in the reaction with sodium ethyl malonate (46). Finally

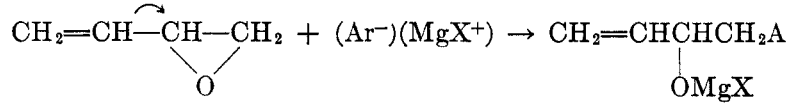
CHART I


1-Naphthylurethan, VI
m.p. 103–104.5°
ArNCO
ArMgBr + CH2=CHCH—CH2 → ArCH2CHOHCH=CH2
O
I
KOH
CS2
Xanthate, VII
m.p. 180.5–181.8° (dec.)
H2 | Pd
ArCH2CHOHCH2CH3
VIII
Xanthate, IX
m.p. 175–176° (dec.)
Ar = 1-Naphthyl
(iso-PrO)3Al
ArCH2COCH2CH3
X
NH2CONHNH2
Semicarbazone, XI
m.p. 165–167°
Zn(Hg)x | HCl
Picrate, XIII
m.p. 104°
Picric acid
ArCH2CH2CH2CH3
XII
Semicarbazone, XVI
m.p. 166–167.5°
NH2CONHNH2
ArCH2Cl
KCN
ArCH2CN
C2H5MgBr
H2O
ArCH2COCH2CH3
X

Trevoy and Brown have shown that lithium aluminum hydride also effects opening of the oxirane ring at the terminal carbon (47).

From these results it seems reasonable that the reaction examined here is an ionic one and probably proceeds in the following way: The vinyl group donates electrons to the carbon to which it is attached, rendering it relatively negative to the distal carbon atom. The electron density is thus lower at the far carbon atom, so that the attack of the carbanion takes place there.

From steric considerations, also, the bulky 1-naphthyl group should militate for addition at the terminal position, which is less sterically hindered.



EXPERIMENTAL

All temperatures are uncorrected.

Starting materials. Ethyl bromide (b.p. 38°, n_D^{20} 1.4239), allyl chloride[2] (b.p. 45°, n_D^{20} 1.4154), and crotonaldehyde (b.p. 103–105°, n_D^{20} 1.4360) were distilled before use.

3,4-Epoxy-1-butene. The commercial product[3] was dried over Drierite and fractionated through a total reflux, partial take-off column [packed section (6-mm. Pyrex helices) 126 cm. long, 2.2 cm. o.d., 1.8 cm. i.d.]. After removing a small amount of a water azeotrope (48), the product distilled at 66.4–66.6°/760, n_D^{25} 1.4152 [reported, b.p. 65–65.8°/739, n_D^{20} 1.4170 (43); b.p. 67°, n_D^{25} 1.4151 (44); b.p. 67.6°/760, $n_D^{20.5}$ 1.4167 (48)].

1-Bromonaphthalene. Direct bromination of naphthalene according to Clarke and Brethen (49) gave the product in 73% yield, b.p. 132°/12, n_D^{20} 1.6582.

Addition of 1-naphthylmagnesium bromide to 3,4-epoxy-1-butene. Several preliminary experiments were carried out to determine the optimum conditions for forming the product. The temperature of the reaction was varied by replacing the ethyl ether with isopropyl ether and also by replacing part of the ethyl ether with benzene until the temperature of the reaction mixture was 70°. It was necessary to remove scrupulously all traces of acid from all apparatus in order to minimize dehydration during distillation of the product. The following experiment represents one which gave the best results.

1-Naphthylmagnesium bromide was prepared under nitrogen from 6.08 g. (0.25 atom) of magnesium turnings and 51.8 g. (0.25 mole) of 1-bromonaphthalene in 175 ml. of absolute ethyl ether (50). A solution of 17.5 g. (0.25 mole) of 3,4-epoxy-1-butene in 50 ml. of ether was added dropwise with stirring at such a rate as to maintain a vigorous reflux (about 45 minutes is required). Stirring was continued for eight hours after the reflux and then the reaction mixture was allowed to stand at room temperature for twelve hours.

The solution was hydrolyzed with 100 ml. of 2.5 *N* hydrochloric acid and 200 g. of ice, the ether layer separated, and the water layer extracted with ether; the combined ether extracts were washed with water until neutral. After drying the ether layer over potassium carbonate, filtering, and concentrating it at reduced pressure, it was steam-distilled at reduced pressure to remove naphthalene. During this codistillation, which required 2 l. of water, the vapor temperature did not exceed 50°. The residue was extracted with ether and dried twice with fresh potassium carbonate. After distillation of the ether, distillation of the residue gave 27.2–28.6 g. (0.137–0.145 mole; 55–58%) of the carbinol (I), b.p. 147.5–153°/0.2, d_4^{20} 1.094. Some dehydration accompanied the distillation.

The carbinol evolved hydrogen slowly when treated with sodium. It slowly decolorized

[2] Kindly supplied by the Shell Development Corporation, Emeryville, California.

[3] Kindly supplied by the Columbia Chemicals Division of the Pittsburgh Plate Glass Company, Pittsburgh 13, Pa.

bromine in carbon tetrachloride, but rapidly decolorized potassium permanganate in acetone.

1-Naphthylurethan (VI). A mixture of 0.65 g. of the carbinol and 0.55 g. of 1-naphthylisocyanate was heated on a steam-bath for fifteen minutes. Upon cooling, an oil appeared which did not solidify after standing five days in a refrigerator. Extraction of the reaction mixture with 10 ml. of hot Skellysolve C (petroleum ether, b.p. 85–100°) gave a solution of the product from which 0.82 g. (68%) of the crude urethan, m.p. 101.4–104°, was obtained. Two more recrystallizations raised the melting point to 103–104.5°.

Xanthate (VII). The procedure was a modification of that of Whitmore and Lieber (51). A solution of 0.47 g. of the carbinol and 0.11 g. of pulverized potassium hydroxide was prepared by heating the mixture on a steam-bath. The supernatant liquid was decanted from undissolved alkali and, after cooling, was diluted with an equal volume of dry ether. Upon the addition, with stirring, of 0.18 ml. of carbon disulfide, the cream-colored xanthate precipitated and was filtered after dilution of the mixture with twice its volume of ether. The crude xanthate (0.12 g., 20% yield) was slurried with ether and filtered. After purification by precipitation with ether from absolute alcohol the xanthate had m.p. 180.5–181.8° (dec.).

Attempted preparation of the acid phthalate. The procedure of Goggans and Copenhaver was employed (52). A solution of the carbinol (0.5 g.) and phthalic anhydride (5 g.) in pyridine (3 ml.) was heated on a steam-bath for ten minutes and then cooled. After extracting with ether to remove excess anhydride, heating with water at 60°, extracting with chloroform to leave behind residual phthalic acid, and drying over sodium sulfate, attempts to crystallize the oily residue from chloroform or benzene-petroleum ether were unsuccessful. The product was still a viscous, brown oil after standing in a refrigerator for two years.

PROOF OF STRUCTURE

Hydrogenation of I to 1-(1-Naphthyl)butan-2-ol (VIII). Ten grams (0.050 mole) of I in a mixture of 100 ml. of methanol and 100 ml. of toluene over 0.5 g. of 5% palladium on charcoal took up the theoretical amount of hydrogen, 1290 ml., in 19 minutes. However, because the rate at the end of that time was as rapid as that at the beginning, a total of 1395 ml. (8.1% excess) of hydrogen was added. The total time consumed was 22 minutes. Upon filtering and distilling at reduced pressure, there was obtained 7.9 g. (0.039 mole; 78%) of product (VIII), b.p. 136–139°/0.3 which did not decolorize permanganate solution.

Xanthate (IX). The xanthate was prepared, as previously described, from the saturated product. The crude xanthate (14% yield) had m.p. 174–176° (dec.) and upon recrystallization this was raised to 175–176° (dec.). A mixed melting point with xanthate VII was depressed to 168° (dec.).

Oxidation to 1-(1-Naphthyl)-2-butanone (X). An Oppenauer oxidation was carried out in a manner similar to that investigated by Adkins and Franklin (53). A mixture of 5.9 g. (0.03 mole) of VIII, 7 g. of aluminum isopropoxide (redistilled Eastman Kodak Technical grade), 100 ml. of distilled methyl ethyl ketone, and 50 ml. of dry benzene was refluxed for 18 hours. After adding 3 ml. of water to the hot solution, the mixture was filtered with suction and the precipitate of aluminum hydroxide washed with four 5-ml. portions of ether. The combined filtrates were dried quickly over potassium carbonate, residual water being removed by azeotropic distillation with 50 ml. of benzene, and distilled at reduced pressure to give 3.1 g. (0.016 mole; 52.5%) of product (X), b.p. 142–143°/0.5.

The product gave no precipitate with phenylhydrazine or 2,4-dinitrophenylhydrazine. A positive von Bitto test (54) was obtained by adding 1 ml. of 0.5% sodium nitroprusside solution to the product in distilled carbonyl-free methanol. Upon making the solution alkaline with sodium hydroxide solution, a yellow-red color was obtained.

Fuchsin-aldehyde and Tollens tests were negative. Attempts to prepare a 2,4-dinitrophenylhydrazone by the usual methods (55) were unsuccessful. An attempt to prepare it by heating the carbonyl compound in a glacial acetic acid solution of the reagent was also unsuccessful.

Semicarbazone (XI). The ketone X (0.25 ml.) was dissolved in 2 ml. of ethanol (56). The solution was made turbid with water, and 0.25 g. of semicarbazide hydrochloride and 0.4 g. of sodium acetate were added and the mixture was agitated. It was heated in boiling water, allowed to cool, and then placed in a refrigerator. After four days, the semicarbazone (XI), (0.23 g.; 41%), was obtained. After recrystallization from 50% ethanol, XI had m.p. 165–167°.

Clemmensen reduction of X *to n-butylnaphthalene* (XII). According to Martin's procedure (57), 4 g. of granulated zinc was shaken with a mixture of 6 ml. of water, 0.2 ml. of concentrated hydrochloric acid, and 0.4 g. of mercuric chloride. The aqueous solution was decanted after 5 minutes and 3 ml. of water, 7 ml. of concentrated hydrochloric acid, 4 ml. of toluene, 1.2 g. of 1-(1-naphthyl)-2-butanone (X), and 0.2 ml. of glacial acetic acid were added to the residue in that order. The mixture was refluxed for 27 hours with 6 ml. of concentrated hydrochloric acid added in three portions at 6-hour intervals. After cooling the mixture, it was extracted with ether, the ether solution dried over potassium carbonate, and the solution concentrated under reduced pressure on a steam-bath. The residual brown oil was treated with a saturated solution of picric acid. A yellow picrate deposited, m.p. 104°.

RELATED SYNTHESES

1-Chloromethylnaphthalene was prepared by the method of Grummitt and Buck (58) in 55% yield, n_D^{20} 1.635.

1-Naphthaldehyde. An attempt was made to convert 1-chloromethylnaphthalene to 1-naphthaldehyde by oxidation with hexamethylenetetramine according to Badger (59) (acetic acid as solvent). The method was attractive due to the stated reaction time of 1 minute. However, troublesome emulsions were encountered so that the procedure of Ruggli and Preuss (60) was modified for this synthesis and is herein given.

In a 3-necked, 5-l. flask equipped with stirrer, thermometer, and reflux condenser, a mixture consisting of 112 g. (0.63 mole) of 1-chloromethylnaphthalene, 89.6 g. (0.64 mole) of hexamethylenetetramine, and 2560 ml. of 60% alcohol was refluxed for six hours. The alcohol was removed under reduced pressure and the brown oil which separated was extracted with two 100-ml. portions of ether. The ether solution was cooled to 5° and 200 ml. of a saturated sodium bisulfite solution was slowly added with stirring. The bisulfite addition product was filtered and washed successively with water and benzene. Heating the addition product on the steam-bath with the calculated amount of 2.5 *N* hydrochloric acid solution was followed by extraction of the resulting brown oil with 100 ml. of ether, drying over potassium carbonate, and finally distillation to give 62.9 g. [0.403 mole; 63.6%; reported yield (60) 45–50%] of colorless oil, b.p. 117–121°/2.4.

1-(1-Naphthyl)-3-buten-1-ol (III). The Grignard reaction was carried out by the method of Arnold and Coyner (61). To a mixture of 6.05 g. (0.25 atom) of magnesium in 150 ml. of ether was added 2 ml. of allyl chloride. After the reaction was started, a solution of 24.4 ml. (total, 25.7 g.; 0.34 mole) of allyl chloride and 28.9 g. (0.185 mole) of 1-naphthaldehyde in 75 ml. of ether was added dropwise over 25 minutes. The mixture was stirred at room temperature for twelve hours, and then was allowed to stand for nine hours. After decomposing the mixture with 100 ml. of 2.5 *N* hydrochloric acid and 200 g. of scraped ice, extracting with three 50-ml. portions of ether, washing the combined ether extracts with water until neutral, and concentrating to 100 ml., the residual water layer was separated. The ether layer was dried over potassium carbonate and distilled to give 34.5 g. [0.174 mole; 94%; recalculation of the reported yield (61) indicated 86% had been obtained] of III, b.p. 141.5–143.5°/0.8, n_D^{25} 1.6099 [reported (61) b.p. 150–151°/5].

Xanthate (XIV). The derivative was prepared from 1.41 g. of carbinol III, 0.33 g. of pulverized potassium hydroxide, and 0.54 ml. of carbon disulfide according to the earlier directions. Recrystallization from ethanol gave the xanthate XIV (0.35 g.; 19%), m.p. 163.8–165° (dec.). A mixed melting point with xanthate VII was depressed to 152° (dec.).

1-Naphthylurethan (XV). The derivative was prepared from 0.65 g. of the carbinol III and 0.55 g. of 1-naphthylisocyanate according to the earlier directions. Recrystallization

from petroleum ether gave the urethan XV (0.90 g.; 74%), m.p. 115.5–117°. A mixed melting point with urethan VI was depressed to 90°.

1-(1-Naphthyl)-2-buten-1-ol (IV). Preliminary experiments indicated the extreme sensitivity of the reaction product to heat and traces of acid. The following procedure was finally adopted as giving the best results. 1-Naphthylmagnesium bromide was prepared in the usual manner from 6.08 g. (0.25 atom) of magnesium and 51.8 g. (0.25 mole) of 1-bromonaphthalene in 175 ml. of ether. Crotonaldehyde (17.5 g., 0.25 mole) in 50 ml. of ether was added over thirty minutes. After stirring for eight hours and standing for eight more, the mixture was hydrolyzed with 100 ml. of 2.5 *N* hydrochloric acid and 200 g. of ice, and extracted with three 50-ml. portions of ether. The combined ether extracts were washed with water until neutral, dried over potassium carbonate, concentrated, and distilled with steam at reduced pressure under nitrogen. When naphthalene ceased codistilling the residue was extracted with 150 ml. of ether in three portions, the ether solution concentrated to 50 ml., dried over potassium carbonate, and distilled under nitrogen at reduced pressure from a modified Claisen flask to give 40 g. (0.20 mole; 80%) of IV, b.p. 147–148°/0.55.

Attempts to prepare the 1-naphthylurethan, acid phthalate, and potassium xanthate were unsuccessful. In all cases, oils resulted which appeared to be polymeric in nature. None of the residues crystallized after standing two years.

1-Naphthaleneacetonitrile. The procedure of Adams and Thal (62) for the preparation of benzyl cyanide was modified for the synthesis of 1-naphthaleneacetonitrile. Sodium cyanide (36 g., 0.74 mole) and 32 ml. of water were placed in a 500-ml. flask equipped with a dropping-funnel and reflux condenser. The mixture was heated on a steam-bath to dissolve the cyanide, and a solution of 100 g. (0.57 mole) of 1-chloromethylnaphthalene in 71 g. of 95% ethanol was added dropwise over one-half hour. The mixture was refluxed on a steam-bath for four hours, cooled, filtered to remove sodium chloride, and the salt washed with a small portion of alcohol. As the filtrate was concentrated on a steam-bath, the nitrile layer separated and was then distilled from a modified Claisen flask to give 59 g. (0.35 mole, 62%) of a colorless oil, b.p. 158–160°/2, 136–137°/0.5; n_D^{25} 1.6173 [reported, b.p. 175–185°/11–14 (63), b.p. 150–152°/1.5 (64)].

1-(1-Naphthyl)-2-butanone. In a preliminary experiment in which the reaction mixture was immediately hydrolyzed with ammonium chloride after addition of the Grignard reagent, no ketone was obtained and a 79% recovery of nitrile was effected. The procedure finally utilized follows.

The Grignard reagent was prepared in the usual way from 4.1 g. (0.17 atom) of magnesium, 18.5 g. (0.17 mole) of ethyl bromide, and 100 ml. of anhydrous ether. A solution of 30 g. (0.18 mole) of 1-naphthaleneacetonitrile in 50 ml. of ether and 50 ml. of benzene was added dropwise over 75 minutes. The mixture was refluxed for two hours, 200 ml. of benzene was added, and the solution distilled until the vapor temperature reached 70°. Refluxing was continued for three hours and the mixture was allowed to stand at room temperature overnight. During the addition of the nitrile a yellow-orange precipitate formed which changed to a viscous, immobile mass after the refluxing period. After decomposing the precipitate with a dilute hydrochloric acid and ice mixture, the organic layer was separated and the aqueous layer extracted with ether. Neutralization of the aqueous acidic layer with ammonium hydroxide gave rise to troublesome emulsions during the extraction with ether. The ether extracts were combined, dried, and the ether removed. No residual imine was found.

The original organic layer was dried, and the ether and benzene evaporated leaving a viscous black oil. Distillation from a Claisen flask gave 5.3 g. (0.027 mole; 16%) of product, b.p. 119–134°/0.5, and a large polymeric residue. On removing the polymeric material from the flask with benzene, a white solid was obtained which did not melt below 300°. No further work was done on this substance.

Semicarbazone (XVI). The derivative was prepared from 0.25 ml. of the ketone and 0.25 g. of semicarbazide hydrochloride according to the earlier directions. Recrystallization gave the semicarbazone; yield 54%, m.p. 166–167.5°. A mixed melting point with semicarbazone XI showed no depression.

TABLE I

PHYSICAL CONSTANTS AND ANALYSES OF COMPOUNDS

COMPOUND	B.P., °C.	MM.	n_D (°C.)	M.P., °C.	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
I	147.5–153	0.2	1.6166(27)		84.81	7.12		84.40	7.18	
VI				103–104.5	81.72	5.76	3.81	81.46	5.77	3.79
VII				180.5–181.8(dec.)	57.65	4.19	2.05(S)	57.18	4.25	2.16(S)
VIII	136–139	0.3			83.97	8.05		84.05	8.01	
IX				175–176(dec.)	57.28	4.81	2.04(S)	56.75	4.42	2.09(S)
XI				165–167	70.56	6.71	16.46	70.25	6.62	16.63
XIII				104						
1-Naphthaldehyde	117–121[a]	2.4	1.6551(20)		84.59	5.16		84.32	5.18	
III	141.5–143.5	0.8	1.6099(25)		84.81	7.12		84.62	7.12	
XIV				163.8–165(dec.)	57.65	4.19	2.05(S)	57.22	4.24	2.09(S)
XV				115.5–117			3.81			3.69
IV	147–148	0.55	1.6185(30)		84.81	7.12		84.56	7.19	
XVI				166–167.5	70.56	6.71	16.46	70.88	6.69	16.69

[a] Previously reported by Ruggli and Preuss (60), b.p. 156–157°/14 mm.; Badger (59), b.p. 150°/13 mm.

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SUMMARY

The major product of the reaction of 1-naphthylmagnesium bromide with 3,4-epoxy-1-butene is 1-(1-naphthyl)-3-buten-2-ol. This was demonstrated in two ways: (a) reduction to 1-(1-naphthyl)-butan-2-ol, oxidation to 1-(1-naphthyl)-2-butanone, reduction to 1-(1-naphthyl)butane, and preparation of the known picrate of the hydrocarbon; (b) comparison of the semicarbazone of the 1-(1-naphthyl)-2-butanone so prepared and that prepared from the same ketone resulting from an unequivocal synthesis.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

PREPARATION OF N-SUBSTITUTED LACTAMIDES BY AMINOLYSIS OF METHYL LACTATE[2, 3]

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Although several investigators have described the preparation of lactamide (1–3) and certain N-substituted lactamides (4–11), little is known about N-substituted lactamides and the relation between the structure of amines and their reactivity with lactic esters. The purpose of the work described here was to prepare and examine several N-substituted lactamides, and to determine qualitatively the reactivity of various types of amines toward methyl lactate. The discovery (10) that acrylamides can be made by pyrolysis of the acetyl derivative of certain lactamides was partially responsible for our interest in lactamides.

In most instances the lactamides were prepared by allowing a mixture of the amine and methyl lactate to stand at about 35° for several days. Inasmuch as the commercially available methyl lactate used was substantially the *dl*-mixture, the resulting lactamides (usually isolated by distillation) were optically inactive. Although methyl lactate was the only ester used in the present work, it is likely that certain other lactic esters could be employed conveniently to make the lactamides.

Methyl lactate and monoalkyl amines reacted readily at about room temperature, giving excellent yields (Table I) of the corresponding N-alkyl lactamides. A high yield of amide was obtained even with an amine of relatively high molecular weight, for example, *n*-octylamine. These and other experiments showed that methyl lactate is much more reactive toward amines than simpler esters such as methyl acetate and methyl propionate; other workers (12) have observed a similar difference in reactivity toward ammonia.

No added catalyst was necessary in the aminolyses, and none was employed in any of the lactamide preparations described. The data in Table I shows that branching on the carbon atom next to the amine nitrogen reduces the yield. The yields based on unrecovered ester were 5–10% higher than the yields listed in Table I for these branched compounds. Amines such as *tert*-butylamine were not studied, but presumably amines of this type would be less reactive toward methyl lactate than isopropyl- and *sec*-butylamine.[4] Unsaturated and hydroxy- and methoxy-substituted amides were obtained in good yield from allyl-, and β-hydroxyethyl-, and β-methoxyethyl-amine, respectively. 6-Aminocaproic acid

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[3] For previous papers, see reference (10).

[4] This statement is supported by the low reactivity of 2-amino-2-ethylpentane (13) and the failure of *tert*-butylamine to react with ethyl acetate and ethyl oxalate (14).

TABLE I

N-SUBSTITUTED LACTAMIDES FROM PRIMARY AND SECONDARY AMINES

AMINE	YIELD[a], %	ANALYSES C Calc'd	C Found	H Calc'd	H Found	N Calc'd	N Found	M.P., °C.	B.P., °C.	MM.	d_4^{20}	n_D^{20}	M_D^{20} Calc'd[b]	M_D^{20} Found
n-Octyl-	96	65.6	65.6	—	—	7.0	6.9	52–52.5[c]	149–154	0.7	—	—	—	—
Isopropyl-	83	54.9	54.9	—	—	10.7	10.7	51–51.5[d]	94–97	0.3	—	—	—	—
Isobutyl-	95.6	57.9	58.1	—	—	9.7	9.7	47–48[d]	104–106	0.1	—	—	—	—
sec-Butyl[e]-	76	57.9	58.0	10.4	10.3	9.7	9.6	23.5–24[f]	98–99	0.6	0.9872	1.4523	39.92	39.70
Isoamyl[g]-	96	60.3	60.4	10.8	10.8	8.8	8.7	Liquid	116	0.7	0.9716	1.4557	44.54	44.51
4-Me-2-pentyl-	92	62.4	62.3	11.1	11.2	8.1	8.0	66–67[h]	113.5–116	0.3–0.5	—	1.4520[i]	—	—
Allyl[j]-	95	55.8	55.6	8.6	8.9	10.9	10.8	Liquid	86–87	0.2	1.0508	1.4753	34.84	34.62
Methallyl[k]-	92	58.7	58.5	9.2	8.8	9.8	9.7	Liquid	128.5–129	2.2	1.0249	1.4750	39.45	39.33
2-Hydroxyethyl[k]-	95	45.1	45.0	8.3	8.4	10.5	10.7	Liquid	137–139	0.003	1.1861	1.4862	32.21	32.16
2-Methoxyethyl-	87	49.0	49.0	8.9	8.6	9.5	9.5	48–50[c]	127	0.5	—	1.4610[i]	—	—
Cyclohexyl-	92	63.1	63.3	10.0	10.1	8.2	8.2	60–60.5[c]	125–136	0.2	—	—	—	—
Phenyl-	59	65.4	65.5	6.7	6.8	8.5	8.6	57–58[c]	147–156	0.1	—	1.5527[i]	—	—
Benzyl-	94[l]	67.0	66.9	7.3	7.2	7.8	7.8	47.5–48.5[h]	—	—	—	—	—	—
Pyrrolidine[k]	91	58.7	58.5	9.2	9.1	9.8	9.6	Liquid	134–135	7	1.1099	1.4900	37.45	37.29
Piperidine	84	61.1	60.8	9.6	9.1	8.9	8.7	Liquid	127–128.5	7	1.0728	1.4890	42.07	42.29
Morpholine	83	52.8	51.8	8.2	8.0	8.8	8.4	Liquid	110–111	1.4	1.1877	1.4940	39.12	39.01
Methylaniline	50	67.0	66.8	7.3	7.5	7.8	7.6	89.5–90.5[c]	—	—	—	—	—	—

[a] Of material isolated by distillation of the reaction mixture. Based on reagents charged. [b] For the atomic refraction of N in the disubstituted compounds the value 2.49 was used (reference 38); for N in the monosubstituted compounds, 2.76 (D'Alelio and Reid, *J. Am. Chem. Soc.*, **59**, 109 (1937); and for the other atoms the values of Eisenlohr (Gilman, *Organic Chemistry*, New York, 1938, p. 1739, John Wiley and Sons., Inc.). [c] From ether. [d] From ether-petroleum ether. [e] d_4^{40} 0.9713; n_D^{40} 1.4448. M_D^{40}: Calc'd, 39.92; Found, 39.76. [f] Freezing point. [g] d_4^{40} 0.9569; n_D^{40} 1.4483. M_D^{40}: Calc'd, 44.54; Found, 44.56. [h] From petroleum ether-benzene. [i] Undercooled liquid. [j] d_4^{40} 1.0372; n_D^{40} 1.4679. M_D^{40}: Calc'd, 34.84; Found, 34.60. [k] On the basis of titration data, the approximate rates of aminolysis were: Methallyl, 80% in 1 day; 2-hydroxyethyl, 75% in 2 hours and 91% in 1 day; and pyrrolidine, 75% in 30 minutes. [l] Of material isolated by crystallization.

reacted with methyl lactate, and methanol was distilled from the reaction mixture in high yield. The product, presumed to be N-5-carboxyamyllactamide, was not isolated in pure condition. Water distilled when the product was heated in a molecular still under a pressure of about 3 microns. Probably the viscous distillation residue contained the polymer $H[OCH(CH_3)CONH(CH_2)_5CO]_xOH$.

When the aminolysis study was extended to include cyclic and aromatic primary amines, aniline reacted incompletely, but both cyclohexyl- and benzylamine gave high yields (Table I). A second experiment with aniline, in which methanol was removed from the refluxing mixture by azeotropic distillation with cyclohexane (15), gave about the same yield (in both experiments the yields of lactanilide based on unrecovered ester were 15–20% higher than the yields given in Table I). The results shown in Table I suggest that primary amines generally are suitable for the preparation of lactamides under the conditions described. In connection with the decreased reactivity of aniline, the relatively low basicity of aromatic amines (16) and the fact that aniline is less reactive than primary aliphatic amines toward phenyl isocyanate (17) may be significant.

Dimethylamine (10), reacted readily with methyl lactate. Diethylamine did not react appreciably with methyl lactate at 35° even in the presence of water or sodium methoxide, both of which have been reported as catalysts for this type of reaction (12, 18–20). Diethylamine was substantially unreactive also toward methyl propionate and methyl glycolate. Diisobutyl-, diisoamyl-, di-*n*-amyl-, diphenyl-, dibenzyl-, diallyl-, and dibutyl-amine also were essentially nonreactive toward methyl lactate at 35°. It was shown by titration that the extent of aminolysis after 23 days at 35° was less than 3% for both diallylamine and dibutylamine.[5] The addition of water to the reaction mixtures caused these amines to be consumed at a higher rate, suggesting that the aminolyses had been accelerated. On examining the products, however, it was found that hydrolysis of methyl lactate and formation of amine lactates were primarily responsible for the utilization of free amine.

Although the results described above indicate that the higher dialkyl-, dialkenyl-, and diaryl-amines were relatively unreactive toward lactic esters under the experimental conditions, certain other secondary amines were reactive. N-Methylaniline for example, gave a moderate conversion (50%) to the corresponding lactamide (Table I). In a second preparation of N-methyl-N-phenyllactamide, methanol was removed during the reaction by azeotropic distillation with cyclohexane, but the conversion decreased to 27%. Possibly increased condensation-polymerization of the methyl lactate was responsible for the lower conversion to the amide.

Titration data indicated that *sym*-dimethylethylenediamine reacted readily with two moles of methyl lactate at 35°, and a high yield of methanol was obtained on distillation of the reaction mixture. Attempts to isolate the amide in pure condition, however, were unsuccessful. The experiments with this amine

[5] Diethylamine and certain higher secondary amines have been observed to be relatively unreactive in the Mannich reaction (21, 22), in the aminolysis of ethyl oxalate (23), and in 1,4-addition to ethyl cinnamate (24).

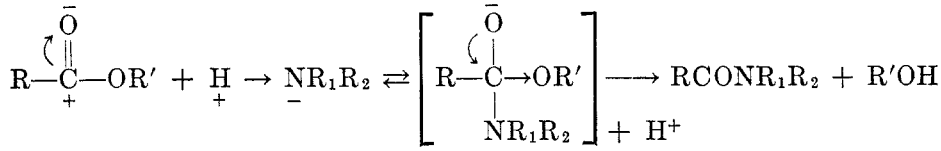
and with methylaniline suggest that methyl secondary amines (CH_3NHR) generally are moderately reactive toward methyl lactate.

Although diethylamine was unreactive toward methyl lactate, a related secondary amine, that is, diethanolamine, reacted readily, giving N,N-di-2-hydroxyethyllactamide in high yields. Attempts to distill the high-boiling, viscous product were unavailing. Ethylethanolamine ($EtNHCH_2CH_2OH$) also reacted with methyl lactate, but its rate of reaction was lower than that of diethanolamine. Presumably alkylethanolamines ($RNHCH_2CH_2OH$) in general are moderately reactive toward methyl lactate. This moderate reactivity can be attributed to the relatively low density of electrons around the nitrogen caused by the electron-attracting influence of the hydroxyl group.

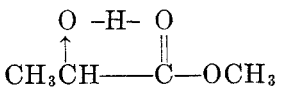
Several cyclic secondary amines (pyrrolidine, piperidine, and morpholine) reacted readily with methyl lactate at 35° and gave high yields of the corresponding lactamides.[6]

The results obtained with secondary amines indicate that, although amines of this class are generally much less reactive than primary amines, certain types of N,N-disubstituted lactamides can be made readily by the aminolysis of methyl lactate. Tertiary amines might be expected (28) to react with methyl lactate to yield quaternary ammonium lactates.

The following mechanism for the ammonolysis of lactic esters and esters in general has been proposed (12):



The electromeric shift in lactic esters would presumably be aided by the weak hydrogen bridge between the hydroxyl group and the carbonyl oxygen (29), and the fractional positive charge on the carbonyl carbon atom would probably be further increased by the inductive effect of the hydroxyl group:



This would facilitate the nucleophilic attack by amine (or amide ion) and may play a part in the reactivity of methyl lactate and methyl glycolate toward amines, as contrasted with the lower reactivity of methyl acetate and methyl propionate (12).

In evaluating the effect of the structure of the amine, there are at least two factors to be considered: (a) The inductive effect of substituents, operating to

[6] Piperidine is more reactive than diethylamine to certain esters (25) in the Mannich reaction (21) and in addition to the vinyl group of vinylpyridine (26). It also reacts readily with ethyl formate under conditions where methylaniline and diphenylamine are unreactive (27).

make nucleophilic attack more or less easy by altering the electron density about the amino nitrogen; and (b) steric effects, described by Brown (30, 31) as "F-strain" and "B-strain." It is evident that in the case of the *n*-alkyl primary amines neither of these factors is interfering with the preparation; for the alkyl primary amines branched next to the amine nitrogen they may be exerting a slight inhibiting effect on the reaction.

The striking difference in the behavior of dimethyl- and diethyl-amine indicates a strong inhibiting force at work for the latter compound. It has been reported (32) that diethylamine is relatively unreactive toward several reagents.[5] Brown (30, 31) has shown that dimethylamine reacts with tri-*tert*-butylboron but that diethylamine fails to do so; this is ascribed to the presence of more "B-strain" in diethylamine and to the high "F-strain" (33) between the amine and the boron compound; that is, to steric factors. The "B-strain" is removed, in whole or in part, by "tying back" the ethyl groups in morpholine, pyrrolidine, and piperidine.

Dimethylamine reacts readily with methyl glycolate and methyl lactate at about 35°, but fails to react with methyl α-hydroxyisobutyrate under similar conditions. Probably steric factors of a different type, that is, those around the carbonyl group of the ester, are largely responsible for the relative nonreactivity of the methyl α-hydroxyisobutyrate.

Acknowledgment. The authors are grateful to Prof. Allan R. Day for helpful discussions, to Edward J. Schaeffer for assistance with the preparations, to C. L. Ogg, C. O. Willits, and their coworkers for analytical data, and to Carbide and Carbon Chemicals Corporation, Commercial Solvents Corporation, E. I. duPont de Nemours and Company, Rohm and Haas Company, Sharples Chemicals, Inc., and Shell Chemical Corporation for generous samples.

EXPERIMENTAL

Materials. Most of the amines were commercial samples. The pyrrolidine was kindly supplied by C. F. Woodward and Abner Eisner of this Laboratory. Octyl- and methoxyethyl-amine were dried over solid potassium hydroxide and then distilled. In the experiments, no attempt was made to exclude traces of water in view of its known catalytic effect in aminolysis reactions. The methyl lactate, obtained commercially, was carefully distilled through an efficient fractionating column. Refractive indices at 20° of amines after fractionation through Podbielniak or Fenske columns are: *sec*-butyl-, 1.3937; *n*-octyl-, 1.4300; 4-methyl-2-pentyl-, 1.4083; ethanol-, 1.4538; ethylethanol-, 1.4410; methallyl-, 1.4328; diallyl-, 1.4402; 2-methoxyethyl-, 1.4062; and dibutyl-, 1.4180. The literature gives the following values: *sec*-butyl-, 1.394 (34); *n*-octyl-, 1.430 (34); 4-methyl-2-pentyl-, 1.4086 (35); ethanol-, 1.4539 (34); ethylethanol-, 1.444 (36); methallyl-, 1.4303 (37); diallyl-, 1.4399 (37); and dibutyl-, 1.4186 (35).

Aminolysis. Most of the lactamides were made by mixing the reagents with the amine in 10% excess and storing at 35° for 1 to 3 weeks; the mixtures containing cyclohexyl-, benzyl-, and β-methoxyethyl-amine were stored for 4 weeks, and that with isopropylamine for 5 weeks.[7] It was established that incomplete reaction was not due to insufficient reaction

[7] Glasoe and Audrieth (5) report a 50% yield of N-cyclohexyllactamide from ethyl lactate after 12 days at 25°. D'Ianni and Adkins (4) prepared N-pentamethylenelactamide in 70–80% yield by refluxing ethyl lactate with 10% excess piperidine for 20 hours. For the

time. In two experiments with *sec*-butylamine—one lasting 4 days, the other 2 weeks—the yields of the lactamide were essentially the same.

Because it typifies the procedures, the preparation of N-*n*-octyllactamide is described in detail: To 1.0 mole of methyl lactate was added 1.1 moles of *n*-octylamine; the mixture was stored for 2 weeks and then distilled through a 20-inch Vigreux column. The distillate collected at atmospheric pressure (24 g.) was identified as methanol (boiling point and refractive index); when the pressure was lowered (oil pump), 12 g. of an intermediate fraction distilled at 30°/30 to 148°/0.5. The last fraction (194 g.) was N-octyllactamide, b.p. 148–154°/0.5; yield, 96%. A sample was recrystallized from ether three times and its melting point and elementary composition were determined (Table I). The lactamides that were solid at room temperature were recrystallized; most of the liquid lactamides were carefully redistilled through the Vigreux column prior to determination of physical properties (Table I).

Because benzyllactamide crystallized in the stillhead and could not be conveniently distilled, it was isolated and purified by crystallization.

In the experiment with methylaniline, marked with a relatively low yield (50%), unreacted methyl lactate was not recovered. A high-boiling material, however, corresponding to 36% by weight of the initial ester, was obtained. This was tentatively identified as a partially aminolyzed polylactate.

When a mixture of ethylethanolamine (0.55 mole) and methyl lactate (0.5 mole) was allowed to stand at 35°, the aminolysis (as determined by titration) was about 70% after 4 days. Aminolysis did not proceed much further even in 5 weeks. On distillation, an 88% yield of methanol and several high-boiling fractions having different refractive indices were obtained. The largest fraction [30 g. distilling at 95–114° (3 to 7 microns)] might have been the impure N,N-ethylhydroxyethyllactamide; d_4^{20} 1.141 and n_D^{20} 1.4728. M_D^{20} Calc'd: 41.18; Found: 39.62. In a second experiment, six fractions (amounting to a conversion of 64% into the lactamide) were obtained by distillation in a molecular still. These had refractive indices (n_D^{20}) ranging from 1.4762 to 1.4811.

Anal. Calc'd for $C_7H_{15}NO_3$: N,8.7; Found: N,8.7.

Dibutylammonium lactate was obtained from a mixture of methyl lactate, dibutylamine and water that had stood for several weeks. After crystallization from ether, m.p. 77.5–79°.

Anal. Calc'd for $C_{11}H_{25}NO_3$: C, 60.2; H, 11.5; N, 6.4.
Found: C, 60.6; H, 11.7; N, 6.4.

Two mixtures of 0.10 mole of methyl lactate and 0.11 mole of diphenylamine—one stored at 35° for 15 days, the other at 100° for 13 days—failed to yield methanol on distillation.

Experiments with dimethylamine. (a) *Methyl propionate.* A mixture of 88 g. (1 mole) of the ester and 49.5 g. (1.1 moles) of amine was stored for 1 month. Titration indicated that only about half the amine had reacted, hence 1 ml. of water was added as catalyst (12). After an additional three months, titration indicated 85% reaction. After drying with calcium sulfate, dimethylpropionamide was distilled in 70% yield. The middle fraction (63% yield) had the following properties, in good agreement with the literature (38): b.p. 81.5–82°/26; n_D^{20} 1.4400; n_D^{25} 1.4382; d_4^{2} 0.9269; M_D^{20} 28.77.

Anal. Calc'd for $C_5H_{11}NO$: N, 13.8; Found: N, 13.9.

(b) *Methyl acetate.* A similar experiment with this ester showed 60% reaction after 1 month and 89% reaction after an additional 3 months in the presence of water; the yield of dimethylacetamide obtained by distillation was 69%. The middle fraction (58% yield) had the following properties, which are in good agreement with the literature (38): b.p. 74–74.5°/26; n_D^{20} 1.4373; n_D^{25} 1.4360; d_4^{20} 0.9429; M_D^{20} 24.22.

Anal. Calc'd for C_4H_9NO: N, 16.1; Found: N, 16.0.

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product, they reported b.p. 128–9°/7, n_D^{20} 1.4850, N, found 8.78. Bischoff and Walden (6) prepared N-methyl-N-phenyllactamide from the amine and lactic acid, lactide, and ethyl lactate, which gave the lowest yield even after 1 day's heating at 200°. They report m.p. 95–96°. Leipen (8) prepared lactanilide from the amine and ethyl lactate, and reports m.p. 58°.

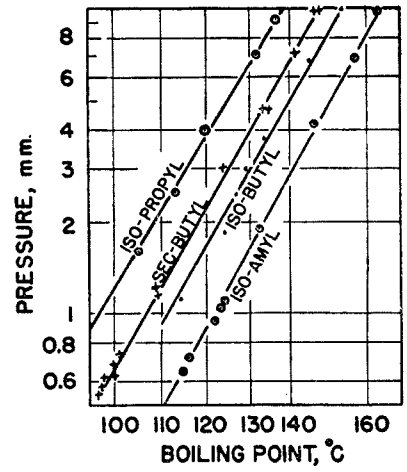

FIG. 1. BOILING POINTS OF N-ALKYL LACTAMIDES

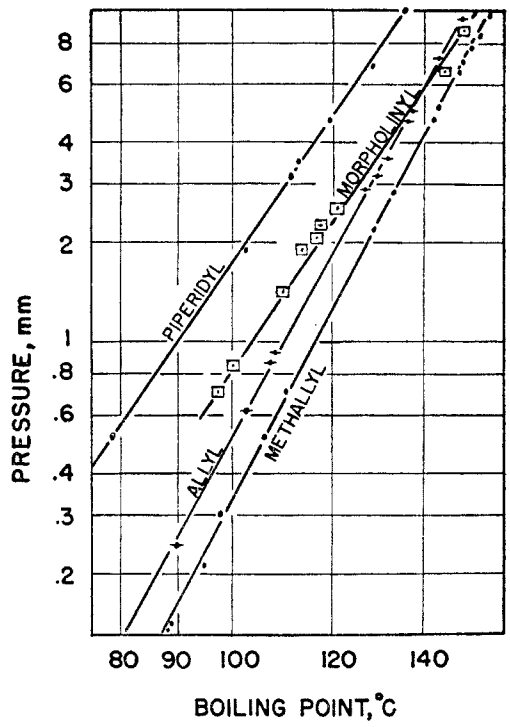

FIG. 2. BOILING POINTS OF N-SUBSTITUTED LACTAMIDES

(c) *Methyl glycolate.* Titration of a mixture of 90 g. (1 mole) of redistilled ester and 1.1 moles of amine that had been stored for 1 week showed 95% reaction; standing for an additional week produced no further change. After distillation of methanol and excess amine, dimethylglycolamide was collected at about 90°/0.5 in 89% yield. After several crystallizations from ether, and thorough drying, it melted at 43–45.5°. This material was deliquescent.

Anal. Calc'd for $C_4H_9NO_2$: N, 13.6; Found: N, 13.4.

Diethylamine was unreactive toward both methyl propionate and methyl glycolate.

Polymerization of N-allyllactamide. (a) Air was passed through allyllactamide containing 0.14% cobalt octanoate. After 10 days the mixture had darkened without perceptible polymerization.

(b) Sealed tubes containing allyllactamide and different amounts of benzoyl peroxide (some sealed under nitrogen and some under air) were kept at 100° for 8 days. Air and nitrogen had approximately the same effect. A 1% concentration of benzoyl peroxide was only slightly more effective than no peroxide, and 5% and 10% concentrations of benzoyl peroxide gave increasingly viscous solutions, indicating some polymerization.

Boiling points at different pressures of some of the lactamides (Figures 1 and 2) were carefully determined with an improved tensimeter-still (39). The boiling points of Table I were observed during the preparation.

SUMMARY

The aminolysis of methyl lactate with primary and secondary amines is shown to be a simple and convenient method for preparing many N-monosubstituted lactamides and certain types of N-disubstituted lactamides.

The preparation and properties of seventeen N-substituted lactamides are described.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

PREPARATION AND PROPERTIES OF N-*n*-ALKYLLACTAMIDES[2]

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Although the preparation of lactamide (3–9) and certain N-substituted lactamides (1) has been described,[2] N-*n*-alkyllactamides have not been studied extensively (1, 10, 11). The effect of increasing the amine chain-length on the reaction of amine with lactic esters has not been investigated.

The purpose of the present work was to prepare and examine several N-*n*-alkyllactamides, determine qualitatively the reactivity of the primary-*n*-aliphatic amines toward methyl lactate, and develop correlations (12) among the various physical properties of the lactamides. Acetic acid esters of some of these lactamides were also prepared and examined.

Methyl lactate and mono-*n*-alkyl amines interacted readily at room temperature, giving excellent yields (Table I) of the corresponding lactamides; no added catalyst was necessary.

The lower reactivity of simpler esters, such as methyl acetate and methyl propionate, in this type of reaction has led to the suggestion that the *alpha* hydroxyl group promotes nucleophilic attack by the amine (1). This effect may mask any difference in reactivity of the amines as the amine chain-length is increased, for all the lactamides studied here were obtained without difficulty.

The lactamides were prepared by the previously described method; that is by mixing redistilled methyl lactate with a 10% excess of the amine, and allowing the mixture to stand for 7 or more days. The mixtures containing the amines of lower molecular weight through *n*-decylamine were kept at room temperature; the rest were kept liquid by storage at 50°. After distillation, a sample of each lactamide (except butyl) was crystallized several times from an appropriate solvent (Table I) and the melting point and analytical data were determined; the butyl derivative was redistilled prior to examination. The lactamides as distilled were of high purity; the yields in Table I refer to the distilled product.

The acetates of five lactamides (Table II) were obtained in 90–98% yield by acetylation with acetic anhydride in the presence of sulfuric acid catalyst.

Repellency and larvicidal tests. Tests conducted by the Bureau of Entomology and Plant Quarantine, U. S. Department of Agriculture, revealed that N-*n*-butyl- and N-*n*-amyllactamide applied to the skin had effective repelling times of 145 and 265 minutes, respectively, against *Aedes aegypti*, as compared with 180 and 360 minutes for dimethyl phthalate and ethyl hexanediol, respectively, the controls. At a concentration of 10 parts per million, N-*n*-tetradecyllactamide

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] For previous papers on lactamides see References (1) and (2). Reference (1) has an extensive bibliography on earlier work.

acetate gave 100% mortality against anopheline larvae in 48 hours. A lactamide described earlier, N-1,3-dimethylbutyllactamide (1), when applied to cotton stockings at 3.3 g. per square foot repelled *Aedes aegypti* for 15 days; five bites

TABLE I

PREPARATION AND PROPERTIES OF $HOCH(CH_3)CONH(CH_2)_nH$

n	YIELD,[a] %	REACTION TIME, DAYS	M.P., °C.	SOLUBILITY[b]	ANALYSES					
					C		H		N	
					Calc'd	Found	Calc'd	Found	Calc'd	Found
1	91	21	71.5–72[c]	—	46.6	46.8	8.8	8.9	13.6	13.9
2	97	14	44.5–45[d]	—	51.3	51.1	9.5	9.6	12.0	11.9
3	87	12	20[e,f]	—	54.9	55.5	10.0	10.4	10.7	10.7
4	98	10	25.5[e]	—	57.9	57.9	10.4	10.5	9.6	9.6
5	97	19	29.5[e,f]	6.60	60.3	60.8	10.8	10.7	8.8	8.8
6	98	15	41.5–42[f]	1.95	62.4	62.4[g]	—	—	8.1	8.2
8	96	13	52–52.5[h]	0.105	65.6	65.6[g]	—	—	7.0	6.9
10	98	10	61.5–62[h]	0.010	68.1	68.3	11.9	11.8	6.1	6.2
12	96.5	7[i]	68.5–69.5[h]	0.004	70.0	70.3	12.1	12.2	5.4	5.4
14	94.5	11[i]	74.5–75[h]	0.003	71.5	71.6	12.4	12.1	4.9	4.9
16	98	11[i]	79.5–80[j]	0.007	72.8	72.7	12.5	12.5	4.5	4.4
18	99	11[i]	83–84[j]	0.003	73.8	73.8	12.7	12.6	4.1	4.1

[a] Based on methyl lactate. [b] Grams per 100 ml. of water, at 25°; with an accuracy of 0.003 g.; the lower amides were completely soluble. [c] From benzene-acetone. [d] From petroleum ether-butanol; reference (10) gives m.p. 48°. [e] Freezing point. [f] From ether-petroleum ether. [g] Found by wet oxidation. [h] From ether. [i] At 50°. [j] From ethanol.

TABLE II

PROPERTIES OF $CH_3COOCH(CH_3)CONH(CH_2)_mH$

m	B.P., °C. (MM.)	M.P., °C.	n_D^{20}	ANALYSES						SAPON. EQUIV.	
				C		H		N			
				Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
2	110(1.5)	54–55[a]	1.4465[b]	52.8	53.0	8.2	8.5	8.8	8.6	159.2	143.2
4	120(1.8)	41.5–44	1.4480[b]	57.7	58.0	9.2	9.1	7.5	7.5	187.2	187.2
8	155(0.4)	10[c]	1.4525[d]	64.2	64.2	10.4	10.4	5.7	5.7	243.3	244.9
14	—	57.5–58.5[e]	—	69.7	70.0	11.4	11.6	4.3	4.3	327.5	316.5
18	—	71–72[f]	—	72.0	72.0	11.8	11.6	3.6	3.8	383.6	380.2

[a] From ether. [b] For the undercooled liquid. [c] Freezing point. [d] Density, d_D^{20} 0.9679; M_D^{20} Calc'd, 67.75; Found, 67.82. [e] From petroleum ether. [f] From ethanol-water.

then occurred in 28 days. The methods used in these tests have been described (13).

Hygroscopicity. Ethyl-, propyl-, butyl-, and amyl-lactamide were somewhat hygroscopic. Approximate equilibrium compositions at 25° of N-propyllactamide-water mixtures (expressed as weight % amide) at various relative humidities

were: 97% (22.5% relative humidity); 94% (32.5% relative humidity); 93% (48% relative humidity); and 89% (64.5% relative humidity). The propyl derivative appeared to be the most hygroscopic.

Physical constants. The boiling points at low pressures (Figures 1 and 2) were carefully determined in equipment known to give accurate results (14, 15). Lactamide and N-*n*-butyllactamide had almost identical boiling points in the

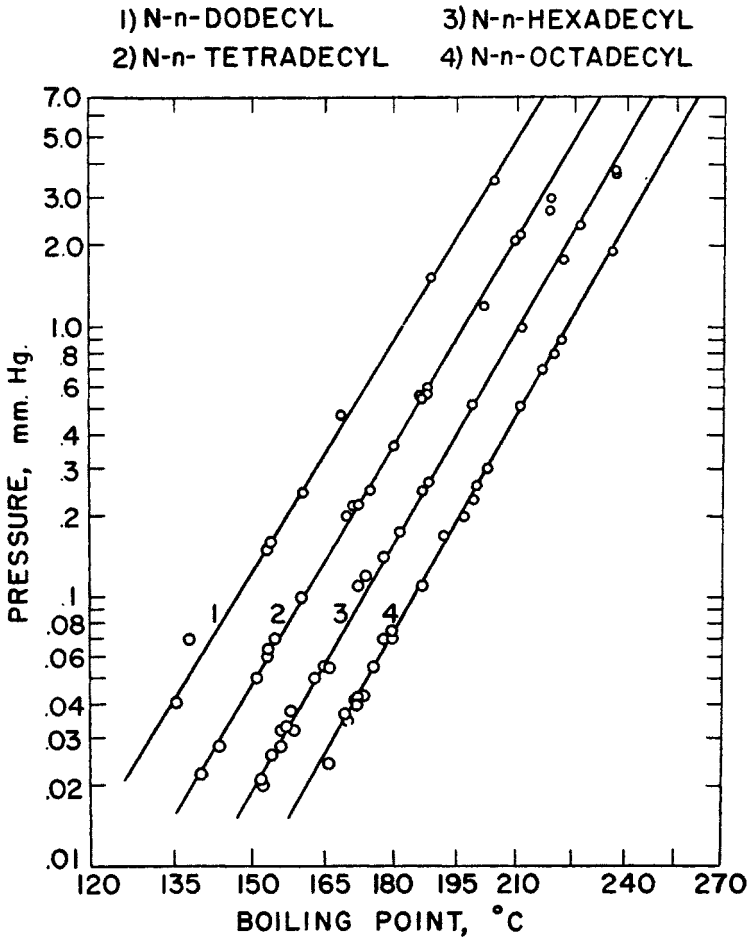

FIG. 1. BOILING POINTS OF LOWER N-*n*-ALKYLLACTAMIDES

range studied. In the figures, the ordinate is laid off as log p, the abscissa as 1/[T(°C.) + 273].

As observed previously (12, 16–18), it is possible to express the boiling points (in °K.) as a function of the total number of carbon atoms (x). For 10 mm. and 1.0 mm., the equations are

$$T_{10}^2 \times 10^{-4} = 0.7605\ x + 13.40 \qquad (x = 5 \text{ to } 21) \qquad [1]$$

$$T_{10}^2 \times 10^{-4} = 0.6620\ x + 10.78 \qquad (x = 5 \text{ to } 21) \qquad [2]$$

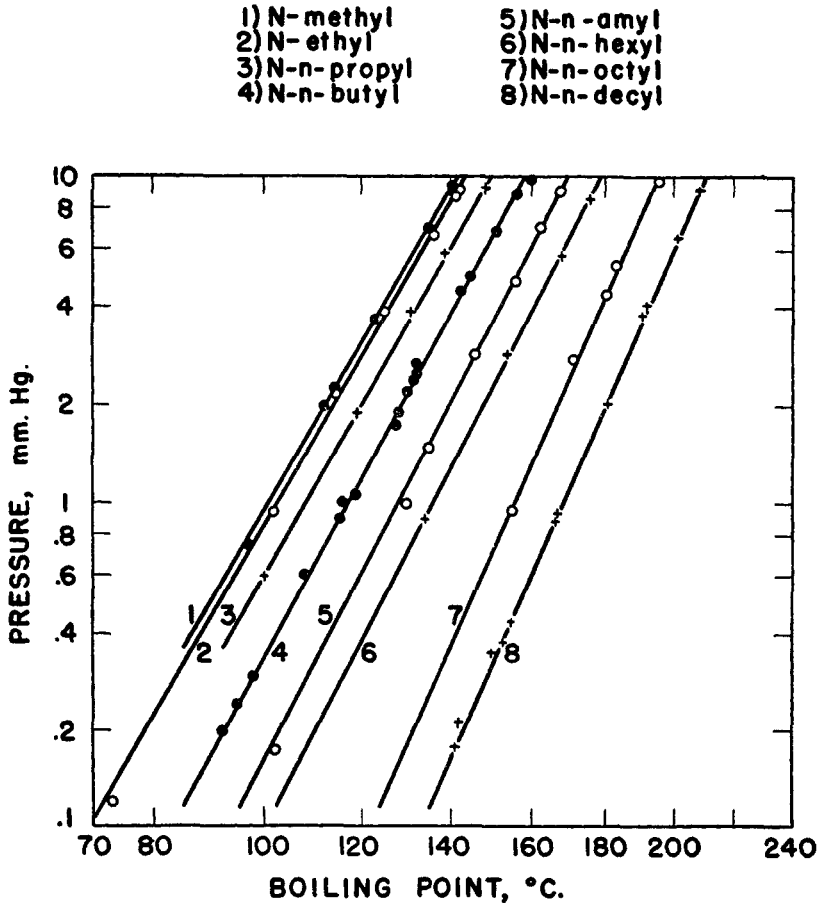

FIG. 2. BOILING POINTS OF HIGHER N-*n*-ALKYLLACTAMIDES

TABLE III

PHYSICAL CONSTANTS OF $HOCH(CH_3)CONH(CH_2)_mH$

m	d_4^{20}	n_D^{20}	M_D^{20}		d_4^{40}	n_D^{40}	M_D^{40}		VISCOSITY[b]
			Calc'd	Found			Calc'd	Found	
2	—	—	—	—	1.0290[a]	1.4480[a]	30.68	30.48	—
3	1.009	1.4560	35.30	35.33	0.9964	1.4487	35.30	35.29	34.6
4	0.9905[a]	1.4563[a]	39.92	39.87	.9764	1.4493	39.92	39.91	36.4
5	—	1.4569[a]	—	—	.9596	1.4496	44.54	44.55	38.1
6	—	1.4573[a]	—	—	—	—	—	—	—

[a] For the undercooled liquid. [b] Centipoises, at 40°.

Equations [1] and [2] give calculated boiling points which agree with the observed boiling points with an average deviation of 1°. They should be useful in estimating the boiling points of the missing members of the series. It was likewise possible

to relate refractive index (n_D^{20} and n_D^{40}) and density (d_4^{40}) (Table III) to the number of carbon atoms (x), using equations similar to those recently reported (12):

$$\frac{x}{d_4^{40}} = 1.1580x - 0.9310 \quad [3]$$

$$\frac{x}{n_D^{20}} = 0.6840x + 0.0189 \quad [4]$$

$$\frac{x}{n_D^{40}} = 0.6885x + 0.0105 \quad [5]$$

Equations [3], [4], and [5] give computed values of density and refractive index agreeing with the observed values with an average deviation of 0.0005 and 0.0001, respectively.

ACKNOWLEDGMENT

The author wishes to thank Sharples Chemicals, Inc.; Rohm and Haas Company; and Armour and Company for generous samples of their amines; J. H. Lengel for his preparation of the lactamide acetates; Edward J. Schaeffer and E. H. Harris for assistance in preparing some of the lactamides; C. O. Willits, Clyde L. Ogg, Mary Jane Welsh, and Ruth Brand for the analyses; and the Bureau of Entomology and Plant Quarantine for the repellency and larvacidal data.

EXPERIMENTAL

Materials. Commercial methyl lactate (made from fermentation acid) was carefully distilled *in vacuo*. This material had only slight optical activity. The ammonia, methylamine, and ethylamine were commercial anhydrous grade. The *n*-propylamine was Eastman Kodak best grade. The remaining amines were commercial samples; each was stored over potassium hydroxide for a few days, then filtered and distilled through a Fenske or Podbielniak column. In view of its catalytic activity (19), no precautions were taken to exclude traces of water. The refractive indices (n_D^{20}) of the liquid amines were: *n*-butyl-, 1.4013; *n*-amyl-, 1.4113; *n*-hexyl-, 1.4198; *n*-octyl-, 1.4300; and *n*-decyl-, 1.4361, all in good agreement with the literature values. For the higher amines neutral equivalents were determined: dodecyl-, 185.0, (calc'd, 185.2); tetradecyl-, 213.5, (calc'd, 213.3); hexadecyl-, 241.5, (calc'd, 241.3); and octadecyl-, 270.8, (calc'd, 269.3).

Lactamides. The preparation of N-*n*-hexyllactamide is typical, and is described in detail. To 208 g. (2.0 moles) of the ester was added 222 g. (2.2 moles) of the amine; after being shaken, the mixture was stored at room temperature. At the end of 15 days, the mixture was distilled (Vigreux column), and 55 g. of methanol (identified by boiling point and refractive index) was collected at atmospheric pressure. Vacuum was then applied (1 mm.), and 3 g. of an intermediate fraction was obtained at 28–120°. The lactamide was then collected at the ultimate pump vacuum, b.p. 120–128° (0.3 mm.); yield, 341 g. (98%). During the vacuum distillation, an additional 18 g. of material (identified as a mixture of methanol and amine) collected in a cooled trap in the vacuum line. A sample of the lactamide was recrystallized thrice from an ether-petroleum ether mixture, m.p. 41–41.5°. After being warmed at 36°/50 for 1.5 hours, the m.p. was 41.5–42°. The sample was then analyzed.

The octadecyl derivative, however, crystallized excessively in the stillhead and was obtained as a residue.

Lactamide was prepared from 1275 g. of methyl lactate by the method of Gucker and Allen (5); during addition of the ammonia the mixture was stirred and cooled with tap water to avoid the discoloration which occurred when the mixture was permitted to warm

spontaneously. When absorption of ammonia was complete, methanol and excess ammonia were evaporated at room temperature under vacuum (50 mm.) for 12 hours, and the crude product was obtained in 97% yield as a porous white mass, m.p. 67–73.5°.

Anal. Calc'd for $C_3H_7NO_2$: N, 15.7. Found: N, 15.4.

Michel (7) reports m.p. 76.4° for the racemic product.

Lactamide acetates. The lactamide acetates were prepared by the method of Fein and Fisher (12), except that the tetradecyl and octadecyl derivatives were isolated by washing the reaction mixture with hot water, filtering, and drying. The butyl and octyl compounds were not further purified before analysis; samples of each of the others were recrystallized several times from an appropriate solvent (Table II).

An attempt to acetylate N-ethyllactamide acetate further, to N-acetyl-N-ethyllactamide acetate, was not successful; a sample of the lactamide acetate was heated to reflux with 100% excess acetic anhydride in the presence of sulfuric acid as catalyst, but the compound was recovered unchanged. The agreement of the observed saponification equivalents (Table II) with those calculated for one saponifiable group indicates that the amide is more resistant than the acetoxy group under the conditions used (2b).

Physical constants. The boiling points (Fig. 1) of the first eight lactamides (Table I), with the exception of butyl, were determined in a tensimeter-still (15); an automanometer still (14) was used for the butyl derivative. For lactamide and for the dodecyl and higher lactamides (Fig. 2), a modification of the tensimeter-still was used, permitting the distillate to be kept molten until it reached the receiver.

Refractive indices, densities, and viscosities were measured by methods already described (12). Water solubility of the lactamides was determined by the method of Badgett, *et al.* (20), except for the amyl derivative, for which the method of Fordyce and Meyer (21) was used.

SUMMARY

N-*n*-alkyllactamides were obtained in 87–99% yield by the aminolysis of methyl lactate with methyl-, ethyl-, *n*-propyl-, *n*-butyl-, *n*-amyl-, *n*-hexyl-, *n*-octyl-, *n*-decyl-, *n*-dodecyl-, *n*-tetradecyl-, *n*-hexadecyl-, and *n*-octadecyl-amine. The acetates of ethyl-, butyl-, octyl-, tetradecyl-, and octadecyl-lactamide were made in 90–98% yield by acetylation with acetic anhydride. Three lactamides were mosquito repellents, and one lactamide acetate was a larvicide.

The properties measured for all the lactamides were the boiling points below a pressure of 10 mm. of mercury, and the melting points; for some, d_4^{20}, d_4^{40}, n_D^{20}, n_D^{40}, viscosity, and water solubility were also determined. The lactamides are low-melting, high-boiling compounds, and the higher homologs have low water-solubility.

PHILADELPHIA 18, PA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE ROYAL HELLENIC NAVY]

o-AMINOPHENOL DERIVATIVES

LUCAS C. GALATIS

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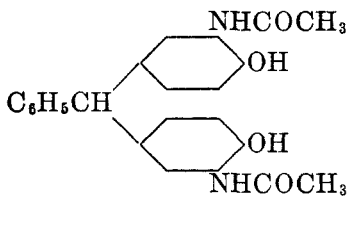
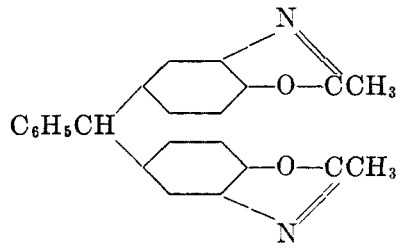
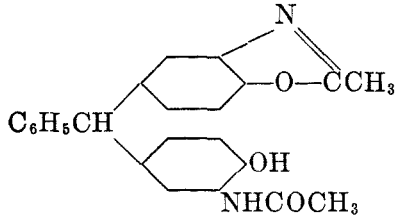
In a preceding paper (1) the opinion was expressed that by heating 3,3′-diacetylamino-4,4′-dihydroxytriphenylmethane (I), the corresponding anhydro base II could probably be obtained. The case was interesting in so far as the expected compound would contain two methylbenzoxazole groups connected through an atom of carbon, whilst the few condensed dioxazoles I was able to find in the literature available to me, bear the oxazole groups either on the same phenyl or symmetrically on the two phenyls of an anthraquinone. The experiment justified this opinion, for when heated at 275°, compound I readily gives off water, leaving a residue which consists principally of the anhydro base II, to which the indexing name 5,5′-*bis*-(2-methylbenzoxazolyl)phenylmethane can be given



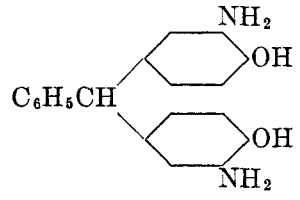
I



II



III



IV

The constitution of this base derives not only from the process of its formation, but also from the fact that when heated with 25% HCl, it yields the same aminophenol IV obtained from I by boiling with the same acid, as described in the preceding paper.[1]

The anhydro base is amorphous. It can be isolated either as a hard, colorless, and transparent resin, or in fine white flakes. As expected, it is insoluble in caustic alkalies and is precipitated from its solutions in strong HCl by dilution with

[1] The identity of the two hydrolysis products was checked not only by their melting points but also by means of their respective benzylidene derivatives, which proved to be identical.

water. It seems to give no crystalline salts with aqueous acids. The only crystalline derivative obtained is a compound with $HgCl_2$.

While studying the conditions of the dehydration, it was noticed that if the flask was lifted from the oil-bath immediately after all solid matter had disappeared, the evolution of water continued for some time, although the temperature of the liquid had fallen considerably. In this particular case, it was found that the caustic alkali with which the benzene solution of the residue was washed in order to eliminate possible phenolic impurities, on acidifying precipitated a certain amount of a new crystalline substance which was converted by further heating into the anhydro base and gave, when heated with strong HCl, the same aminophenol as I and II. It was further found that when the dehydration of I was carried out from the beginning at lower temperatures the amount of this substance increased considerably, and it separated from the benzene solution of the residue on standing as a crystalline powder. When the temperature was kept at 230°, the yield reached 30% of the quantity of I worked up. These facts proved that under milder conditions only one molecule of water was split off and an intermediate product was formed, a semianhydride corresponding to formula III. But the dehydration cannot be conducted in such a manner that only this intermediate product is formed, and the residue is always more or less rich in the anhydro base, according to the temperature and time of heating.

The preparation of I by condensation of acetyl-*o*-aminophenol and benzaldehyde, as described previously gives a very poor yield. It was therefore considered necessary to improve the reaction. The principal reason for the low yield was found in the fact that the condensation is not complete at the end of the third day, as one is inclined to believe from the apparent amount of the precipitate formed, but after two weeks. In addition, the considerable quantity of unreacted benzaldehyde agglutinates the liberated base when the hydrochloride is hydrolyzed, and prevents it from separating in a fine, easily filtrable form. A description of the improved method, which gives a yield of 75–80% is given below.

EXPERIMENTAL[2]

3,3'-Diacetylamino-4,4'-dihydroxytriphenylmethane (*I*). Acetylaminophenol (151 g., 1 mole) is dissolved in 750 ml. of concentrated HCl in a glass-stoppered bottle, 55 ml. (0.5 mole) of freshly distilled benzaldehyde added, and the mixture left in a dark place. The next day a considerable deposit of the hydrochloride of the condensation product appears at the bottom of the vessel; this increases from day to day. Every morning the hard cake is broken up to a coarse powder with a flattened glass rod. After two weeks the condensation is practically complete. The light green hydrochloride is filtered through sintered-glass, washed with 2:1 hydrochloric acid (by volume), and hydrolyzed. For this purpose it is first treated with 2 liters of cold water, the resulting gray flakes left to settle, the supernatant liquid poured off, and the decantation repeated once more. The deposit is then steam-distilled in order to eliminate some unreacted benzaldehyde. After cooling, the fine grayish powder is washed by decantation until neutral, filtered, and dried on porous plates. It is

[2] Corrections for Ref. (1): p. 335, read yield of *o*-aminophenol as 25 g., not 35 g. The statements on pp. 332, 333, and 340 concerning oxidation of the condensation product must be revised; the reaction is being reinvestigated.

finally purified by refluxing with alcohol or still better with acetone, to dissolve a red-brown impurity; yield, 75–80%.

Anhydro base (II). Compound I (20 g.) is heated at 275° and 10 mm. for 1.5 hours. By this time the powder is converted into a dark, red-brown oil which gathers at the bottom of the flask.[3] The transparent red-brown residue is extracted with boiling ligroin (b.p. 60–100°) and the combined extracts washed with 2 *N* KOH in order to eliminate all phenolic impurities. The light orange solution is concentrated, shaken with a few drops of concentrated HCl which absorb most of the coloring matter, filtered, washed with water, and transferred in portions into a distillation flask bearing a special side tube for materials which rapidly solidify. The rest of the ligroin is driven off and the anhydro base distilled under 1–2 mm. It appears as a thick, transparent, slightly colored oil which solidifies in the receiver to a hard resin. In order to obtain a colorless product it may be necessary to repeat the distillation.

If desired to have the base in the form of flakes, the decolorized ligroin solution is extracted with a cold mixture of 100 ml. of HCl and 200 ml. of water. The acid layer containing the base is then passed through a dry filter in order to keep back any trace of ligroin that could cause the flakes to stick together, and diluted gradually under stirring with five times its volume of cold water. The base separates in white flakes that are filtered and dried on a porous plate. It is absolutely necessary that all operations with the base, when in form of flakes, be carried out at a temperature as low as possible, always below 15°, otherwise the flakes will soften and stick together. Because of this tendency of the flakes to agglutinate it is not advisable to filter them by suction.

The anhydro base is sparingly soluble in boiling water, moderately so in ligroin at ordinary temperature, and soluble in all proportions in the other usual organic solvents. From these solutions it is obtained upon spontaneous evaporation as a hard transparent resin. When heated above room temperature it softens gradually and is liquid at about 130°. It can be distilled under 1–2 mm. at about 250°. At ordinary temperature the flakes agglutinate in the course of several months and are transformed into the resin. Chemically, the anhydro base is insoluble in caustic alkalies, but it is soluble in HCl stronger than 10%, from which it is precipitated upon dilution with water. However, after standing for several days at room temperature, the acid solutions will no longer yield a precipitate with water and upon evaporation give the hydrochloride of the aminophenol (IV). This hydrolysis can be performed in one hour by heating the base with 25% HCl on the water-bath. On cooling, especially after seeding or rubbing, the hydrochloride will separate in white needles.

Anal. Calc'd for $C_{23}H_{18}N_2O_2$: C, 77.97; H, 5.08; N, 7.91.
Found: C, 77.67, 77.91; H, 5.3, 5.36; N, 7.9, 7.91.

Compound with $HgCl_2$. Equimolecular amounts of the anhydro base and $HgCl_2$ in 5% alcoholic solutions are mixed. Soon a white crystalline precipitate is formed, that melts at 182° after crystallization from alcohol. For the determination of mercury it was recrystallized twice from alcohol (25 parts), dissolved in HCl (1:2), the mercury precipitated cold with H_2S and the HgS washed with the same dilute HCl.

Anal. Calc'd for $C_{23}H_{18}N_2O_2 \cdot HgCl_2$: Hg, 32.00; N, 4.48.
Found: Hg, 31.70; N, 4.59.

Reaction of the anhydro base with $FeCl_3$. A 5% solution of the anhydro base in concentrated HCl is poured into a similar solution of $FeCl_3$. Immediately a thick, pale yellow amorphous precipitate is formed, that is readily hydrolyzed by water or alcohol, and cannot be recrystallized from concentrated HCl. Heated above room temperature it softens grad-

[3] During the dehydration a white sublimate of acetylaminophenol collects on the cooler parts of the flask and a few drops of the anhydro base are condensed in the receiver. At ordinary pressure some water, acetylaminophenol, and 2-methylbenzoxazole (formed by dehydration of the latter) fall back into the boiling liquid causing a continual bumping. It is therefore advisable to work under reduced pressure; however, below 10 mm. the losses by evaporation are excessive.

ually and is liquid at about 120°. Upon oxidation with sulfuric acid and KNO_3 the substance proved to have 13.58% Fe.

Semianhydride (III). The substance (I), 20 g., is heated at 230° and 10 mm. until all solid matter is converted into a dark red-brown liquid. This takes more than two hours. After cooling, the solidified transparent residue is dissolved in 40 ml. of boiling benzene, filtered, and left for two days. By this time 6–7 g. of the semianhydride separates as a reddish crystalline powder. Recrystallized twice from alcohol it is obtained perfectly white.

Anal. Calc'd for $C_{23}H_{20}N_2O_3$: N, 7.53. Found: 7.41.

In a capillary tube the semianhydride melts at 191°. Heated in a test tube under reduced pressure it begins to melt at 190–191°, and an intense boiling of the molten mass shows that dehydration has already begun. In the amorphous state, *e.g.*, as obtained by evaporation of a solution in an organic solvent, or by acidifying an alkaline solution, it is very soluble in ether, alcohol, benzene, and chloroform; scarcely so in ligroin, and insoluble in water. Its tendency to crystallize is not great, and the solutions need to be seeded and scratched to induce crystallization, and even then the separation takes one or two days. However, when crystalline it is very moderately soluble in the above mentioned solvents, even at the b.p. It behaves towards mineral acids like the anhydro base, but is more sensitive to their hydrolyzing action. Heating for half an hour with 20% HCl is sufficient to convert it into the aminophenol (IV). It is readily soluble in NaOH, but almost immediately the sodium salt begins to precipitate as a fine grayish powder, or if the alkali is concentrated (20%), as a greenish, viscous mass, that can easily be transformed by rubbing into a gray powder. The sodium salt is hydrolyzed by cold water. On the contrary the potassium salt is very soluble in an excess of KOH. This is of importance in case one wishes to extract the semianhydride from a solution in an organic solvent. From the solution in KOH, the sodium salt is precipitated by sodium chloride.

Reaction with $FeCl_3$. Under the same conditions as the anhydro base, the semianhydride gives a similar pale yellow amorphous precipitate with $FeCl_3$.

Supplementary notes concerning the aminophenol (IV). In addition to the description of IV given in the preceding paper, the following facts may be noted: The *hydrochloride*, as obtained by boiling I with HCl, is usually of a greenish gray color. It can be easily purified by adding ammonia dropwise and with shaking to its concentrated aqueous solution. The first flakes of the liberated aminophenol adsorb the coloring matter and the solution soon appears colorless. After filtration, 1.5 volumes of concentrated HCl are added. On cooling, the pure hydrochloride separates slowly in white needles. Should the original product be very dark, this treatment must be preceded by boiling with charcoal. The air-dried hydrochloride obstinately retains HCl that can only be eliminated by heating at 110°. It is further preferable, if one desires to isolate the free aminophenol from its hydrochloride, to add sodium acetate to the dilute solution instead of neutralizing with sodium bicarbonate. Here also, if the solution of the hydrochloride is colored, the acetate is first added dropwise until the solution is colorless, and the rest of the aminophenol precipitated after filtration.

Benzylidene derivative of IV. One mole of IV and 2 moles of benzaldehyde are heated together on a water-bath for one hour. The mixture first liquefies, then gradually becomes solid. Then 5 parts of benzene are added and the flask again heated until the cake, which meanwhile is transformed into a crystalline powder, is dissolved, and an equal volume of ligroin added. On cooling and standing, the thick precipitate formed is filtered, washed with a little benzene, and dried. The benzylidene derivative forms fine, pale yellow crystals that melt at 183°. It is very soluble in benzene and chloroform, scarcely so in alcohol and ligroin. It can be recrystallized from the two first-mentioned solvents but it is advantageous to use them diluted with an equal volume of ligroin.

Anal. Calc'd for $C_{33}H_{26}N_2O_2$: N, 5.81. Found: N, 5.5.

SALAMIS, GREECE

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

STUDIES ON γ-PYRONES. II. SYNTHESIS OF 4-PIPERIDINOLS FROM PYRONES[1]

KENNETH N. CAMPBELL, JOSEPH F. ACKERMAN,[2] AND BARBARA K. CAMPBELL[3]

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4-Piperidinols, which are of considerable pharmacological interest, have usually been prepared from the corresponding 4-piperidones which, in turn, have been synthesized by various ring-closures such as the Dieckmann condensation (1, 2). Since many 4-pyrones are readily available, and are easily converted to pyridones by treatment with ammonia or primary amines, reduction of these pyridones might furnish a new route to 4-piperidinols, and permit the preparation of substituted piperidinols not accessible by other methods.

Some 4-pyridones have been reduced to 4-piperidinols by sodium in ethanol or amyl alcohol (3, 4), but in general they are resistant to chemical reducing agents (5). Armit and Nolan (5) found that 5-methoxy-1,2-dimethyl-4-pyridone was partially demethylated to the 5-hydroxy compound by sodium in amyl alcohol, but that the ring was unattacked. Emmert (6) claimed to have reduced some pyridones catalytically, at low pressures and temperatures over platinum black, but Armit and Nolan (5) and Ruzicka (7) were unable to hydrogenate these compounds over platinum or palladium catalysts.

In the present work it has been found that 4-pyridones are reducible to 4-piperidinols by sodium in liquid ammonia, but isolation of the product is difficult, and the yields are not high. No reduction occurred when 1,2,6-trimethyl-4-pyridone was treated with lithium aluminum hydride in ether, but this may have been due to the low solubility of the pyridone in ether.

In agreement with Armit and Nolan (5) we were unable to hydrogenate 1,2,6-trimethyl-4-pyridone catalytically at room temperature and 2–3 atmospheres pressure, using pre-reduced platinum oxide or palladium-charcoal catalysts in glacial acetic acid as solvent. When, however, 1,2,6-trimethyl-4-pyridone in ethanol was hydrogenated in the presence of Raney nickel at 125° and 1500 psi, 3 moles of hydrogen were taken up in four hours, and an 85% yield of 1,2,6-trimethyl-4-piperidinol was isolated. Nickel on silica catalyst gave similar results. Hydrogenation could also be brought about in the presence of copper chromite, but with this catalyst higher temperatures were required (140°) and occasionally the catalyst was converted to the "inactive red form", and only a small yield of piperidinol was obtained. It was possible to extend the reaction to methoxy-γ-pyridones, although in general these required somewhat higher temperatures (140–155°). No hydrogenolysis of the methoxyl groups was observed.

[1] This paper is abstracted from the Ph.D. Dissertation of Joseph F. Ackerman, University of Notre Dame, June, 1949.

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The stereochemical course of hydrogenation of 4-pyridones is not clear. When 1,2,6-trimethyl-4-pyridone was hydrogenated over Raney nickel the product was identical with Mannich's *cis*-1,2,6-trimethyl-4-piperidinol (b.p. 105–107°/11, hydrochloride m.p. 267–268°) (8), but when nickel on silica was used the product was separable into two components, one of which was the *cis*-piperidinol and the other, m.p. 65°, hydrochloride m.p. 184–186°, corresponded to Mannich's *trans*-1,2,6-trimethyl-4-piperidinol.[4] With other pyridones only one product was isolated in each case; as this appeared homogeneous, it is concluded that reduction gave but one stereoisomer.

It was hoped to oxidize the 4-piperidonols to 4-piperidones and convert these to analogs of Demerol. Although the closely related tropine can be oxidized to tropinone (9), and 1,2,2,6-tetramethyl-4-piperidinol to the corresponding piperidone (10), by chromic acid in sulfuric acid, this method was unsuccessful with 1,2,6-trimethyl-4-piperidinol, and most of the piperidinol was recovered. Better results were obtained with aluminum *tert*-butoxide and acetone, and a 53% yield of 1,2,6-trimethyl-4-piperidone was isolated. Treatment of this compound with phenyllithium followed by propionic anhydride (11) gave the Demerol analog; 1,2,6-trimethyl-4-propionoxypiperidine, which was isolated as the oxalate.

Application of the Oppenhauer oxidation to 1,2,-dimethyl-5-methoxy-4-piperidinol was less successful, as the piperidone could not be separated from unreacted piperidinol by distillation through an efficient column. Infrared spectra indicated that the distillate contained about 50% of the piperidone (based on the carbonyl absorption at 5.83 mμ), but it could not be obtained in a pure state.

Two of the 4-piperidinols prepared in this work have been converted to esters for testing as spasmolytics.

EXPERIMENTAL[5, 6, 7]

4-Pyridones. Armit and Nolan (5) used alcoholic solutions of amines to convert 4-pyrones to 4-pyridones. We have obtained satisfactory results with aqueous solutions and found the procedure to be simpler. The following is a typical example: A solution of 70 g. (0.56 mole) of 2,6-dimethylpyrone (12) in 200 ml. of water was added with stirring to 150 ml. of 40% aqueous methylamine at such a rate that the temperature remained below 40°. Addition required one hour, and toward the end of this time the reaction mixture became very thick and difficult to stir. It was allowed to stand for 1–2 hours and was then cooled to 0° and filtered. The pyridone was recrystallized from hot water. The pyridones prepared in this work are recorded in Table I.

Reduction of 1,2,6-trimethyl-4-pyridone with sodium and alcohol in liquid ammonia. To a solution of 4 g. of 1,2,6-trimethyl-4-pyridone in 500 ml. of liquid ammonia there was added

[4] The terms *cis* and *trans* refer to the positions of the methyl groups only. The configuration of the hydroxyl group in the *cis*-piperidinol is not known.

[5] Analyses for C, H, and N were carried out by the Clark Microanalytical Laboratories, Urbana, Illinois.

[6] All melting points are uncorrected.

[7] We wish to thank the Northern Regional Laboratory and Corn Products Refining Company for the kojic acid used in this work, and the Cliff-Dow Company for a generous sample of maltol.

over a period of 1½ hours 27.5 g. (1.2 mole) of sodium metal in small pieces. A solution of 9.7 g. of the pyridone (total 13.7 g., 0.10 mole) in 50 ml. of dry ethanol was then added very slowly (several drops per minute). When the addition was complete, ethanol was added slowly until the blue color of sodium disappeared. The mixture became thick and more liquid ammonia was added occasionally to keep the mixture fluid. On completion of the reaction, concentrated ammonium hydroxide was added slowly to effect hydrolysis. Finally 200 ml. of water was added and the solution was extracted with 500 ml. of ether. The ether was removed by distillation and the residue was distilled to give 5.5 g. (40%) of a pale yellow oil, b.p. 105–111°/12 mm. (mainly 105–107°), n_D^{20} 1.4784–1.4801. Mannich (8) reported the same boiling point for 1,2,6-trimethyl-4-piperidinol.

The *hydrochloride* of the product was prepared in propanolic hydrogen chloride and recrystallized from ethanol, m.p. 266°. Mannich (8) reported m.p. 267–268° for the *cis*-piperidinol hydrochloride.

Anal. Calc'd for $C_8H_{18}ClNO$: Cl, 19.72. Found: Cl, 19.61, 19.62.

Catalytic hydrogenation of 1,2,6-trimethyl-4-pyridone. A mixture of 27.4 g. (0.20 mole) of 1,2,6-trimethyl-4-pyridone, 125 ml. of absolute ethanol, and about 4 g. of Raney nickel was shaken with hydrogen at 130 atmospheres and 125° for four hours. The alcohol was removed from the reaction mixture under reduced pressure and the residual oil was distilled *in vacuo* from a 100-ml. conical flask fitted with 30-cm. Vigreux side arm. The yield was 24.0

TABLE I

4-PYRIDONES FROM 4-PYRONES

PYRIDONE	YIELD, %	M.P., °C.	LIT. M.P., °C.	REF.
1,2,6-Trimethyl	88	245–246	245	5
1,2-Dimethyl-5-methoxy	70	98	95	5
1,2-Dimethyl-3-methoxy	67	79–80[a]	—	—
1-Methyl-2-hydroxymethyl-5-methoxy	71	205–206	203–204	5
2,6-Dimethyl-	55	225	225	16

[a] The compound was isolated as the monohydrate, which lost its water of crystallization on prolonged drying; the anhydrous material was analyzed. Calc'd for $C_8H_{11}NO_2$: C, 62.72; H, 7.24; N, 9.15. Found: C, 62.4; H, 6.90; N, 9.00.

g. (85%) of colorless oil, b.p. 105–107°/11 mm., n_D^{20} 1.4734–1.4755. The *hydrochloride* had m.p. 265–266°. Mannich (8) reported m.p. 267–268° for the hydrochloride of the *cis*-isomer of 1,2,6-trimethyl-4-piperidinol.

When the Raney nickel was replaced by activated nickel on silica[8] the reduction occurred as above but the distillate of the product in each of three runs partially crystallized. The crystals were recrystallized from low-boiling petroleum ether, m.p. 65°. The hydrochloride from the material was separable into 2 fractions, one of which, m.p. 265–266°, was probably the *cis*-isomer; the other fraction had m.p. 184–186°.

Mannich (8) reported m.p. 70° for the *trans*-piperidinol, and m.p. 185° for its hydrochloride.

Catalytic hydrogenation of other 4-pyridones. These reactions were carried out essentially as described above, and the products isolated by distillation. The results are summarized in Tables II and III.

Oxidation of 1,2,6-trimethyl-4-piperidinol with acetone and aluminum tert-butoxide. A solution of 21 g. (0.14 mole) of 1,2,6-trimethyl-4-piperidinol in 200 ml. of dry acetone was added rapidly to 38 g. (0.15 mole) of aluminum *tert*-butoxide (13) in 300 ml. of dry benzene, and the mixture was heated with stirring at 55° for nine hours and allowed to stand at room temperature for twelve hours. It was then hydrolyzed by the addition of 200 g. of ice and

[8] Obtained from the Harshaw Chemical Company, Cleveland, Ohio.

acidified with 25% sulfuric acid. The benzene layer was extracted several times with 50-ml. portions of 25% sulfuric acid. The combined acid solutions were made strongly alkaline with 40% sodium hydroxide in an ice-bath and extracted with a liter of ether in portions. Distillation of the oil left after evaporation of the dried extract gave 8.5 g. of the piperidone, b.p. 95–106°/16 mm., n_D^{20} 1.4620–1.4662. Mannich (8) reported the b.p. to be 78–90°/14 mm. The yield was 53% based on piperidinol consumed (4 g. was recovered unchanged) or 42.5% on the amount of piperidinol originally used.

TABLE II

HYDROGENATION OF 4-PYRIDONES TO 4-PIPERIDINOLS

SUBSTITUENTS	CATALYST	MAX. TEMP., °C.	INITIAL PRESSURE, PSI.	TIME, HRS.	YIELD, %
1,2,6-Trimethyl	Raney Ni[a]	125	1500	4	85
1,2,6-Trimethyl	Ni–SiO_2	125	1500	4	83
1,2,6-Trimethyl	Cu chromite[b]	140	1600	4	80, 30[c]
1,2-Dimethyl-5-methoxy	Raney Ni	150	1500	4	87
1-Methyl-2-hydroxymethyl-5-methoxy	Raney Ni	155	1500	5	85
1-Methyl-2-hydroxymethyl-5-methoxy	Cu chromite	170	1500	4	49
1,2-Dimethyl-3-methoxy	Raney Ni	155	1900	5	50
2,6-Dimethyl	Raney Ni	155	1400	5	60

[a] Commercial Raney nickel and that prepared by Mozingo's method (17) gave essentially the same results. [b] Both commercial material and that prepared according to Adkins (18) were used. [c] Low yields were obtained when the catalyst was converted to the red form.

TABLE III

PHYSICAL CONSTANTS OF 4-PIPERIDINOLS

SUBSTITUENTS	B.P., °C./MM.	n^{20}	ANALYSES					
			Calculated			Found		
			C	H	N	C	H	N
1,2,6-Trimethyl	105–107	1.4734–1.4755	—	—	—	—	—	—
2,6-Dimethyl		m.p. 132.5°	65.05	11.60	10.80	64.83	11.42	10.72
1,2-Dimethyl-5-methoxy	104–107/11	1.4740	60.34	10.76	8.80	60.20	10.90	8.89
1,2-Dimethyl-3-methoxy	110–111/13	m.p. 86–88°	60.34	10.76	8.80	60.00	10.64	8.65
1-Methyl-2-hydroxymethyl-5-methoxy	143–147/4	—	54.84	9.78	8.00	54.73	9.92	8.33

The *oxime hydrochloride* was prepared and melted at 198–200° (dec.). Mannich (8) found the m.p. to be 198–200°. (dec.).

1,2,6-Trimethyl-4-phenyl-4-piperidinol. The method of Ziering, *et al.* (11) was used. Phenyllithium was prepared under helium in the usual manner (14) from 1.0 g. of lithium (0.14 mole) and after cooling the solution to −20°, 10 g. (0.07 mole) of 1,2,6-trimethyl-4-piperidone in 25 ml. of dry ether was added over a period of forty-five minutes. The cooling-bath was removed, stirring was continued for another 2½ hours, and the mixture was hy-

drolyzed by pouring on to cracked ice. The aqueous layer was extracted with two portions of ether and the combined ether layers were extracted with 200 ml. of 20% sulfuric acid. The acid layer was made strongly basic with potassium hydroxide and extracted with 250 ml. of ether. The ether extract was dried over potassium carbonate and evaporated. The oily residue was dissolved in 20 ml. of hexane, allowed to stand for twelve hours in the refrigerator, and the crystals which separated were recrystallized from hexane (25 ml. to the gram); the yield was 3.5 g. (22.5%), m.p. 120°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.66; H, 9.65; N, 6.39.
Found: C, 76.26; H, 9.67; N, 6.36.

1,2,6-Trimethyl-4-phenyl-4-propionoxypiperidine monooxalate. To 20 ml. of propionic anhydride there was added two grams of 1,2,6-trimethyl-4-phenyl-4-piperidinol and the solution was heated at 90° for three hours. The excess propionic anhydride was then removed under reduced pressure. The residue was taken up in water, adjusted to *p*H 10 with sodium carbonate, and extracted with ether. The ether extract, after drying over magnesium sulfate, was evaporated and the residue was converted to the oxalate which was purified by slow recrystallization from an isopropanol-ether mixture. It had m.p. 192° and weighed 2.0 g. (60%).

Anal. Calc'd for $C_{19}H_{27}NO_6$: C, 62.45; H, 7.45; N, 3.83.
Found: C, 61.80; H, 7.52; N, 3.89.

The *hydrochloride* was too unstable to handle.

1,2,6-Trimethyl-4-mandeloxypiperidine meconate. The general procedure was similar to one described earlier (15). A solution of 10 g. (0.07 mole) of 1,2,6-trimethyl-4-piperidinol in 75 ml. of water was neutralized with concentrated hydrochloric acid and 27 g. (0.18 mole) of mandelic acid and two drops of concentrated hydrochloric acid were added. The solution was evaporated to dryness and the residue was taken up in 100 ml. of water containing two drops of hydrochloric acid. It was again evaporated to dryness and the procedure was repeated another time. After the third evaporation the residue was dissolved in dilute hydrochloric acid and extracted with ether to remove excess mandelic acid. The solution was made basic with sodium carbonate and the ester was extracted with ether. About 10 g. (52%) of an oily solid was obtained. This was converted to the meconate by treatment with one equivalent of meconic acid in warm ethanol. Addition of dry ether yielded an oil which solidified on repeated trituration with ether and vigorous stirring. It was recrystallized from ethanol-ether from which it first separated as an oil but crystallized upon trituration with dry ether. Yield 8 g., m.p. 138–140°.

Anal. Calc'd for $C_{23}H_{27}NO_{10}$: C, 57.85; H, 5.70; N, 2.93.
Found: C, 58.08; H, 5.94; N, 2.97.

1,2-Dimethyl-5-methoxy-4-diphenylacetoxypiperidine meconate. A two-fold excess of purified thionyl chloride was added to 10 g. (0.047 mole) of diphenylacetic acid and the mixture was refluxed for two hours. The excess thionyl chloride was removed by warming *in vacuo* and the residue was dissolved in 30 ml. of dry benzene. To this solution there was added 8.8 g. (0.055 mole) of 1,2-dimethyl-5-methoxy-4-piperidinol in 50 ml. of dry benzene. The mixture became warm and after standing for fifteen minutes was refluxed for two hours. The solvent was removed under reduced pressure, the residue was dissolved in 100 ml. of water, made basic with sodium carbonate, and extracted with ether. The ether extract after drying over magnesium sulfate yielded 9 g. (48%) of oil which was converted to the meconate salt as above, giving 6 g., m.p. 105–107°. The salt decarboxylated on drying for analysis.

Anal. Calc'd for $C_{28}H_{31}NO_8$: C, 65.99; H, 6.13; N, 2.75.
Found: C, 65.96; H, 5.70; N, 2.80.

SUMMARY

1. It has been found that 4-pyridones can be converted to 4-piperidinols by catalytic hydrogenation at high pressures and temperatures.

2. 1,2,6-trimethyl-4-piperidinol has been oxidized to 1,2,6-trimethylpiperi-

done by aluminum *tert*-butoxide and acetone, but this procedure failed with 1,2-dimethyl-5-methoxy-4-piperidinol.

3. Some derivatives of 4-piperidinols of pharmacological interest have been synthesized.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY[1]]

ANTISPASMODICS. III.[2] TERTIARY AMINOALKYL ESTERS OF CYCLOPENTYL AND Δ^2-CYCLOPENTENYL SUBSTITUTED ACETIC ACIDS

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In Part I (2) of this series it was found that β-diethylaminoethyl esters of aliphatic acids substituted in the α-position by cyclopentyl or Δ^2-cyclopentenyl groups are active antispasmodics. In this paper the preparation and properties of more of these esters, as well as esters of other tertiary amino alcohols, are reported. The methods of preparation by way of the corresponding malonic esters and substituted acetic acids are similar to those described previously. In some cases where the malonic esters were difficult to prepare because of the steric hindrance of the groups involved, cyanoacetic esters were made instead. Monosubstituted cyanoacetic esters were made by the excellent method of Alexander and Cope (3), whereby an aldehyde or ketone is condensed with ethyl cyanoacetate and hydrogenated in one operation. The sodio derivatives of the monosubstituted cyanoacetates were alkylated with Δ^2-cyclopentenyl chloride to give the desired disubstituted cyanoacetates.

These cyanoacetic esters could be prepared in considerably better yields than the corresponding malonic esters, but this advantage was offset by the difficulty of hydrolysis and decarboxylation to the corresponding substituted acetic acids. Whereas the malonic esters usually yielded 85% to 95% of the desired acid, when hydrolyzed with 30% alcoholic potassium hydroxide in a bomb at 140–150° for three hours, the cyanoacetic esters gave only about 30% to 70% of the desired acid when heated with 50% alcoholic potassium hydroxide at 160–180° for forty hours. Most of the remaining material proved to be the corresponding substituted acetamides. More drastic conditions of hydrolysis led to decomposition.

The cyclopentyl-malonic and -cyanoacetic esters were prepared, with the exception of diethyl cyclopentyl-(2-methylallyl)malonate, by the hydrogenation of the corresponding Δ^2-cyclopentenyl-malonic or -cyanoacetic esters, under low pressure unless otherwise indicated. Diethyl cyclopentyl-(2-methylallyl) malonate was made by alkylating the sodio derivative of cyclopentylmalonic ester with 2-methylallyl chloride.

The esters of the tertiary amino alcohols were prepared by two methods. Method A is essentially that described previously (1, 2), whereby the sodium salt of the acid was allowed to react with a chloroalkylamine. Method B involves

[1] The functions of the George A. Breon and Company laboratories have been assumed by the Sterling-Winthrop Research Institute, Rensselaer, N. Y., and any requests for reprints should be addressed there. Other inquiries may be addressed to the first author.

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the preparation of the acid chlorides, which were isolated in several instances, followed by their reaction with the amino alcohols. Either method usually gave good yields of the distilled free amino esters which were converted to their hydrochlorides in absolute ether by hydrogen chloride. In most cases, these hydrochlorides needed no further purification, but, nevertheless, some of them (noted in Table III) were recrystallized, usually from methyl isobutyl ketone. When low yields of hydrochlorides are reported in Table III, it is usually due either to the fact that some of the hydrochlorides were appreciably soluble in absolute ether containing an excess of hydrogen chloride, or failure to work up the filtrates from recrystallization.

Preliminary pharmacological screening in these laboratories indicates that these compounds all have some antispasmodic activity. However, only β-diethylaminoethyl Δ^2-cyclopentenyl-(1,2-dimethylpropyl)acetate hydrochloride and β-diethylaminoethyl cyclopentylisobutylacetate hydrochloride can be considered highly active. The series of + and − signs (Table III) indicate the relative activities, ++++ being highly active and − being inactive at dilutions of 1:8,000,000. A ++++ rating is the equivalent of about 0.1 the activity of atropine sulfate.

We are indebted to Dr. Willard M. Hoehn, Director of these laboratories, for valuable help and guidance in this work. The nitrogen analyses are by Miss Elizabeth Beard in these laboratories, and the carbon, hydrogen, and sulfur analyses are by Micro-Tech Laboratories, Skokie, Illinois.

EXPERIMENTAL

The specific examples given below illustrate the general methods used in this work. Any exceptions are listed in the footnotes of the tables.

Diethyl Δ^2-cyclopentenyl-(2-methylbutyl)malonate. To 23 g. (1 mole) of sodium, melted under 200 ml. of dry toluene in a 1-l. flask, was slowly added, with vigorous stirring (with a Hershberg wire stirrer), 226.3 g. (1 mole) of diethyl Δ^2-cyclopentenylmalonate. The mixture was refluxed until practically all the sodium had reacted, and then 181 g. (1.2 moles) of 2-methylbutyl bromide was added. After refluxing for thirteen hours, a 1-cc. sample titrated with 0.1 *N* acid required 0.9 cc. of the acid for neutralization. The reaction mixture was cooled and neutralized with acetic acid. Enough water was added to dissolve the salt, and the organic layer was separated. After removing the solvent, the product was distilled, first from a modified Claisen flask, and then through a twelve-inch fractionating column packed with 1/8-inch glass helices, giving 138 g. (46.6%) of nearly colorless liquid.

Ethyl (1,2-dimethylpropyl)cyanoacetate. A mixture of 56.6 g. (0.55 mole) of methyl isopropyl ketone, 6 ml. of glacial acetic acid, 3.9 g. of ammonium acetate, 75 ml. of 95% ethanol, and 2 g. of palladium on charcoal was hydrogenated at room temperature and 50 pounds pressure. The reduction was complete in about one hour. Five runs were combined, filtered, and the solvent was removed *in vacuo* on a steam-bath. The residue was taken up in ether, washed with water, sodium bicarbonate solution, and saturated salt solution, and dried over sodium sulfate. After removal of the solvent, the product was distilled twice from a Claisen flask and then through an efficient fractionating column, giving 143 g. (31.3%) of nearly colorless liquid, b.p. 60° (0.12 mm.); n_D^{25} 1.4322, d_4^{25} 0.9552.

Anal. Calc'd for $C_{10}H_{17}NO_2$: M_D, 49.80; N, 7.65.
Found: M_D, 49.78; N, 7.67.

Ethyl Δ^2-cyclopentenyl-(1-methylbutyl)cyanoacetate. To 18.4 g. (0.8 mole) of sodium, melted under 180 ml. of dry toluene in a 1-l. flask, was slowly added (with vigorous stirring) 124 g. (0.8 mole) of ethyl (1-methylbutyl)cyanoacetate (3). When practically all the sodium

had reacted, 123 g. (1.2 moles) of Δ^2-cyclopentenyl chloride was added. Salt separated and the reaction mixture became acidic almost immediately. Water was added, the layers were separated, and the aqueous layer was extracted with ether. The organic layer was washed with saturated salt solution and the solvent was removed *in vacuo*. The product was distilled, first from a Claisen flask and then through an efficient column, giving 125 g. (62.6%) of nearly colorless liquid.

Ethyl cyclopentyl-(1-methylbutyl)cyanoacetate. A solution of 62.4 g. (0.25 mole) of ethyl Δ^2-cyclopentenyl-(1-methylbutyl)cyanoacetate in 100 ml. of ethanol was hydrogenated with 0.2 g. of platinum oxide catalyst at room temperature and 50 pounds pressure. In about one hour the reduction was complete. The catalyst was removed by filtration, and the solvent was distilled off *in vacuo*. The product was distilled from a Claisen flask, giving 62 g. (98.6%) of colorless liquid.

Diethyl cyclopentyl-(2-thienylmethyl)malonate. A solution of 40 g. (0.125 mole) of diethyl Δ^2-cyclopentenyl-(2-thienylmethyl)malonate in 100 ml. of ethanol was hydrogenated with about 6 g. of Raney nickel catalyst in a bomb at 1800 pounds pressure. The temperature was slowly raised during twelve hours to 100°. After filtration, the solvent was removed *in vacuo*, and the residue was distilled through a six-inch fractionating column packed with 1/8-inch glass helices. A colorless liquid, weighting 31 g. (77%), was obtained.

Anal. Calc'd for $C_{17}H_{24}O_4S$: C, 63.00; H, 7.45.
Found: C, 63.39; H, 7.49.

Cyclopentyl-(2-methylbutyl)acetic acid. A mixture of 40 g. of diethyl cyclopentyl-(2-methylbutyl)malonate with a solution of 40 g. of potassium hydroxide in 100 ml. of 95% ethanol was heated for three hours in a bomb immersed in an oil-bath at 140–160°. The contents were diluted with water, extracted with ether, and the aqueous solution was acidified with hydrochloric acid. The acid was taken up in ether, washed thoroughly with water, and dried over sodium sulfate. After removing the solvent, the product was heated to 180° and then distilled from a Claisen flask, giving 25 g. (94%) of colorless liquid.

Cyclopentyl-(1-methylbutyl)acetic acid and amide. A mixture of 40 g. of ethyl cyclopentyl-(1-meth lbutyl)cyanoacetate with a solution of 70 g. of potassium hydroxide in 115 ml. of 90% ethanol was heated in a bomb immersed in an oil-bath at 170–180° for 46 hours. On diluting the contents of the bomb with water, a crystalline precipitate separated which was collected, washed with water, and dried; weight, 11 g. (35%). This proved to be cyclopentyl-(1-methylbutyl)acetamide. A sample recrystallized from petroleum hexane melted at 94–109°.

Anal. Calc'd for $C_{12}H_{24}NO_2$: N, 7.10. Found: N, 7.04.

The basic aqueous filtrate was extracted with ether and then acidified with hydrochloric acid. It was worked up as described above and the acid was distilled from a Claisen flask, giving about 11 g. (35%) of colorless liquid.

Hydrolysis and decarboxylation of ethyl Δ^2-cyclopentenyl-sec-butylcyanoacetate. Forty grams of this cyanoacetate was hydrolyzed under conditions similar to those described above for the preparation of cyclopentyl-(2-methylbutyl)acetic acid. The acidic fraction was heated to 175° and then distilled from a Claisen flask, giving 5.5 g. of a viscous oil, b.p. 150° (0.56 mm.); n_D^{25} 1.4830. This compound gave correct neutral equivalent and nitrogen analysis for Δ^2-cyclopentenyl-*sec*-butylcyanoacetic acid.

Anal. Calc'd for $C_{12}H_{17}NO_2$: N.E., 207.26; N, 6.76.
Found: N.E., 208.05; N, 6.78.

The neutral fraction was distilled from a Claisen flask, giving 15.7 g. of crystalline solid, b.p. 120° (0.1 mm.), which, after recrystallization from benzene, gave 12.3 g., m.p. 114–115°. This proved to be Δ^2-cyclopentenyl-*sec*-butylacetamide.

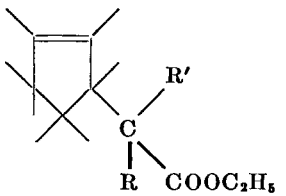
Anal. Calc'd for $C_{11}H_{19}NO$: N, 7.73. Found: N, 7.79.

This amide could not be hydrolyzed by refluxing for eight hours with 50% potassium hydroxide solution, but it was hydrolyzed to the corresponding acid (Table II) by heating with alcoholic potassium hydroxide in a bomb under conditions similar to those described above for the preparation of cyclopentyl-(1-methylbutyl)acetic acid.

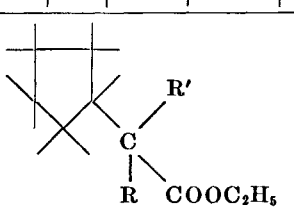
Δ^2-Cyclopentenylisopropylacetamide. This amide was isolated from the neutral fraction

TABLE I

MALONIC AND CYANOACETIC ESTERS



R	R′	YIELD, %	B.P., °C.	MM.	n_D^{25}	d_4^{25}	EMPIRICAL FORMULA	MOLECULAR REFRACTIVITY		ANALYSIS N	
								Calc'd	Found	Calc'd	Found
H—[a]	—CN	41.6	70	0.09	1.4623	1.0435	$C_{10}H_{13}NO_2$	47.13	47.23	7.82	7.73
$CH_3CH_2CH_2$—	—CN	65.7	73	.04	1.4620	0.9975	$C_{13}H_{19}NO_2$	60.99	60.99	6.33	6.27
$CH_3CH(CH_3)$—	—CN	71.6	70	.04	1.4660	1.0077	$C_{13}H_{19}NO_2$	60.99	60.80	6.33	6.13
$CH_3CH(CH_3)CH_2$—[b]	—$COOC_2H_5$	45.7	73	.02	1.4580	1.0157	$C_{16}H_{26}O_4$	76.75	75.81	—	—
$CH_3CH_2CH(CH_3)$—	—CN	66.	93	.26	1.4680	1.004	$C_{14}H_{21}NO_2$	65.61	65.41	5.95	5.80
$CH_3CH(CH_3)CH_2CH_2$—[c]	—$COOC_2H_5$	45.	99	.038	1.4580	1.0007	$C_{17}H_{28}O_4$	81.37	80.84	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	46.6	83	.03	1.4581	0.9970	$C_{17}H_{28}O_4$	81.37	81.14	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	62.6	95	.21	1.4678	.9893	$C_{15}H_{23}NO_2$	70.23	70.04	5.62	5.67
$CH_3CH(CH_3)CH(CH_3)$—	—CN	67.4	84	.07	1.4709	.9974	$C_{15}H_{23}NO_2$	70.23	69.86	5.62	5.70
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	49.6	90	.01	1.4616	.9966	$C_{18}H_{30}O_4$	86.00	85.56	—	—
CH_2=$CClCH_2$—	—$COOC_2H_5$	60.	121	.28	1.4793	1.1214	$C_{15}H_{21}ClO_4$	76.52	76.09	—	—
$C_6H_5OCH_2CH_2$—	—$COOC_2H_5$	39.	161	.37	1.5069	1.0923	$C_{20}H_{26}O_5$	93.26	94.12	—	—
SCH=CHCH=CCH$_2$—	—$COOC_2H_5$	70.7	138	.17	1.5136	1.1373	$C_{17}H_{22}O_4S$	86.20	85.27	[d]	—

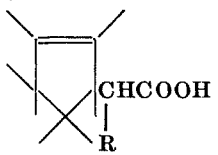


$CH_3CH(CH_3)$—	—CN	—	84	0.22	1.4578	0.9922	$C_{13}H_{21}NO_2$	61.46	61.39	6.27	6.37
$CH_3CH(CH_3)CH_2$—	—$COOC_2H_5$	98.[e]	96	.04	1.4536	1.0023	$C_{16}H_{28}O_4$	77.21	76.72	—	—
$CH_3CH_2CH(CH_3)$—	—CN	97.	96	.25	1.4603	0.9865	$C_{14}H_{23}NO_2$	66.08	65.93	5.90	5.98
$CH_2=C(CH_3)CH_2$—	—$COOC_2H_5$	63.	71	.01	1.4619	1.0170	$C_{16}H_{26}O_4$	76.75	76.32	—	—
$CH_3(CH_2)_3CH_2$—	—$COOC_2H_5$	86.3	98	.04	1.4525	0.9887	$C_{17}H_{30}O_4$	81.84	81.49	—	—
$CH_3CH(CH_3)CH_2CH_2$—[c]	—$COOC_2H_5$	100.	101	.04	1.4524	.9914	$C_{17}H_{30}O_4$	81.84	81.26	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	99.	109	.25	1.4527	.9874	$C_{17}H_{30}O_4$	81.84	81.39	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	98.6	95	.27	1.4606	.9762	$C_{15}H_{25}NO_2$	70.71	70.61	5.57	5.32
$CH_3CH(CH_3)CH(CH_3)$—	—CN	88.5	76	.01	1.4637	.9850	$C_{15}H_{25}NO_2$	70.71	70.38	5.57	5.51
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	94.7	95	.005	1.4571	.9884	$C_{18}H_{32}O_4$	86.47	86.11	—	—
SCH=CHCH=CCH$_2$—[f]	—$COOC_2H_5$	77.	112	.018	1.5068	1.1252	$C_{17}H_{24}O_4S$	86.67	85.8	—	—

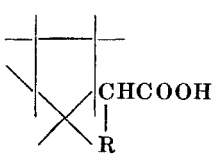
[a] Prepared by a method similar to the example in the Experimental part except that sodium ethoxide in ethanol was used in place of sodium and toluene. [b] Centolella, Nelson, and Kolloff, *J. Am. Chem. Soc.*, **65,** 2091 (1943). [c] Braun and Kurtz, *Ber.*, **70,** 1224 (1937). [d] *Anal.* Calc'd: S, 9.94. Found: S, 10.13. [e] The yield and physical constants are on material prepared by the hydrogenation of diethyl Δ^2-cyclopentenylisobutylmalonate in the usual way. The same compound was also prepared by the high pressure hydrogenation of diethyl cyclopentyl-(2-methyl allyl)malonate using Raney nickel catalyst. [f] For method of preparation, see Experimental part.

TABLE II

SUBSTITUTED ACETIC ACIDS



R	YIELD, %	B.P., °C.	MM.	n_D^{25}	d_4^{25}	EMPIRICAL FORMULA	MOLECULAR REFRACTIVITY		NEUTRAL EQUIVALENT	
							Calc'd	Found	Calc'd	Found
$CH_3CH(CH_3)$—[a, b]	60.	80	0.03	1.4680	0.9913	$C_{10}H_{16}O_2$	47.24	47.17	168.2	171.4
$CH_3CH(CH_3)CH_2$—[b]	75.	78	.07	1.4650	.9718	$C_{11}H_{18}O_2$	51.87	51.86	182.3	182.8
$CH_3CH_2CH(CH_3)$—	69.5	82	.013	1.4702	.9858	$C_{11}H_{18}O_2$	51.87	51.60	182.3	185.1
$CH_3CH(CH_3)CH_2CH_2$—	94.	101	.026	1.4653	.9626	$C_{12}H_{20}O_2$	56.50	56.40	196.3	196.5
$CH_3CH_2CH(CH_3)CH_2$—	87.6	123	1.0	1.4662	.9618	$C_{12}H_{20}O_2$	56.50	56.54	196.3	194.9
$CH_3(CH_2)_2CH(CH_3)$—	68.2	93	0.05	1.4710	.9733	$C_{12}H_{20}O_2$	56.50	56.38	196.3	197.6
$CH_3CH(CH_3)CH(CH_3)$—	58.5	87	.012	1.4729	.9816	$C_{12}H_{20}O_2$	56.50	56.08	196.3	196.0
$CH_3CH_2CH(C_2H_5)CH_2$—	97.5	98	.02	1.4687	.9620	$C_{13}H_{22}O_2$	61.13	60.91	210.3	207.7
SCH=CHCH=CCH$_2$—	83.4	130	.06	1.5449	1.1649	$C_{12}H_{14}O_2S$	60.33	60.34	222.3	224.9

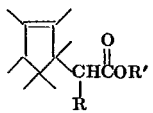


$CH_3CH(CH_3)$—	43.4	78	0.022	1.4582	0.9732	$C_{10}H_{18}O_2$	47.71	47.75	170.2	174.3
$CH_3CH(CH_3)CH_2$—	91.	79	.08	1.4549	.9525	$C_{11}H_{20}O_2$	52.34	52.48	184.3	184.6
$CH_3CH_2CH(CH_3)$—	46.6	89	.08	1.4618	.9693	$C_{11}H_{20}O_2$	52.34	52.26	184.3	186.0
$CH_2=C(CH_3)CH_2$—	55.	86	.04	1.4694	.9768	$C_{11}H_{18}O_2$	51.92	51.98	182.2	180.1
$CH_3(CH_2)_3CH_2$—	84.	96	.02	1.4569	.9481	$C_{12}H_{22}O_2$	56.97	56.95	198.3	197.1
$CH_3CH(CH_3)CH_2CH_2$—	89.	94	.055	1.4559	.9438	$C_{12}H_{22}O_2$	56.97	57.10	198.3	198.8
$CH_3CH_2CH(CH_3)CH_2$—	94.	114	.35	1.4570	.9483	$C_{12}H_{22}O_2$	56.97	57.09	198.3	196.4
$CH_3(CH_2)_2CH(CH_3)$—	35.	96	.07	1.4623	.9591	$C_{12}H_{22}O_2$	56.97	56.88	198.3	201.8
$CH_3CH(CH_3)CH(CH_3)$—	31.5	96	.062	1.4651	.9668	$C_{12}H_{22}O_2$	56.97	56.77	198.3	198.5
$CH_3CH_2CH(C_2H_5)CH_2$—	95.6	103	.028	1.4600	.9436	$C_{13}H_{24}O_2$	61.60	61.48	212.3	213.3
SCH=CHCH=CCH$_2$—	91.	135	.07	1.5330	1.1422	$C_{12}H_{16}O_2S$ [c]	60.80	60.94	224.3	224.6

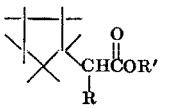
[a] Perkins and Cruz, *J. Am. Chem. Soc.*, **49**, 518 (1927). [b] For exceptions to general method of preparation, see Experimental part. [c] *Anal.* Calc'd: C, 64.25; H, 7.19. Found: C, 64.70, 64.96; H, 7.37, 7.22.

TABLE III

Esters of Amino Alcohols



R	R′	Method of Preparation	Free Base										Hydrochloride						Anti-spasmodic Activity
			Yield, %	B.p., °C.	mm.	n_D^{25}	d_4^{25}	Empirical Formula	Molecular Refractivity Calc'd	Molecular Refractivity Found	Analysis % Nitrogen Calc'd	Analysis % Nitrogen Found	Yield, %	M.p., °C.	Analysis N Calc'd	Analysis N Found	Analysis Cl Calc'd	Analysis Cl Found	
$CH_3CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	74.	106	0.025	1.4628	0.9344	$C_{16}H_{29}NO_2$	79.20	78.80	5.44	5.24	93.	93–98	–	–	11.67	11.77	++
$CH_3CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	–	93	.06	1.4595	.9245	$C_{17}H_{31}NO_2$	83.82	83.30	–	–	–	106–109	4.41	4.54	11.15	11.32	+
$CH_3CH_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	80.	106	.027	1.4642	.9334	$C_{17}H_{31}NO_2$	83.82	83.23	4.98	4.83	92.	101–103	–	–	11.15	11.10	±
$CH_3(CH_2)_3CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	70.	112	.04	1.4617	.9230	$C_{18}H_{33}NO_2$	88.44	87.96	–	–	84.	93.5–95	4.22	4.31	10.68	10.88	–
$CH_3CH(CH_3)CH_2CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	63.	100	.025	1.4618	.9209	$C_{18}H_{33}NO_2$	88.44	88.17	4.74	4.60	86.	99–100	–	–	10.68	10.67	±
$CH_3CH_2CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	90.5	110	.005	1.4612	.9208	$C_{18}H_{33}NO_2$	88.44	88.08	4.74	4.73	78.	99.5–101	–	–	10.68	10.72	–
$CH_3(CH_2)_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	25.1	106	.062	1.4638	.9279	$C_{18}H_{33}NO_2$	88.44	87.83	4.74	4.67	45.6[a]	99–103	–	–	10.68	10.85	–
$CH_3CH(CH_3)CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	49.4	118	.18	1.4673	.9392	$C_{18}H_{33}NO_2$	88.44	87.26	4.74	4.77	27.4[a]	120–123	–	–	10.68	10.48	+++
$SCH{=}CHCH{=}CCH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	86.	120	.015	1.5128	1.0483	$C_{18}H_{27}NO_2S$	93.27	92.13	4.36	4.30	94.	111–113	–	–	9.82	9.91	–
$CH_2(CH_2)_2CH{=}CHCH-$	$(CH_3)_2NCH_2CH_2-$	B	46.	110	.05	1.4948	1.0012	$C_{17}H_{27}NO_2$	81.15	80.77	–	–	94.[b]	129–133.5	4.46	4.48	11.30	11.00	–
$CH_2(CH_2)_2CH{=}CHCH-$	$(C_2H_5)_2NCH_2CH(CH_3)-$	B	30.	116	.03	1.4882	0.9786	$C_{20}H_{33}NO_2$	95.01	94.09	–	–	84.	118–120	3.94	4.10	9.96	9.97	±
$CH_2(CH_2)_2CH{=}CHCH-$	$(C_2H_5)_2NCH_2CH_2CH_2-$	B	86.	131	.07	1.4900	.9761	$C_{20}H_{33}NO_2$	95.01	94.63	–	–	95.	115–118	3.94	4.07	9.96	9.94	+
$CH_2(CH_2)_2CH{=}CHCH-$	$CH_2(CH_2)_4NCH_2CH_2-$	B	59.	125	.03	1.5070	1.0222	$C_{20}H_{31}NO_2$	92.81	92.42	–	–	94.	133–142	3.96	4.02	10.02	9.93	–
$CH_2(CH_2)_2CH{=}CHCH-$	$CH_2CH_2OCH_2CH_2NCH_2CH_2-$	B	28.	130	.018	1.5083	1.0655	$C_{19}H_{29}NO_3$	89.83	89.41	–	–	90.	144–145	3.94	3.96	9.96	9.96	–



R	R′	Method	Yield, %	B.p., °C.	Mm.	n_D^{25}	d_4^{25}	Formula	Calcd. C	Found C	Calcd. H	Found H	Yield, %	M.p., °C.	Calcd. N	Found N	Calcd. S	Found S	Activity[g]
$CH_3CH_2CH_2-$	$(CH_3)_2NCH_2CH_2-$	B	83.	73	0.05	1.4520	0.9267	$C_{14}H_{27}NO_2$	70.43	70.04	5.80	5.73	69.[a]	111–113	—	—	12.76	12.52	—
$CH_3CH(CH_3)-$	$(CH_3)_2NCH_2CH_2-$	B	—	68	.02	1.4542[c]	.9310[c]	$C_{14}H_{27}NO_2$	70.43	70.17	5.80	5.60	81.[a]	114–115	—	—	12.76	12.71	—
$CH_3CH(CH_3)-$	$(C_2H_5)NCH_2CH_2$	A	48.4	111	.28	1.4563	.9212	$C_{16}H_{31}NO_2$	79.67	79.50	5.20	5.15	80.5[a]	115–118	—	—	11.59	11.60	++
$CH_3CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	68.	113	.03	1.4527	.9119	$C_{17}H_{33}NO_2$	84.29	83.97	—	—	94.	118.5–119.5	4.38	4.51	11.08	11.22	+++
$CH_3CH(CH_3)CH_2-$	$(CH_3)_2NCH_2CH_2$	B	51.	90	.03	1.4519	.9204	$C_{15}H_{29}NO_2$	75.05	74.84	5.49	5.52	82.	111–114.5	—	—	12.15	12.10	±
$CH_3CH(CH_3)CH_2-$	$CH_2(CH_2)_4NCH_2CH_2-$	B	85.	106	.02	1.4717	.9600	$C_{18}H_{33}NO_2$	86.71	86.13	4.74	4.57	82.	177.5–180	—	—	10.68	10.67	++
$CH_3CH(CH_3)CH_2-$	$HOCH_2CH_2N(C_2H_5)CH_2CH_2-$	B	43.	106	.012	1.4653	.9706	$C_{17}H_{33}NO_3$	85.81	85.26	4.68	4.75	—	59–62	—	—	10.56	10.83	+
$CH_3CH(CH_3)CH_2-$	$CH_2CH_2CH=CHCHN(C_2H_5)CH_2CH_2-$	B	53.3	114	.008	1.4760	.9548	$C_{20}H_{35}NO_2$	95.48	94.97	4.36	4.22	[f]	—	—	—	—	—	—
$CH_3CH_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	73.0	110	.14	1.4591	.9198	$C_{17}H_{33}NO_2$	84.29	84.24	4.94	4.85	79.5[a]	115–116	—	—	11.09	11.28	—
$CH_3CH_2CH(CH_3)-$	$(CH_3)_2NCH_2CH_2-$	B	89.	76	.02	1.4565[c]	.9402[c]	$C_{16}H_{29}NO_2$	75.05	73.90	5.49	5.60	84.[a]	105–109	—	—	12.15	12.01	+
$CH_2=C(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	92.	108	.19	1.4629	.9276	$C_{17}H_{31}NO_2$	83.82	83.54	—	—	48.2[d]	99–105	4.41	4.37	11.15	11.28	++
$CH_3(CH_2)_8CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	85.	106	.02	1.4561	.9118	$C_{18}H_{35}NO_2$	88.91	88.71	—	—	91.	103.5–105	4.20	4.33	10.62	10.76	—
$CH_3CH(CH_3)CH_2CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	85.	83	.025	1.4550	.9100	$C_{18}H_{35}NO_2$	88.91	88.69	4.71	4.61	94.	117–118.5	—	—	10.62	10.52	±
$CH_3CH_2CH(CH_3)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	80.	97	.02	1.4552	.9110	$C_{18}H_{35}NO_2$	88.91	88.63	4.71	4.53	80.	116–117	—	—	10.62	10.65	±
$CH_3(CH_2)_2CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	66.1	124	.35	1.4594	.9161	$C_{18}H_{35}NO_2$	88.91	88.80	4.71	4.66	58.2[a]	99–103	—	—	10.62	10.80	+
$CH_3CH(CH_3)CH(CH_3)-$	$(C_2H_5)_2NCH_2CH_2-$	A	67.5	108	.06	1.4601	.9272	$C_{18}H_{35}NO_2$	88.91	87.90	4.71	4.69	61.3[a]	141–146	—	—	10.62	10.51	+
$CH_3CH_2CH(C_2H_5)CH_2-$	$(C_2H_5)_2NCH_2CH_2-$	B	79.	95	.005	1.4568[c]	.9176[c]	$C_{19}H_{37}NO_2$	93.53	92.44	4.50	4.35	55.[e]	111.5–113	—	—	10.19	10.11	+
$SCH=CHCH=CCH_2-$	$(C_2H_5)_2NCH_2CH_2-$	A	94.	113	.015	1.5051	1.0353	$C_{18}H_{29}NO_2S$	93.74	92.68	4.33	4.52	85.	130–133	—	—	9.85	9.85	—

[a] *Recrystallized from methyl isobutyl ketone.* [b] *Yield and analysis on material from absolute ether. Melting point taken on sample recrystallized from ethyl acetate plus absolute ether.* [c] Determined by Miss Elizabeth Beard in these laboratories. [d] Recrystallized from methyl ethyl ketone. [e] Recrystallized from ethyl acetate. [f] The hydrochloride of this amine separated as an oil from absolute ether and has not been obtained crystalline. [g] Tested on isolated intestinal muscle, stimulated by acetylcholine (1:5,000,000). The activities are estimated for dilution of 1:8,000,000 of the compounds being tested.

after the hydrolysis of ethyl Δ^2-cyclopentenylisopropylcyanoacetate. Yield, 50%; m.p. 118–121°.

Anal. Calc'd for $C_{10}H_{17}NO$: N, 8.38. Found: N, 8.26.

A sample of this amide was hydrolyzed as described above to the corresponding acid (Table II).

Cyclopentylisopropylacetamide. In a similar way this amide was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentylisopropylcyanoacetate. Yield, 33%, m.p. 142–143°.

Anal. Calc'd for $C_{10}H_{19}NO$: N, 8.27. Found: N, 8.14.

Cyclopentyl-sec-butylacetamide. Likewise, this amide was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentyl-*sec*-butylcyanoacetate. Yield, 30.6%; m.p. 131–132°.

Anal. Calc'd for $C_{11}H_{21}NO$: N, 7.64. Found: N, 7.47.

Cyclopentyl-(1,2-dimethylpropyl)acetamide. Similarly, this was isolated from the neutral fraction after the hydrolysis of ethyl cyclopentyl-(1,2-dimethylpropyl)cyanoacetate. Yield, 33.5%; m.p. 87–93°.

Anal. Calc'd for $C_{12}H_{23}NO$: N, 7.10. Found: N, 7.17.

Method A. β-Diethylaminoethyl cyclopentyl-(2-methylbutyl)acetate and hydrochloride. A solution of 20.6 g. (0.104 mole) of cyclopentyl-(2-methylbutyl)acetic acid in 40 ml. of isopropanol was neutralized to phenolphthalein with alcoholic sodium ethoxide, and then a solution of 13.6 g. (0.104 mole) of β-diethylaminoethyl chloride in 40 ml. of isopropanol was added. After standing for several days (or refluxing several hours), the solution was filtered from salt and the solvent removed. The basic ester was taken up in ether, washed with water, and extracted with cold dilute hydrochloric acid. The acid solution was washed with ether, made basic with sodium carbonate, and the amine was taken up in ether and dried over sodium sulfate. After removing the ether, the basic ester was distilled from a Claisen flask, giving 24.4 g. (80%) of liquid.

The hydrochloride was prepared from 23 g. of this amine by passing hydrogen chloride gas into its solution in absolute ether. The precipitate crystallized and was collected, thoroughly washed with absolute ether, and dried in a vacuum desiccator. Yield, 20.7 g. (80%).

Method B. Cyclopentyl-(n-propyl)acetyl chloride. A solution of 255 g. (1.5 moles) of cyclopentyl-(*n*-propyl)acetic acid (2) in 185 ml. (2.5 moles) of thionyl chloride was allowed to stand at room temperature overnight and then refluxed on a steam-bath for one hour. After removal of the excess thionyl chloride *in vacuo*, the acid chloride was distilled from a Claisen flask, b.p. 108° (17 mm.); n_D^{25} 1.4620.

Anal. Calc'd for $C_{10}H_{17}ClO$: Cl, 18.79. Found: Cl, 18.38.

β-Dimethylaminoethyl cyclopentyl-(n-propyl)acetate and hydrochloride. To a solution of 18.8 g. (0.1 mole) of the above acid chloride in 50 ml. of dry benzene was added 17.2 g. (0.2 mole) of β-dimethylaminoethanol. The mixture became hot and crystals separated. After standing overnight (or refluxing for an hour), the mixture was diluted with ice-water, made strongly acidic with hydrochloric acid, and extracted with ether. The aqueous solution was made basic with cold dilute sodium hydroxide and extracted with ether. The ether solution was thoroughly washed with water and dried over sodium sulfate. After removing the ether, the free base was distilled from a Claisen flask, giving 20 g. (83%) of colorless liquid.

Hydrogen chloride was passed into a solution of 18.9 g. of this amine in absolute ether. The gelatinous precipitate was collected, washed with absolute ether, and dried; weight, 20 g. This was recrystallized from methyl isobutyl ketone and washed with absolute ether, giving 15 g. (69%) of a white hygroscopic powder.

Cyclopentylisobutylacetyl chloride. By a method similar to that described above, 814 g. (4.42 moles) of cyclopentylisobutylacetic acid was converted to its acid chloride. It was distilled from a Claisen flask, giving 866.2 g. (96.5%) of colorless liquid; n_D^{25} 1.4608, d_4^{25} 0.9913.

Anal. Calc'd for $C_{11}H_{29}ClO$: M_D, 55.69; Cl, 17.49.
Found: M_D, 55.91; Cl, 17.26.

Δ^2-Cyclopentenyl-Δ^2-cyclohexenylacetyl chloride. A solution of 41.2 g. (0.2 mole) of Δ^2-cyclopentenyl-Δ^2-cyclohexenylacetic acid (2) and 35.7 g. (0.3 mole) of thionyl chloride in 100 ml. of dry benzene was refluxed for 2½ hours. The solvent was removed by distillation, more benzene was added and also removed. The residue was distilled *in vacuo*. Yield, 85%; b.p. 110° (0.3 mm.); n_D^{25}, 1.5180; d_4^{25}, 1.0974.

Anal. Calc'd for $C_{13}H_{17}ClO$: M_D, 61.79; Cl, 15.8.
Found: M_D, 62.05; Cl, 15.9.

β-[(Δ^2-Cyclopentenyl)ethylamino]ethanol.[5] One mole of Δ^2-cyclopentenyl chloride was added to a solution of 178 g. of ethylethanolamine in 300 ml. of ether. When the exothermic reaction had subsided, a hydrochloride crystallized rapidly and exothermically from the reaction mixture. After five days at room temperature, the mixture was shaken with 250 ml. of 20% sodium hydroxide. The ether layer was separated and combined with ether extracts of the alkaline solution. The ether solution was dried over potassium hydroxide pellets and distilled using a water-pump vacuum; no fractionation was attempted during the first distillation. The distillate was then distilled through a 12-inch column packed with glass helices to give 60 g. of product, b.p. 110–112° at 34 mm.; n_D^{25} 1.477.

Anal. Calc'd for $C_9H_{17}NO$: N, 9.02. Found: N, 9.11.

SUMMARY

1. The preparation and properties are reported for thirty-two new esters of tertiary amino alcohols with substituted acetic acids containing cyclopentyl or Δ^2-cyclopentenyl groups in the alpha position.

2. Twenty intermediate acetic acids are reported.

3. Many new malonic and cyanoacetic esters are described.

4. Preliminary tests of antispasmodic activity of the hydrochlorides of these basic esters indicate desirable properties for some of them.

KANSAS CITY, MISSOURI

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(1) MOFFETT, HART, AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1854 (1947).
(2) MOFFETT, HART, AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1849 (1947).
(3) ALEXANDER AND COPE, *J. Am. Chem. Soc.*, **66**, 886 (1944).

[5] Prepared by Dr. Louis H. Goodson, in these laboratories.

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF GEORGE A. BREON AND COMPANY[1]]

ANTISPASMODICS. IV. TERTIARY AMINOALKYL ESTERS OF Δ^2-CYCLOHEXENYL SUBSTITUTED ACETIC ACIDS

ROBERT BRUCE MOFFETT[2] AND JANICE NEIL

Received September 6, 1949

In Part II (1) of this series are reported a number of β-diethylaminoethyl esters of acetic acids substituted in the α-position by a Δ^2-cyclohexenyl group. In this work the series is extended and esters of other basic alcohols are included.

The methods used in these preparations are for the most part very similar to those already reported (1, 2, 3). These methods involved the synthesis of the necessary acids through malonic or cyanoacetic ester syntheses, and then their esterification by the appropriate tertiary amino alcohols. In the preparation of the malonic esters (Table I) the Δ^2-cyclohexenyl group was introduced first, while in the case of the cyanoacetic esters the alkyl group was introduced first. Unless otherwise stated, the hydrochlorides of the amino esters (Table III) were recrystallized from methyl isobutyl ketone.

Preliminary pharmacological screening in these laboratories, indicates that these compounds all have some degree of antispasmodic activity. However, only β-diethylaminoethyl Δ^2-cyclohexenylisoamylacetate hydrochloride can be considered very highly active. The series of + and − signs (Table III) indicates the relative activities, ++++ being highly active and −− being inactive at dilutions of 1:8,000,000. A ++++ rating is the equivalent of about 0.1 the activity of atropine sulfate.

We are indebted to Dr. Willard M. Hoehn, Director of these laboratories, for valuable help and guidance in this work. The nitrogen analyses are by Miss Elizabeth Beard in these laboratories, and the carbon and hydrogen analyses are by Micro-Tech Laboratories, Skokie, Illinois.

EXPERIMENTAL

Ethyl Δ^2-Cyclohexenyl-sec-butylcyanoacetate. To sodium ethoxide, prepared in a 1-l. flask from 36.8 g. (1.6 moles) of sodium and 600 ml. of absolute ethanol, was added 127 g. (0.75 mole) of ethyl *sec*-butylcyanoacetate (4), and then 194 g. (0.8 mole) of 1,2-dibromocyclohexane. After refluxing for 3½ hours, a 1-ml. sample used only 0.7 ml. of 0.1 *N* acid for neutralization. Most of the solvent was removed by distillation, water was added, and the layers were separated. The aqueous solution was extracted with ether which was added to the ester and washed with saturated salt solution. After removing the solvent, the product was distilled, first from a Claisen flask, and then through a 12-inch column packed with ⅛-inch glass helices, giving 110.2 g. (59%) of nearly colorless liquid.

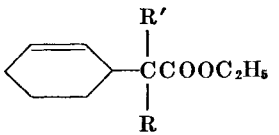
Δ^2-Cyclohexenylisobutylacetonitrile.[3] During the preparation of ethyl Δ^2-cyclohexenylisobutylcyanoacetate, by a method essentially similar to that described above, a fraction

[1] The functions of the George A. Breon and Company Laboratories have been assumed by the Sterling-Winthrop Research Institute, Rensselaer, New York, and any requests for reprints should be addressed there. Other inquiries may be addressed to the first author.

[2] Present address: The Upjohn Company, Kalamazoo, Michigan.

TABLE I

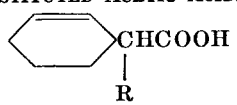
Malonic and Cyanoacetic Esters



R	R′	Yield, %	B.P., °C.	Mm.	n_D^{25}	d_4^{25}	Empirical formula	Molecular refractivity		Analysis, N	
								Calc'd	Found	Calc'd	Found
$CH_3CH(CH_3)$—	—$COOC_2H_5$	30.	83	0.022	1.4675	1.0265	$C_{16}H_{26}O_4$	76.74	76.40	—	—
$CH_3CH(CH_3)CH_2$—	—CN	20.	92	.05	1.4727	0.9913	$C_{15}H_{23}NO_2$	70.23	70.52	5.62	5.48
$CH_3CH_2CH(CH_3)$—	—CN	59.	94	.02	1.4750	1.0015	$C_{15}H_{23}NO_2$	70.23	69.88	5.62	5.42
$CH_3CH(CH_3)CH_2CH_2$—	—$COOC_2H_5$	48.5	97	.02	1.4643	0.9993	$C_{18}H_{30}O_4$	86.00	85.77	—	—
$CH_3CH_2CH(CH_3)CH_2$—	—$COOC_2H_5$	42.4	98	.018	1.4648	1.0071	$C_{18}H_{30}O_4$	86.00	85.64	—	—
$CH_3(CH_2)_2CH(CH_3)$—	—CN	55.	101	.05	1.4750	0.9882	$C_{16}H_{25}NO_2$	74.85	74.87	5.32	5.13
$CH_3CH(CH_3)CH(CH_3)$—	—CN	59.5	96	.045	1.4778	.9974	$C_{16}H_{25}NO_2$	74.85	74.73	5.32	5.29
$CH_3CH_2CH(C_2H_5)CH_2$—	—$COOC_2H_5$	47.5	106	.026	1.4684	.9984	$C_{19}H_{32}O_4$	90.63	90.35	—	—

TABLE II

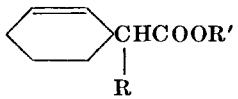
Substituted Acetic Acids



R	Yield, %	B.P., °C.	Mm.	n_D^{25}	d_4^{25}	Empirical formula	Molecular refractivity		Neutral equivalent	
							Calc'd	Found	Calc'd	Found
$CH_3CH(CH_3)$—	96.4	90	0.048	1.4783	0.9968	$C_{11}H_{18}O_2$	51.87	51.78	182.3	179.9
$CH_3CH(CH_3)CH_2$—	85.	110	.013	1.4754	.9810	$C_{12}H_{20}O_2$	56.50	56.37	196.3	198.1
$CH_3CH_2CH(CH_3)$—	68.8	92	.01	1.4800	.9912	$C_{12}H_{20}O_2$	56.50	56.25	196.3	197.9
$CH_3CH(CH_3)CH_2CH_2$—	100.	104	.07	1.4746	.9669	$C_{13}H_{22}O_2$	61.13	61.19	210.3	208.2
$CH_3CH_2CH(CH_3)CH_2$—	90.8	103	.03	1.4758	.9715	$C_{13}H_{22}O_2$	61.13	61.04	210.3	207.4
$CH_3(CH_2)_2CH(CH_3)$—	60.	106	.046	1.4790	.9778	$C_{13}H_{22}O_2$	61.13	60.99	210.3	213.8
$CH_3CH(CH_3)CH(CH_3)$—	15.4	108	.04	1.4806	—	$C_{13}H_{22}O_2$	—	—	210.3	206.6
$CH_3CH_2CH(C_2H_5)CH_2$—	97.6	111	.026	1.4775	.9660	$C_{14}H_{24}O_2$	65.76	65.67	224.3	224.1

TABLE III

Esters of Amino Alcohols



R	R'	FREE BASE											HYDROCHLORIDE				
		Method of Preparation[a]	Yield, %	B.p., °C.	MM.	n_D^{25}	d_4^{25}	Empirical Formula	Molecular Refractivity Calc'd	Molecular Refractivity Found	Analysis N Calc'd	Analysis N Found	Yield, %	M.p., °C.	Analysis Cl Calc'd	Analysis Cl Found	Antispasmodic Activity[f]
$CH_3CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	87.0	122	0.5	1.4700	0.9414	$C_{17}H_{31}NO_2$	83.86	83.41	4.98	4.98	88.	102–104	11.15	10.81	+
$CH_3CH(CH_3)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	43.9	108	.01	1.4669	.9305	$C_{18}H_{33}NO_2$	88.48	88.08	4.74	4.67	46.	116–118	10.68	10.31	+++
$CH_3CH_2CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	—	109	.04	1.4701	.9428	$C_{18}H_{33}NO_2$	88.48	87.46	4.74	4.83	24.	105–110	10.69	11.19	+
$CH_3CH(CH_3)CH_2CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	54.2	109	.029	1.4660	.9285	$C_{19}H_{35}NO_2$	93.06	92.41	4.52	4.44	56.4	101–105	10.25	10.32	++++
$CH_3CH(CH_3)CH_2CH_2$—	$(CH_3)_2NCH_2CH_2$—	B	89.	93	.015	1.4665[b]	.9373[b]	$C_{17}H_{31}NO_2$	83.82	83.23	4.98	4.75	46.4	114–115	11.12	10.93	−
$CH_3CH(CH_3)CH_2CH_2$—	$CH_2(CH_2)_4NCH_2$- CH_2—	B	76.6	130	.01	1.4832[b]	.9768[b]	$C_{20}H_{35}NO_2$	95.48	94.00	4.36	4.29	76.4	157–159	9.91	9.94	+
$CH_3CH_2CH(CH_3)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	A	46.2	110	.025	1.4664	.9324	$C_{19}H_{35}NO_2$	93.06	92.04	4.52	4.48	82.7	102–104	10.25	10.48	−
$CH_3(CH_2)_2CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	A	80.4	130	.5	1.4695	.9319	$C_{19}H_{35}NO_2$	93.06	92.70	4.52	4.32	74.1[c]	102–107	10.24	10.41	−
$CH_3CH(CH_3)CH(CH_3)$—	$(C_2H_5)_2NCH_2CH_2$—	B	—	124	.15	1.4720[b]	.9454[b]	$C_{19}H_{35}NO_2$	93.06	91.66	4.52	4.46	73.3	128–132	10.25	10.16	+
$CH_3CH_2CH(C_2H_5)CH_2$—	$(C_2H_5)_2NCH_2CH_2$—	B	70.	114	.016	1.4690[b]	.9358[b]	$C_{20}H_{37}NO_2$	97.08	96.28	4.33	4.49	78.7[d]	100–102	9.85	10.08	+
$CH_3CH(CH_3)CH_2$—and C_6H_{11}[e]	$(C_2H_5)_2NCH_2CH_2$—	A	76.3	112	.07	1.4597	.9174	$C_{18}H_{35}NO_2$	88.95	88.84	4.71	4.51	89.	134–135	10.62	10.96	+

[a] Examples of Methods A and B are given in the foregoing article (3). [b] Determined by Miss Elizabeth Beard, in these laboratories. [c] This separated from absolute ether in crystalline form and was not recrystallized. [d] Recrystallized from ethyl acetate. [e] Cyclohexyl in place of Δ^2-cyclohexenyl. [f] Tested on isolated intestinal muscle, stimulated by acetylcholine (1:5,000,000). The activities are estimated for dilutions of 1:8,000,000 of the compounds being tested.

was isolated by distillation through an efficient column which proved to be this nitrile, b.p. 65° (0.06 mm.); n_D^{25} 1.4720, d_4^{25} 0.91075.

Anal. Calc'd for $C_{12}H_{19}N$: M_D, 54.79; N, 7.92.
Found: M_D, 54.51; N, 8.09.

This nitrile doubtless arose through hydrolysis and decarboxylation of the desired ester during the working up of the product.

The acetonitrile could be hydrolyzed under the usual conditions to give Δ^2-cyclohexenylisobutylacetic acid (Table II).

Cyclohexylisobutylacetic acid.[3] This was prepared in 55% yield by the low pressure hydrogenation of Δ^2-cyclohexenylisobutylacetic acid using Adams' catalyst; b.p. 98° (0.025 mm.); n_D^{25} 1.4651; d_4^{25} 0.9604.

Anal. Calc'd for $C_{12}H_{22}O_2$: M_D, 56.97; N.E., 198.3.
Found: M_D 57.09; N.E., 199.8.

Δ^2-Cyclohexenylisoamylacetyl chloride. A solution of 44 g. (0.21 mole) of Δ^2-cyclohexenylisoamylacetic acid in 36.3 ml. of thionyl chloride was warmed at 50° until the reaction was complete. The excess thionyl chloride was removed *in vacuo*, and the product was distilled, b.p. 85° (0.07 mm.), giving 45 g. (94%) of colorless liquid; n_D^{25} 1.4800, d_4^{25} 1.0017.

Anal. Calc'd for $C_{13}H_{21}ClO$: M_D, 64.35; Cl, 15.51.
Found: M_D, 64.88; Cl, 15.89.

SUMMARY

1. The preparation and properties are reported for eleven new esters of tertiary aminoalcohols, ten of which contain the Δ^2-cyclohexenyl group in the alpha position.

2. Many new substituted acetic acids and malonic and cyanoacetic esters were prepared as intermediates.

3. Preliminary tests for antispasmodic activity are reported for the hydrochlorides of these basic esters, and one of them appears to be highly active.

KANSAS CITY, MISSOURI

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(2) MOFFETT, HART, AND HOEHN, *J. Am. Chem. Soc.*, **69**, 1849 (1947).
(3) MOFFETT, HART, AND NEIL, *J. Org. Chem.*, **15**, preceding paper.
(4) ALEXANDER AND COPE, *J. Am. Chem. Soc.*, **66**, 886 (1944).

[3] Prepared by Miss Charlotte Anne Hart in these laboratories.

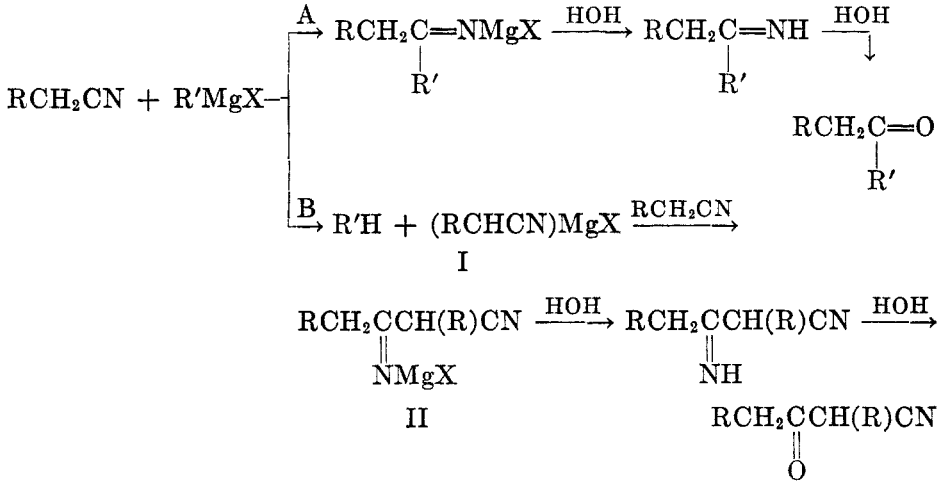
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF DUKE UNIVERSITY]

THE INFLUENCE OF STRUCTURE ON THE REACTIONS OF GRIGNARD REAGENTS WITH NITRILES HAVING α-HYDROGEN[1]

CHARLES R. HAUSER AND WILBERT J. HUMPHLETT[2]

Received September 20, 1949

The reaction of nitriles having α-hydrogen with Grignard reagents may involve course A or B:[3]



Course B, which is initiated by reaction of the Grignard reagent with the α-hydrogen of the nitrile, may be extended to form trimers. Thus, I may condense with the nitrile group of II to form III which cyclizes leading to an aromatic trimer (IV), and II may condense with unchanged nitrile to form V which cyclizes to another aromatic trimer (VI). Trimer IV (R = C_6H_5) has been isolated in 35% yield from the reaction mixture of phenylacetonitrile and phenylmagnesium bromide (1) and trimer VI (R = CH_3) in 10% yield, from propionitrile and ethylmagnesium bromide (2).

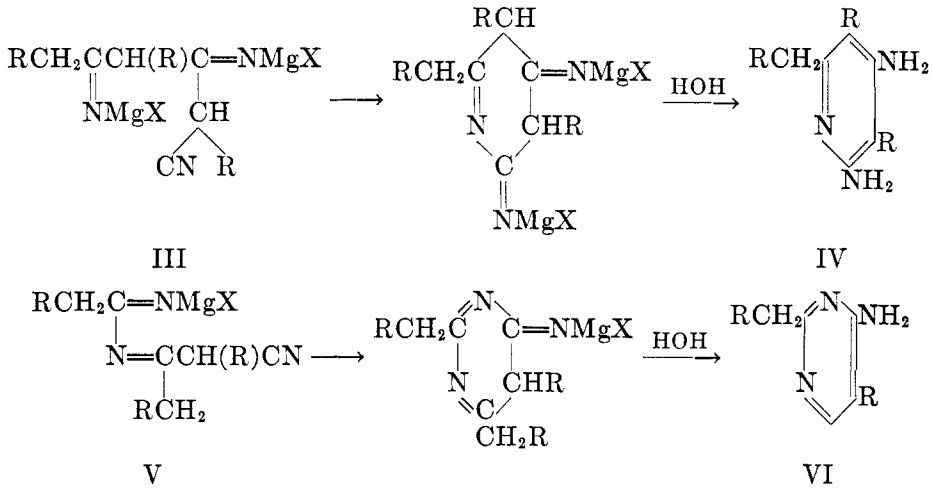
In the presence of a large excess of Grignard reagent the magnesium derivative (I) appears to be capable of adding a molecule of the reagent to form the dimagnesium derivative (VII) which on hydrolysis would produce the ketone. This would account for the observation of Shriner and Turner (3) that, with acetonitrile and phenylmagnesium bromide, the yield of acetophenone is in-

[1] This work was supported in part by a grant from the Duke University Research Council.

[2] Eli Lilly Fellow, 1949–1950.

[3] It seems probable that the magnesium of the Grignard reagent first coordinates with the nitrogen of the nitrile and that the two courses of reaction (A and B) take place within the resulting coordination complex. For a discussion of the analogous reactions with esters see Hauser, Saperstein, and Shivers, *J. Am. Chem. Soc.*, **70**, 606 (1948).

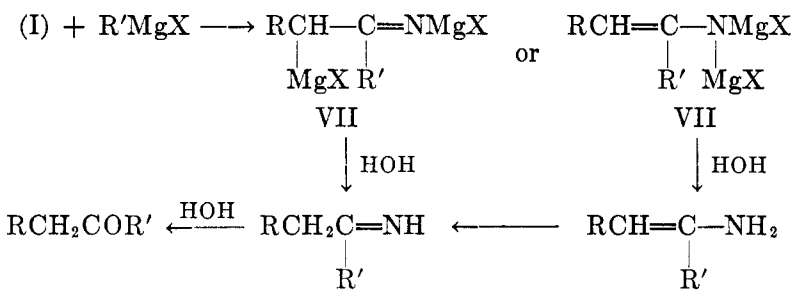
creased considerably by the use of a large (300%) excess of the reagent. Similarly we have found that the yields of ketone are increased somewhat (7–14%) in the reactions of propionitrile or capronitrile with methylmagnesium iodide and of



III IV

V VI

phenylacetonitrile with phenylmagnesium bromide by employing a 300% excess of the reagent. However, with propionitrile or higher aliphatic nitriles and phenylmagnesium bromide, a large excess of the reagent is not required to produce maximum yields of ketones (4).



The main purpose of the present investigation has been to determine the influence of structure of both the nitrile and the Grignard reagent on the relative extent of courses A and B. Relatively simple nitriles were treated with a 10% excess of the Grignard reagent, and the acidified reaction mixture was heated to hydrolyze the ketimine to the ketone and the β-imino nitrile to the β-keto nitrile. The yields of these products are given in Table I. For comparison, two of our earlier results, those from propionitrile and capronitrile with phenylmagnesium bromide (4), are included in the table. Also in this table are given the yields of residue calculated as the trimer which earlier workers have reported to be the main constituent (1, 2, 5). The 10% excess of Grignard reagent was employed in order to minimize somewhat the formation of trimers. A larger excess was usually avoided in order to be reasonably certain that the ketone would be formed practically entirely by course A and not appreciably by course B in the

manner described above. Under the conditions employed, the yields of ketone may be considered a rough measure of the relative extent of course A and the combined yields of β-keto nitrile and the residue (calculated as the trimer), a rough measure of the relative extent of course B. Although the total yields given in Table I may be regarded as satisfactory in most cases, certain of them were only fair, especially when the products were water-soluble. Earlier workers have similarly reported (1, 6) only fair total yields in such reactions employing various proportions of reactants.

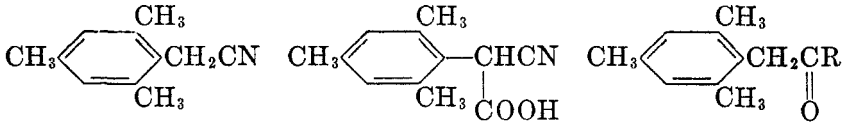
It can be seen from Table I that, with a particular Grignard reagent, the yields of ketone increase, and the combined yields of β-keto nitrile and residue (calculated as trimer) decrease as the R group of the nitrile, RCH_2CN, is varied in the order: phenyl, hydrogen, alkyl. For example, with *n*-amylmagnesium bromide, the yields of ketone were 0%, 14%, and 61% whereas the combined yields of β-keto nitrile and residue were 82%, 49%, and 5% when R of the nitrile was phenyl, hydrogen, and methyl, respectively. Since this is the order of decreasing activation of the α-hydrogen, the relative extent of course A appears to increase and that of course B to decrease as the relative reactivities of the α-hydrogen are decreased. In agreement with this, cyanocyclopropane in which the α-hydrogen may be considered to be deactivated by two alkyl groups has previously been reported to react with a slight excess of ethylmagnesium bromide to form predominantly (70%) the corresponding ketone (1). However, alkyl groups appear not only to deactivate the α-hydrogen but also to deactivate (presumably to a smaller degree) the nitrile group, since we have found that diethylacetonitrile failed to react appreciably with ethylmagnesium bromide in refluxing ethyl ether even after eleven hours.

With a particular nitrile, phenylmagnesium bromide and apparently most aromatic Grignard reagents[4] react relatively more with the nitrile group (course A) and relatively less with the α-hydrogen (course B) than alkylmagnesium halides. For example, with phenylacetonitrile, phenylmagnesium bromide gave a 33% yield of ketone and a 51% combined yield of β-keto nitrile and residue whereas *n*-amylmagnesium bromide gave no ketone and an 82% combined yield of β-keto nitrile and residue. In general, increasing the size or complexity of the Grignard reagent appears to favor the α-hydrogen reaction. Thus with phenylacetonitrile, phenylmagnesium bromide gave a 33% yield of ketone whereas the more sterically hindered mesitylmagnesium bromide gave no ketone. Apparently only α-hydrogen reaction products were formed with the hindered Grignard reagent. With propionitrile, *n*-amylmagnesium bromide gave a much better yield of ketone and a lower yield of α-hydrogen products than the more complex *tert*-butylmagnesium chloride although the total yield of products with the latter Grignard reagent was only 25%.[5]

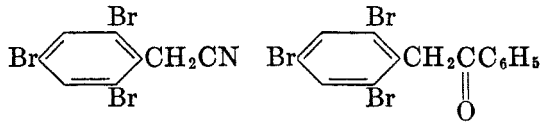
[4] Various arylmagnesium halides have been found to react with the nitrile group of γ-diethylaminobutyronitrile to give good yields of ketones [Humphlett, Weiss, and Hauser, *J. Am. Chem. Soc.*, **70**, 4020 (1948)] whereas we have been unable to obtain an appreciable amount of ketone from the reaction of methylmagnesium iodide with this nitrile.

[5] Since reduction of the nitrile group by a β-hydrogen of the Grignard reagent to form an aldimine magnesium derivative (RCH=NMgX) seemed possible, we carried out the reaction of capronitrile with *tert*-butylmagnesium chloride, and attempted to isolate the cor-

With the hindered phenylacetonitriles, mesitylacetonitrile (VIII) and 2,4,6-tribromophenylacetonitrile (XI) which undergo self-condensation only sluggishly, the extent of the α-hydrogen reaction (course B) was determined conveniently by carbonation of the magnesium derivative (I) and isolation of the corresponding carboxylic acid (such as IX). As usual the extent of course B was determined by the yield of ketone (X and XII).



VIII IX X



XI XII

Mesitylacetonitrile gave with phenylmagnesium bromide apparently only the corresponding ketone (X, R = C_6H_5) and, with methylmagnesium iodide, a 63% yield of the corresponding ketone (X, R = CH_3) and a 27% yield of the acid (IX).[6] 2,4,6-Tribromophenylacetonitrile gave with phenylmagnesium bromide a 42% yield of the corresponding ketone (XII) and none of the corresponding acid, 46% of the nitrile being recovered. The tribromo nitrile failed to react with methylmagnesium iodide even after eight hours of refluxing.

The predominant formation of the ketone with these *ortho*-substituted phenylacetonitriles is in contrast to the main formation of α-hydrogen reaction products obtained in the analogous reaction with phenylacetonitrile itself (see Table I). The decrease in the rate of reaction at the α-hydrogen in the *ortho*-substituted nitriles relative to the rate at the nitrile group appears to be due to a steric factor.

Similarly to phenylmagnesium bromide, mesitylmagnesium bromide gave with mesitylacetonitrile (after a relatively long reflux period) none of the acid (IX). Reaction occured apparently only at the nitrile group to form the ketimine (obtained as its hydrochloride), although this product was not identified. However, with *tert*-butylmagnesium chloride, mesitylacetonitrile gave (after a rela-

responding aldehyde which would have been readily formed from the aldimine. However, after decomposition of the reaction mixture, no aldehyde could be isolated as its sodium bisulfite derivative.

[6] In a preliminary experiment by Miss Passie Saperstein in this laboratory, the ether solution of mesitylacetonitrile (0.055 mole) and methylmagnesium bromide (0.075 mole) was refluxed for two days. There was isolated a 30% yield of the ketone [m.p. 56–59°; reported m.p. 56–60° (17)] and, after recrystallization from ethanol a 20% yield of the self-condensation product of the nitrile. The latter product melts at 183–184°.

Anal. Calc'd for $C_{22}H_{25}NO$: C, 82.76; H, 8.00.
Found: C, 82.76; H, 8.17.

TABLE I

YIELDS OF PRODUCTS FROM NITRILES WITH 10% EXCESS OF GRIGNARD REAGENTS

NITRILE	R in RMgBr	KETONE	B.P., °C.	MM.	YIELD, %	β-KETONITRILE	B.P., °C.	MM.	YIELD, %	RESIDUE, % TRIMER?
Phenylaceto	Phenyl	Phenyl benzyl	M.P. 55		33	α-Phenylacetylphenylaceto	197–202	2	15	36
Aceto	Phenyl	Acetophenone	200–205	atm.	37					*ca.* 50
Propio	Phenyl	Propiophenone	105–106	17	83					
Capro	Phenyl	Caprophenone	137–138	13	89					
Phenylaceto	*n*-Amyl					α-Phenylacetylphenylaceto	197–202	2	51	31
Aceto	*n*-Amyl	Methyl *n*-amyl	140–150	atm.	14					49
Propio	*n*-Amyl	Ethyl *n*-amyl	164–172	atm.	61					*ca.* 5
Phenylaceto	Methyl[a]	Methyl benzyl	86–87	6	8	α-Phenylacetylphenylaceto	197–202	2	71	
Propio	Methyl[a]	Methyl ethyl	77–78	atm.	21	α-Propionylpropio	190–194	atm.	28	
Capro	Methyl[a]	Methyl *n*-amyl	140–150	atm.	40	Caproylcapro[c]			>20	
Phenylaceto	*tert*-Butyl[b]					α-Phenylacetylphenylaceto	197–202	2	80	
Propio	*tert*-Butyl[b]	Ethyl *tert*-butyl	120–125	atm.	5	α-Propionylpropio	190–194	atm.	20	
Phenylaceto	Ethyl					α-Phenylacetylphenylaceto	197–202	2	51[d]	36
Phenylaceto	Isopropyl					α-Phenylacetylphenylaceto	197–202	2	64[e]	*ca.* 15
Phenylaceto	*n*-Butyl					α-Phenylacetylphenylaceto	197–202	2	23[f]	46
Phenylaceto	Mesityl					α-Phenylacetylphenylaceto	197–202	2	45	43

[a] Methylmagnesium iodide. [b] tert-Butylmagnesium chloride. [c] This product was not obtained sufficiently pure for analysis; it boiled at 224–228° at 22 mm. [d] Phenylacetonitrile (10%) was recovered. [e] Phenylacetonitrile (9%) was recovered. [f] Phenylacetonitrile (24%) was recovered.

tively long reflux period) a 37% yield of the acid (IX) and none of the ketone, 48% of the nitrile being recovered. Under similar conditions, 2,4,6-tribromophenylacetonitrile failed to react with *tert*-butylmagnesium chloride, 83% of the nitrile being recovered.

Thus, although the hindered aromatic Grignard reagent, mesitylmagnesium bromide, reacts only at the nitrile group, the hindered aliphatic Grignard reagent reacts apparently only at the α-hydrogen. This is in line with the observation made above that, in general, aliphatic Grignard reagents react relatively more at the α-hydrogen and relatively less at the nitrile group than aromatic Grignard reagents. It may seem rather remarkable that *tert*-butylmagnesium chloride reacts only at the α-hydrogen of mesitylacetonitrile, but it is to be noted that this Grignard reagent also reacts only at the α-hydrogen of phenylacetonitrile (see Table I).

It should be mentioned that Hellerman (7) has observed the predominant formation of the corresponding ketone with β,β,β-triphenylpropionitrile and aromatic or aliphatic Grignard reagents.

EXPERIMENTAL[7]

*Mesitylacetonitrile.*This nitrile (m.p. 78–80°) was prepared as described in Organic Syntheses (8) from α^2-chloroisodurene (b.p. 126–128° at 21 mm.) which was obtained conveniently in 80% yield from mesitylene and chloromethyl ether (9).

2,4,6-*Tribromophenylacetonitrile.* 2,4,6-Tribromotoluene (10) (100 g., 0.305 mole) was brominated in the side chain by the dropwise addition of 56 g. (0.35 mole) of bromine beneath the surface of the molten mass at 200–220° over a period of five hours as indicated by Asinger (11). The reaction mixture was cooled to 75°, taken up with carbon tetrachloride, diluted with ether, and washed with a saturated solution of sodium bicarbonate. The ether phase was dried over Drierite, filtered, and the solvent removed. The residue was distilled *in vacuo* through a 15-cm. Vigreux column yielding 104 g. (84%) of 2,4,6-tribromobenzyl bromide, b.p. 154–158° at 1 mm. and 174–178° at 6 mm.; reported b.p. 202° at 18 mm. (11).

To 55 g. (0.135 mole) of 2,4,6-tribromobenzyl bromide dissolved in one liter of 95% ethanol was added 10.5 g. (0.162 mole) of potassium cyanide dissolved in a minimum of water, and the resulting clear solution was gently refluxed for five hours. The reaction mixture was diluted with water, cooled, and the precipitated nitrile filtered. The product was recrystallized from ethanol yielding 38 g. (79%) of 2,4,6-tribromophenylacetonitrile, m.p. 126°.

Anal. Calc'd for $C_8H_4Br_3N$: N, 3.95; Br, 67.75.
Found: N, 3.81; Br, 67.46.

Henraut (12) reported that this nitrile, prepared from 2,4,6-tribromobenzyl chloride in 25% yield, melted at 138–139°.

Grignard reagents. Most of these reagents were prepared in a concentration of approximately 2 *N* in yields of 90–95% as determined by titration (13).

Mesitylmagnesium bromide was obtained in 80% yield according to the procedure described in Organic Syntheses (14) in which the yield (55–61%) of only the carbonation product was reported.

tert-Butylmagnesium chloride was obtained in 83% yield by the Organic Syntheses method (15) except that the addition period was increased to 15 hours using a drying tube filled with a mixture of calcium chloride and soda-lime.

Reaction of unhindered nitriles and Grignard reagents. In a three-necked, round-bottomed

[7] Melting points and boiling points are uncorrected. Microanalyses are by the Microchemical Laboratory of the University of Pittsburgh.

flask equipped through ground-glass joints with a mercury-sealed stirrer, dropping-funnel, and a reflux condenser (having a drying tube) was placed the ether solution of the Grignard reagent. To the stirred refluxing solution of the reagent was added an ether solution of the nitrile over twenty minutes. Stirring and refluxing were continued 4–6 hours. The cooled mixture was decomposed by the cautious addition of dilute hydrochloric acid and the ether removed on the steam-bath. After heating for one hour longer to insure hydrolysis of the ketimine, the ketone was extracted four times with ether. The solvent was distilled from the dried, combined ether solutions and the residue fractionated through a 15-cm. Vigreux column or recrystallized from ethanol.

The results are summarized in Table I. All of the ketones listed in this table were identified by means of suitable derivatives. The β-keto nitrile, α-phenylacetylphenylacetonitrile, was identified by its oxime, m.p. 107°; the reported melting point is 107–108° (16). Although reported by earlier workers (2) we have been unable to prepare the oxime or semicarbazone of α-propionylpropionitrile.

Reaction of mesitylacetonitrile with Grignard reagents. To 60 ml. of an ether solution of 0.083 mole of methylmagnesium iodide was added 10 g. (0.055 mole) of mesitylacetonitrile dissolved in 100 ml. of anhydrous ether, followed by stirring and refluxing for eight hours. A ten-fold excess of finely powdered Dry Ice was added with vigorous stirring. After coming to room temperature, the mixture was decomposed by a dropwise addition of dilute hydrochloric acid and stirred vigorously until a clear solution of two layers resulted. The ether phase was separated and the remaining aqueous phase extracted with ether. The combined ether phases were extracted with 10% sodium hydroxide. The ether solution was dried over Drierite, the solvent distilled, and the residue fractionated *in vacuo* through a 15-cm. Vigreux column yielding 6.0 g. (63%) of mesitylacetone, b.p. 104–107° at 2 mm. The semicarbazone melted at 204°; reported m.p. 204° (17).

The sodium hydroxide extract was cooled, acidified with concentrated hydrochloric acid, and the liberated mesitylcyanoacetic acid extracted with ether. The combined ether portions were washed with water, dried over Drierite and the solvent distilled leaving a clear, viscous oil. After washing with water and ligroin (b.p. 60–90°), the oil solidified on standing 2–3 hours. One recrystallization from ligroin (b.p. 60–90°) yielded 3.0 g. (27%) of of crude mesitylcyanoacetic acid, m.p. 145–148° dec. Further recrystallization from a mixture of benzene and petroleum ether (b.p. 30–60°) gave the pure acid, m.p. 149–150° dec.

Anal. Calc'd for $C_{12}H_{13}NO_2$: C, 70.91; H, 6.44; N, 6.88; Neut. equiv., 203.
Found: C, 71.15; H, 6.03; N, 6.89; Neut. equiv., 203.

In a similar manner, 8.0 g. (0.05 mole) of mesitylacetonitrile in 75 ml. of ether was added to 75 ml. of an ether solution of 0.075 mole of *tert*-butylmagnesium chloride. The mixture was refluxed for 25 hours under nitrogen, employing a nitrogen safety trap (18). The mixture was carbonated, and the ether solution extracted with dilute sodium hydroxide. From the alkaline phase there was obtained 3.8 g. (37%) of mesitylcyanoacetic acid, m.p. 150°, and from the ether phase, mesitylacetonitrile (40%), m.p. 78–80° after recrystallization from ethanol-water.

Similarly, mesitylacetonitrile (6.4 g., 0.04 mole) in 50 ml. of ether was reacted with 100 ml. of an ether solution of 0.08 mole of phenylmagnesium bromide, the mixture being refluxed for six hours. Omitting the carbonation, the solution was poured onto a mixture of 100 g. of ice and 50 ml. of concentrated hydrochloric acid. Distillation of the ether phase yielded a small amount of mesitylacetophenone and no nitrile. On standing, the aqueous phase yielded a precipitate of mesitylacetophenone (9.3 g., 97%) obtained by the hydrolysis of the water-soluble ketimine hydrochloride. After recrystallization from ethanol-water, the ketone was obtained in a total yield of 78% as white crystals, m.p. 159–160° and at 162° after further recrystallization.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.67; H, 7.61.
Found: C, 86.06; H, 7.90.

Reaction of 2,4,6-tribromophenylacetonitrile with phenylmagnesium bromide. To 60 ml. of an ether solution of 0.028 mole of phenylmagnesium bromide was added 6 g. (0.017 mole) of 2,4,6-tribromophenylacetonitrile (m.p. 126°) in 160 ml. of ether. The solution was stirred

and refluxed for eight hours forming after the first few minutes a yellow precipitate. The reaction mixture was carbonated. After treating with acid, the two phases were separated. On standing the aqueous phase, containing the water-soluble ketimine hydrochloride gave, after recrystallization from ethanol, 3.2 g. (42%) of white crystals of 2,4,6-tribromophenylacetophenone, m.p. 147–148°.

Anal. Calc'd for $C_{14}H_9Br_3O$: C, 38.83, H, 2.09; Br, 55.37.
Found: C, 38.97; H, 2.10; Br, 55.27.

From the ether phase, which was extracted with alkali, there was recovered on fractionation 2.8 g. (46%) of crude 2,4,6-tribromophenylacetonitrile which, after one recrystallization from ethanol, melted at 126°. Acidification of the alkali extract yielded no carboxylic acid.

SUMMARY

A study has been made of the influence of structure of nitriles having α-hydrogen and of Grignard reagents on the relative extent of reaction at the α-hydrogen and at the nitrile group of the nitrile.

In general, reaction at the α-hydrogen decreases and that at the nitrile group increases as the nitrile is varied in the order: phenylacetonitrile, acetonitrile, propionitrile or higher aliphatic nitriles. Phenylmagnesium bromide reacts at the α-hydrogen of nitriles relatively less and at the nitrile group relatively more than aliphatic Grignard reagents.

Hindrance in the Grignard reagent, as with mesitylmagnesium bromide or *tert*-butylmagnesium chloride, favors reaction at the α-hydrogen whereas hindrance in the nitrile, as with mesitylacetonitrile or 2,4,6-tribromophenylacetonitrile, favors reaction at the nitrile group.

Cyclic products reported in the literature are accounted for on the basis of reaction at the α-hydrogen followed by reaction at nitrile groups.

The synthesis of several new compounds and improvements in the synthesis of certain known compounds are reported.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE STATE UNIVERSITY OF IOWA]

THE NITRATION OF TRIPHENYLCARBONIUM SULFATE

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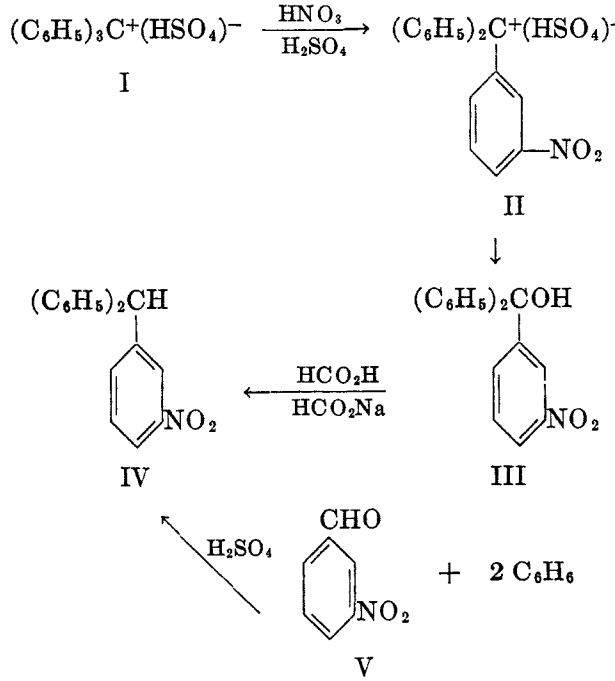
Vorländer (1) studied the stepwise nitration of triphenylcarbonium salts and after hydrolysis obtained carbinols whose analyses indicated them to be approximately mononitro-, dinitro-, and trinitro- derivatives. However, these compounds could not be isolated in the pure crystalline state and attempts to establish their structure by oxidation to nitrobenzoic acids were unsuccessful. Since acid reduction of the trinitrotriphenyl carbinol to the triamino compound did not give a fuchsin dye, it was concluded that the nitro groups were not in the *para*-position. No other data are available on orientation.

The mononitration of triphenylcarbonium sulfate (I) has been reinvestigated. Nitration studies at different temperatures and concentrations of sulfuric and nitric acids showed that mixtures of mono-, di- and tri-nitrated products were always formed in varying ratios. The best conditions for obtaining some of the mononitro derivative consisted in nitration of I in concentrated sulfuric acid at 25° with fuming nitric acid. Dilution with water and neutralization gave a mixture of carbinols containing the *m*-nitroderivative (III) as one component. It was found impossible to separate III in the pure state. However, by reduction



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to the nitrotriphenylmethanes by the formic acid-sodium formate method of Kovache (2) followed by fractional distillation under low pressure there was isolated a 15.4% yield of the *m*-nitrotriphenylmethane (IV); m.p. 91–92°. No other mononitro derivative could be detected.

Since triphenylmethane, and the isomeric *ortho*-, *meta*-, and *para*-nitrotriphenylmethanes all melt within the temperature range of 90 to 94° it was necessary to synthesize these compounds for comparison with the above product. The isomeric nitro compounds were made by condensing *o*-, *m*-, and *p*-nitrobenzaldehyde with benzene with concentrated sulfuric acid (3). It was found that the product from *m*-nitrobenzaldehyde (V) did not depress the melting point of the compound (IV) whereas all the others did cause marked lowering of the melting point of IV.

It was not possible to find experimental conditions which would give exclusively a high yield of the mononitrated compound. Although the yield of the *meta*-nitro derivative (IV) was only 15.4%, the present work taken in conjunction with Vorländer's (1) data on the trinitrotriphenylcarbinol (which must be the *tri-m*-nitrophenylcarbinol) shows that the triphenylmethyl cation (I) is a *meta*-directing structure and hence should be added to the list of compounds (4) containing a positively charged atom attached to the ring which orients the entering nitro group to the *meta* position.

EXPERIMENTAL PART

Nitration of triphenylcarbonium sulfate (I). A solution of 10 g. of triphenylcarbinol in 8 ml. of conc'd sulfuric acid was treated with 100 ml. of fuming nitric acid (*d.* 1.50), allowed to stand at 25° for 24 hours, poured into 1 l. of cold water, and neutralized by the addition of conc'd ammonium hydroxide. The precipitate was washed and dried. The tan powder weighed 12.2 g., m.p. 70–85°. It was a mixture of triphenylcarbinol and nitrated triphenylcarbinols which could not be separated by fractional crystallization although numerous solvents and conditions were studied.

Formic acid reduction of carbinols. The crude nitration product described above was refluxed for eight hours with 150 ml. of 98% formic acid containing 5 g. of sodium formate and then allowed to stand at 25° for two hours. The liquid was decanted from the dark viscous oil which had separated from the solution, and the oil was dissolved in 50 ml. of benzene. The benzene solution was washed with 100-ml. portions of water, 5% sodium bicarbonate, and water. After removal of the benzene by distillation, the residual oil weighed 9.7 g. Distillation of this oil under reduced pressure gave 1.8 g. (15.4%) of pale yellow crystals, b.p. 170–180° (0.35 mm.), m.p. 87–89°. The remainder of the material decomposed with a vigorous evolution of gas. Recrystallization of the crude distillate from 10 ml. of Skellysolve B gave 1.4 g. (12%) of *m*-nitrotriphenylmethane (III), m.p. 90–91°. Mixed melting points with a sample of *m*-nitrotriphenylmethane whose synthesis is described below showed no depression. However, the melting point was depressed upon admixture with samples of *p*-nitrotriphenylmethane (5) (m.p. 91°) and *o*-nitrotriphenylmethane (6) (m.p. 91°).

m-Nitrotriphenylmethane (III). A mixture of 10 g. of *m*-nitrobenzaldehyde, 25 ml. of conc'd sulfuric acid, and 150 ml. of benzene was placed in a bottle with a wired-on glass stopper and shaken at 25° for 24 hours. The benzene layer was separated and washed with 100 ml. each of water, 5% sodium carbonate, 5% sodium bisulfite, and water. The benzene was removed by distillation, and the residual yellow oil was crystallized from 20 ml. of Skellysolve B. The yield of white crystals was 14.5 g. (76%); m.p. 91–92° which checked

the value given by Tschacher (3) who made the compound by the above method but gave no description of the procedure. This compound has recently been prepared by Ungnade and Crandall (7) from the same reactants but using aluminum chloride as the condensing agent; they reported m.p. 91.5–93°.

p-Nitrotriphenylmethane. A sample of this compound was prepared by the same procedure as described for the *meta*-isomer. A 75% yield of white crystals melting at 90–91° was obtained. Lit. value, 90° [Baeyer and Lohr (5)]; 90–91° [Ungnade and Crandall (7)]. The latter authors mention that purification by chromatographic adsorption raised the m.p. to 93–94°.

o-Nitrotriphenylmethane. The above sulfuric acid condensation gave only a 10% yield of the *ortho* compound; m.p. 90–91°. Lit. values 88–89° [Ungnade and Crandall (7)]; 93–94° [Kliegl (6)].

SUMMARY

The nitration of triphenylcarbonium sulfate produced a mixture of nitration products which yielded a mixture of nitrated triphenylcarbinols. By reduction to the nitrotriphenylmethanes, there was isolated a 15.4% yield of *m*-nitrotriphenylmethane. This compound was identical with that obtained by the condensation of *m*-nitrobenzaldehyde with benzene, thus establishing the *meta* orientation of the nitro group.

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ACETYLATION OF 1,2-DIETHYLNAPHTHALENE. I.[1]

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The reaction of 1,2-diethylnaphthalene with acetyl chloride and aluminum chloride in nitrobenzene has been reported to yield a solid acetyl derivative, m.p. 61.5–62.5° (1). This ketone has now been identified as 1-aceto-3,4-diethylnaphthalene. A small quantity (3% yield) of an isomeric ketone, possibly 2-aceto-5,6-diethylnaphthalene,[2] has also been isolated from the acetylation reaction.

1-Aceto-3,4-diethylnaphthalene was reduced, by the Clemmensen method, to 1,2,4-triethylnaphthalene, which was shown to be identical with a sample of the hydrocarbon prepared in an unequivocal manner (formulas I–VII) similar to that previously employed for the synthesis of 1,2,4-trimethylnaphthalene (3).

Methyl β-benzoylpropionate reacted with ethylmagnesium bromide to yield 4-phenyl-3-hexenoic acid (I), which was quantitatively reduced over Adams' catalyst. The resulting 4-phenylhexanoic acid was converted to 4-ethyl-1-tetralone (II) in 70–80% yield through a Friedel-Crafts intramolecular condensation of the acid chloride. This method was found to be superior to ring closure of 4-phenylhexanoic acid with 80% sulfuric acid (4), which afforded only 50–55% yields of II. Condensation of the cyclic ketone (II) with dimethyl oxalate yielded a glyoxalate, from which carbon monoxide was eliminated by heating with powdered soft glass (5). When the sodio derivative of the resulting methyl 4-ethyl-1-tetralone-2-carboxylate (III) reacted with ethyl iodide, methyl 2,4-diethyl-1-tetralone-2-carboxylate (IV) was obtained. Hydrolysis and subsequent decarboxylation of this ester yielded 2,4-diethyl-1-tetralone (V). Treatment of this cyclic ketone with ethylmagnesium bromide in the usual manner yielded 1,2,4-triethyl-1-tetralol (VI), which was dehydrated with anhydrous formic acid and dehydrogenated at 290° over a palladium on charcoal catalyst to give the desired 1,2,4-triethylnaphthalene (VII).

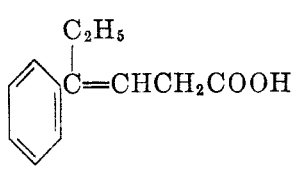
The liquid hydrocarbon, 1,2,4-triethylnaphthalene, formed a solid derivative, m.p. 95–96°, with 1,3,5-trinitrobenzene, but failed to form a satisfactory picrate.

Recently it was shown (6) that certain alkylnaphthalenes can be made to undergo a Diels-Alder type reaction with maleic anhydride, similar to that which has been demonstrated for anthracene derivatives (7, 8). When 1,2,4-triethylnaphthalene was heated to 100° with excess maleic anhydride, it likewise yielded an adduct. This substance, 1,2,4-triethyl-1,4-dihydronaphthalene-1,4-*endo*-α-β-

[1] Abstracted from the thesis submitted by Hershel L. Herzog to the Graduate School of the University of Southern California in partial fulfillment of the requirements for the degree of Master of Science.

[2] Bachmann and Cronyn (2) have shown that acetylation of 1,2,3,4-tetrahydrophenanthrene results in the formation of 9- and 7-aceto-1,2,3,4-tetrahydrophenanthrene, in the ratio of 2:1.

succinic anhydride (VIII), proved to be useful as an additional solid derivative suitable for characterization of the liquid hydrocarbon.



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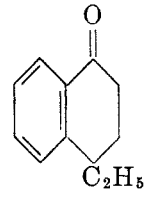

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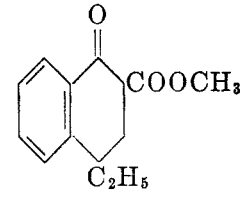

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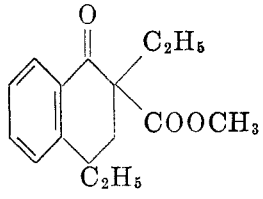

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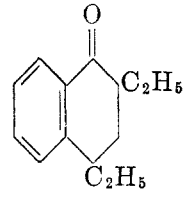

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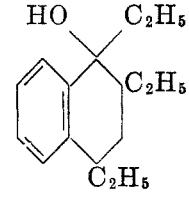
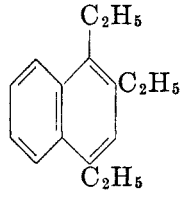
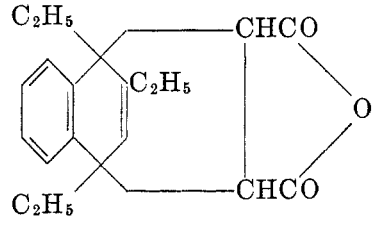


VI



VII



VIII

EXPERIMENTAL[3]

4-Ethyl-1-tetralone (II). Methyl β-benzolypropionate was allowed to react with ethylmagnesium bromide as described for the analogous reaction with methylmagnesium iodide (3). When the Grignard reaction mixture had warmed up to 25°, 150 c.c. of dry toluene was added and ether was removed as completely as possible by distillation on a steam-bath. After being heated on the steam-bath for five hours, the mixture was hydrolyzed with 3 *N* hydrochloric acid and worked up in the customary manner; yield, 60–70% of *4-phenyl-3-hexenoic acid* (I), b.p. 163–167° at 5 mm.

Hydrogenation of 96.5 g. of 4-phenyl-3-hexenoic acid in 250 c.c. of glacial acetic acid over 500 mg. of Adams' catalyst, at 10–40 lbs. pressure, was complete within two hours, and yielded 89.5 g. (92%) of *4-phenylhexanoic acid*, b.p. 160–163° at 5 mm. Levy (9), who prepared this acid in a different manner, reported a b.p. of 185° at 22 mm.

The *acid chloride* prepared by warming a mixture of 31.5 g. of 4-phenylhexanoic acid and 16.5 g. of thionyl chloride on a steam-bath for fifteen minutes, and removing excess thionyl chloride by distillation under reduced pressure, was dissolved in 175 c.c. of carbon disulfide. To the solution, at 0°, was added 25 g. of anhydrous aluminum chloride and the mixture was then refluxed for ten minutes. After hydrolysis in the customary manner, 4-

[3] Melting points are uncorrected. Analyses are by Dr. G. Oppenheimer, California Institute of Technology.

ethyl-1-tetralone (II), b.p. 131–135° at 4 mm., was obtained in 70–80% yield, and formed a *semicarbazone*, m.p. 182–183°. Levy (9) reported the cyclization of 4-phenylhexanoyl chloride to yield 60% of 4-ethyl-1-tetralone; semicarbazone, m.p. 183°

Methyl 2,4-diethyl-1-tetralone-2-carboxylate (IV). 4-Ethyl-1-tetralone was condensed with dimethyl oxalate, following the procedure described for 1-tetralone by Bachmann and Thomas (5), to yield 92% of liquid *methyl 4-ethyl-1-tetralone-2-glyoxalate*. Carbon monoxide was evolved when 30.5 g. of the glyoxalate was heated to 150° with 15 g. of powdered soft glass. The temperature was finally raised to 180° until gas evolution ceased (total period of heating, 25 minutes) and the resulting *methyl 4-ethyl-1-tetralone-2-carboxylate* (III) was purified by distillation in a vacuum; yield, 18 g. (66%), b.p. 164–170° at 4 mm.

The sodio derivative was prepared from 40 g. of the aforementioned β-keto ester, and was treated with ethyl iodide as described for methyl 1-tetralone-2-carboxylate (1). There was isolated 13.5 g. of unreacted keto ester and 20.5 g. of *methyl 2,4-diethyl-1-tetralone-2-carboxylate* (IV), b.p. 152–155° at 1 mm.

Anal. Calc'd for $C_{16}H_{20}O_3$: C, 73.82; H, 7.74.
Found: C, 73.92; H, 7.93.

2,4-Diethyl-1-tetralone (V). Hydrolysis of ester IV (20.5 g.) was accomplished by refluxing for three hours with ethanol (36 c.c.) and 20% sodium hydroxide solution (140 c.c.). Acidification of the resulting solution with sulfuric acid caused a vigorous evolution of carbon dioxide. Complete decarboxylation was effected by warming the mixture on a steam-bath and the *2,4-diethyl-1-tetralone* was extracted with benzene; yield, 11 g. (69%), b.p. 118–121° at 1 mm.

The *semicarbazone* of *2,4-diethyl-1-tetralone*, prepared in ethanolic pyridine solution as previously described for 2,4-dimethyl-1-tetralone (3), melted at 181–183°.

Anal. Calc'd for $C_{15}H_{21}N_3O$: N, 16.20.
Found: N, 15.94.

1,2,4-Triethyl-3,4-dihydronaphthalene. To the ice-cold Grignard reagent prepared from 10.9 g. of ethyl bromide, 2.43 g. of magnesium, and 80 c.c. of ether was added dropwise, with swirling, 10 g. of 2,4-diethyl-1-tetralone dissolved in 40 c.c. of ether. The reaction mixture was allowed to warm up to room temperature and was then refluxed for 2½ hours. Hydrolysis with ice and ammonium chloride, followed by extraction of the reaction mixture with ether, yielded 10 g. of liquid *1,2,4-triethyl-1-tetralol* (VI).

The crude carbinol was added to 40 c.c. of anhydrous formic acid and, after standing for two hours at room temperature, the mixture was diluted with 200 c.c. of water and extracted with several portions of ether. Evaporation of the washed extracts left an oil which was distilled from metallic sodium; yield, 6 g. (57%) of colorless *1,2,4-triethyl-3,4-dihydronaphthalene*, b.p. 106–109° at 1 mm.

Anal. Calc'd for $C_{16}H_{22}$: C, 89.65; H, 10.34.
Found: C, 89.46; H, 10.52.

1,2,4-Triethylnaphthalene (VII) was obtained in 86% yield by heating the aforementioned dihydronaphthalene with one-tenth of its weight of palladium on charcoal catalyst (10) to 290° until evolution of hydrogen ceased. The hydrocarbon distilled as a colorless oil, b.p. 125–127° at 1 mm.

Anal. Calc'd for $C_{16}H_{20}$: C, 90.50; H, 9.49.
Found: C, 90.49; H, 9.57.

The *1,3,5-irinitrobenzene derivative* of *1,2,4-triethylnaphthalene* separated from methanol in flat yellow needles, m.p. 95–96°.

Anal. Calc'd for $C_{22}H_{23}N_3O_6$: N, 9.88.
Found: N, 9.93.

1,2,4-Triethyl-1,4-dihydronaphthalene-1,4-endo-α,β-succinic anhydride (VIII). One gram of 1,2,4-triethylnaphthalene was heated in a sealed tube for 24 hours at 100° with 13.9 g. of maleic anhydride. The resulting solution was poured into 100 c.c. of water and the mixture was stirred until all excess maleic anhydride had dissolved. Separation of the oily residue was accomplished with the aid of ether and, after evaporation of the ether, the mix-

ture of adduct and unreacted hydrocarbon was allowed to stand at room temperature for 24 hours with 20 c.c. of 5% aqueous potassium hydroxide. Unreacted hydrocarbon was extracted with ether and the alkaline solution was acidified with 10% hydrochloric acid. There was precipitated 0.25 g. of 1,2,4-triethyl-1,4-dihydronaphthalene-1,4-*endo*-α,β-succinic acid, which was converted to the corresponding anhydride (VIII) by dissolving in several c.c. of warm acetyl chloride and finally evaporating the excess acetyl chloride. The anhydride (VIII) separated from ether-hexane in colorless massive prisms, m.p. 136–137°.

Anal. Calc'd for $C_{20}H_{22}O_3$: C, 77.39; H, 7.14.
Found: C, 77.00; H, 7.15.

Acetylation of 1,2-diethylnaphthalene (10 g.) was effected in nitrobenzene as previously described (1). When the mother liquor from crystallization of *1-aceto-3,4-diethylnaphthalene* was evaporated, there remained an oily residue (1.9 g.) which could not be induced to crystallize. This material yielded 0.8 g. of the picrate of an isomeric *acetodiethylnaphthalene* upon treatment with a saturated ethanolic solution of picric acid; yellow needles, m.p. 118–118.5°.

Anal. Calc'd for $C_{22}H_{21}N_3O_8$: N, 9.22.
Found: N, 9.26

The isomeric acetodiethylnaphthalene, liberated by shaking a benzene solution (20 c.c.) of the aforedescribed picrate (0.8 g.) with 10% aqueous lithium hydroxide until all color had been extracted from the benzene solution, was refluxed for two hours with a solution of semicarbazide hydrochloride (0.4 g.) and pyridine (1 c.c.) in ethanol (20 c.c.). The *semicarbazone*, which precipitated when the reaction mixture was poured into water, separated from dioxane-ethanol in colorless leaflets, m.p. 234–235°.

Anal. Calc'd for $C_{17}H_{21}N_3O$: N, 14.83.
Found: N, 14.68.

Reduction of 1-aceto-3,4-diethylnaphthalene was accomplished by refluxing for 24 hours a mixture of 11.9 g. of the ketone, 35 c.c. of benzene, 68 c.c. of methanol, 45 c.c. of concentrated hydrochloric acid, and 29 g. of amalgamated mossy zinc. The organic layer yielded 8 g. (72%) of colorless *1,2,4-triethylnaphthalene*, b.p. 125–127° at 1 mm., whose solid 1,3,5-trinitrobenzene derivative and maleic anhydride adduct caused no depression of m.p. when mixed with samples of these respective derivatives prepared as described from authentic 1,2,4-triethylnaphthalene.

SUMMARY

Acetylation of 1,2-diethylnaphthalene has been shown to yield 1-aceto-3,4-diethylnaphthalene and a small amount of an isomeric ketone. Clemmensen reduction of the 1-aceto-3,4-diethylnaphthalene yielded 1,2,4-triethylnaphthalene, which was shown to be identical with the hydrocarbon synthesized in an unequivocal manner.

LOS ANGELES, CALIF.

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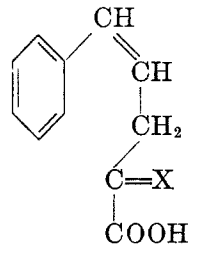
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

AROMATIC CYCLODEHYDRATION. XXIV. CYCLIZATION OF DERIVATIVES OF (2-BIPHENYLYL)PYRUVIC ACID[1]

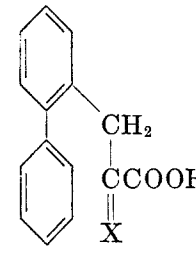
CHARLES K. BRADSHER AND RICHARD S. KITTILA[2]

Received October 10, 1949

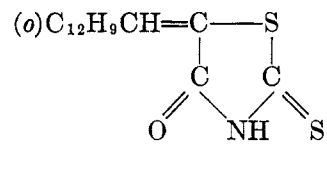
It is reported (1, 2) that α-benzimino-β-(β-styryl)propionic acid (I), in the presence of hydrochloric acid, undergoes cyclization to yield α-naphthoic acid, presumably (2) through (β-styryl)pyruvic acid as an intermediate. This suggests that (2-biphenylyl)pyruvic acid (III), or substances yielding this keto acid in strongly acid solutious, might be expected to yield 9-phenanthroic acid. It has been postulated (3) that the cyclization of ethyl α-keto-β-(2-biphenylyl)succinate (4) to yield 9-phenanthroic acid is an example of such a cyclization. The present communication records the results of some preliminary experiments directed toward the synthesis and cyclization of some derivatives of (2-biphenylyl)pyruvic acid.



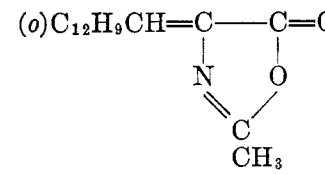
I, X = $NCOC_6H_5$
II, X = O



III, X = O
IV, X = S
V, X = NOH



VI



VII

The first derivative selected was α-oximino-β-(2-biphenylyl)propionic acid (V). The required *o*-phenylbenzaldehyde, conveniently prepared (68% yield) by the method of Zaheer and Fahsee (5), was condensed with rhodanine, essentially as described by Julian and Sturges (6). The resulting product (VI) underwent cleavage in alkali slowly, but on acidification, α-thioketo-β-(2-biphenylyl)-propionic acid (IV) was obtained in excellent yield. Conversion to the oximino acid (V) was effected by the action of hydroxylamine.

[1] For the preceding communication of this series see Bradsher and Kittila, *J. Am. Chem. Soc.*, **72**, 277 (1950).

[2] Public Health Service Fellow, 1948–1949.

Cyclization of the oximino acid (V) in a hydrobromic-acetic acid mixture, gave a small quantity of 9-phenanthroic acid. More remarkable was the behavior of the thioketo acid (IV), which, under the same conditions, cyclized with the evolution of hydrogen sulfide to produce 9-phenanthroic acid in 23–25% yield. Since the yields were excellent for both steps in the preparation of the thioketo acid (IV) from the *o*-phenylbenzaldehyde, the over-all yield (22% in one instance) is large enough to give the method some preparative significance.

Another compound of the type expected to yield biphenylylpyruvic acid (III) on hydrolysis is the azlactone of α-acetamino-*o*-phenylcinnamic acid (VII). It was found that when this product was added to hydrobromic-acetic acid, no isolable amount of phenanthroic acid was produced.

EXPERIMENTAL

5-(o-Phenylbenzylidene)rhodanine (VI). To a hot solution containing 5.5 g. of *o*-phenyl benzaldehyde (5) and 4 g. of rhodanine in 20 ml. of glacial acetic acid, 7.5 g. of fused sodium acetate was added. The mixture was refluxed for thirty minutes, cooled, and poured into water. The solid was collected and washed with water and ethanol. The yield of yellow needles was 7.8 g. (87%), m.p. 243–244°. An analytical sample prepared by recrystallization from benzene melted at 245–246°.

Anal. Calc'd for $C_{16}H_{11}NOS_2$: C, 64.62; H, 3.73.
Found: C, 64.95; H, 3.77.

α-Thioketo-β-(2-biphenylyl)propionic acid (IV). The crude rhodanine derivative above (VI, 3.5 g.) was suspended in 15 ml. of 15% sodium hydroxide solution and heated in a water-bath until a clear solution had been formed and had again become cloudy (one hour). The solution was cooled in an ice-salt bath and 15 ml. of cold 10% hydrochloric acid was added with stirring. The amorphous material which precipitated, slowly solidified on stirring. It was collected, washed, and dried in a desiccator. The yellow crystals, m.p. 154–167°, weighed 3 g. (100%) and were pure enough for further reactions. An analytical sample was obtained as orange needles from chloroform, m.p. 172.5–173°.

Anal. Calc'd for $C_{15}H_{12}O_2S$: S, 12.51.
Found: S, 12.54.

α-Oximino-β-(2-biphenylyl)propionic acid (V). Sodium (0.56 g.) was dissolved in 16 ml. of ethanol and to this was added a warm solution of 1.7 g. of hydroxylamine hydrochloride in 2 ml. of water. The filtered solution was poured on 2 g. of crude thioketo acid (IV, m.p. 150–160°). The resulting solution was heated for twenty minutes on a steam-bath, hydrogen sulfide being evolved. The solvent was removed under reduced pressure. The residue was dissolved in 10% sodium hydroxide solution, filtered, cooled in an ice-salt bath, and acidified with 10% hydrochloric acid. The amorphous product which crystallized on standing, was dried over potassium hydroxide in a vacuum desiccator, yielding 1.7 g. of coarse white crystals suitable for the cyclization reaction.

An analytical sample was obtained by twice repeating the reprecipitating process; a white powder, m.p. 143.5–144°. A sodium fusion test showed sulfur to be absent.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.57; H, 5.13.
Found: C, 70.20; H, 5.24.

The azlactone of α-acetamino-o-phenylcinnamic acid (VII). A mixture of 9.1 g. of *o*-phenylbenzaldehyde, 8.2 g. of acetylglycine, 2.9 g. of sodium acetate and 12.8 g. of acetic anhydride was warmed on the steam-bath until solution was almost complete and then refluxed for one and one-half hours (7). The mixture was extracted with benzene and the solution washed, dried, and concentrated. Yellow crystals, 4.2 g. (32%), were deposited, m.p. 234–236°. An analytical sample was prepared by repeated recrystallization from methyl ethyl ketone as orange crystals, m.p. 241–242° (with decomposition).

Anal. Calc'd for $C_{17}H_{13}NO_2$: N, 5.32. Found: N, 5.54.

CYCLIZATION EXPERIMENTS

With α-oximino-β-(2-biphenylyl)propionic acid (V). Two grams of the crude acid was dissolved in 50 ml. of acetic acid and added slowly to refluxing 48% hydrobromic acid (30 ml.) over a period of 45 minutes. After refluxing for a total of three hours, the mixture was cooled, diluted with water, and the solid collected. The product, purified by vacuum sublimation and by crystallization from ethanol, melted at 254–255°. This material did not depress the melting point of an authentic sample of 9-phenanthroic acid, (m.p. 253.5–254.5°) obtained by hydrolysis of 9-phenanthronitrile.

With α-thioketo-β-(2-biphenylyl)propionic acid (IV). One gram of the crude thioketo acid was dissolved in 25 ml. of acetic acid and added dropwise to 15 ml. of boiling 48% hydrobromic acid. The mixture was refluxed for two hours during which hydrogen sulfide was evolved. The mixture was cooled and the product collected and washed with 50% acetic acid. The white needles (0.5 g.) melted at 238–250°. This material was completely soluble in alkali, and, on reprecipitation, showed no improvement in melting point. Recrystallization from ethanol yielded 0.2 g. (23%) of phenanthroic acid, m.p. 254–255°. Essentially the same results were obtained in larger scale reactions, 9 g. of crude thioketo acid yielding 2 g. of phenanthroic acid, m.p. 254–255°.

In another experiment, phenanthroic acid was obtained in 23% yield when (*o*-phenylbenzylidene)rhodanine (2 g.) was heated in 75 ml. of 15% sodium hydroxide for 1½ hours and the alkaline solution run directly into a refluxing mixture of hydrobromic and acetic acids.

With the azlactone of α-acetamino-o-phenylcinnamic acid (VII). The azlactone was suspended in acetic acid and added to hydrobromic acid and the mixture refluxed for seventeen hours. On dilution of the mixture and recrystallization of the resulting product, an unidentified red solid was obtained, m.p. 258–263°. This was not studied further.

SUMMARY

It has been shown that α-oximino- and α-thioketo-β-phenylpropionic acids are cyclized to 9-phenanthroic acid by the action of boiling hydrobromic and acetic acids.

DURHAM, N. C.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF ANTIOCH COLLEGE AND THE UNIVERSITY OF ARIZONA]

CYCLIZATION OF 2-AMINOPYRIDINE DERIVATIVES. II. THE REACTION OF SUBSTITUTED 2-AMINOPYRIDINES WITH ETHYL MALONATE[1]

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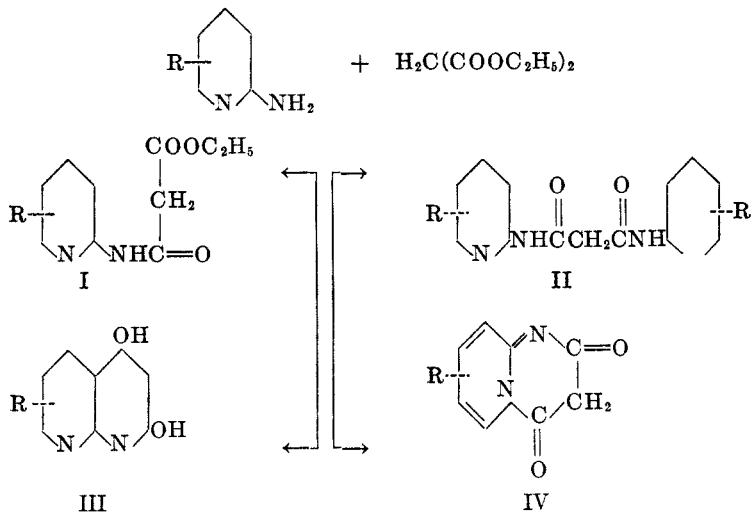
The reaction of ethyl malonate with 2-aminopyridines might proceed to give several non-cyclic or cyclic products as indicated below. Chichibabin (1) investigated the reaction of 2-aminopyridine with ethyl malonate, heating the mixture



under vacuum to 300° or higher. The only product isolated was 2H-pyrido-[1,2-a]pyrimidine-2,4-(3H)dione (IV, R = H) obtained in nearly quantitative yield. More recently the reaction of ethyl malonate with 5-chloro-, 5-bromo-, 5-nitro-, and 3,5-dichloro-2-aminopyridine was investigated by Kucherova, *et al.* (2). They reported that the monohaloaminopyridines gave only non-cyclic products, both Type I and Type II being obtained, and that the nitro- and dichloro-aminopyridine failed to react with the ester.

We were led to investigate this reaction in a search for a means of synthesis of certain 1,8-naphthyridine derivatives (Type III) and herein report the results of the reaction of a number of 2-aminopyridines with ethyl malonate. Both non-cyclic and cyclic products were obtained, the former appearing as by-products of the cyclizations. No attempt was made to prepare the non-cyclic products in

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high yield and the actual yields varied widely from one cyclization to another. Both Type III and Type IV cyclic products were obtained, although a given 2-aminopyridine led to either one or the other exclusively. The structures of these

TABLE I

NON-CYCLIC PRODUCTS

R	TYPE I			TYPE II		
	M.P., °C.	Analyses[a], N		M.P., °C.	Analyses[a], N	
		Calc'd	Found		Calc'd	Found
H	[b]			235 dec.	21.85	21.41
4-CH_3	[b]			167–168	19.73	19.78
5-CH_3	69–70	12.60	12.83	200 dec.	19.73	19.97
6-CH_3	72–73	12.60	12.85	145–146	19.73	19.76
5-I	[b]			230 dec.	11.07	10.88
6-NH_2	[c]			[c]		
6-NHAc	[c]			145–146	22.70	22.54
6-OC_2H_5	[b]			[b]		

[a] Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill. [b] No exhaustive attempt made to isolate. [c] Not found on exhaustive attempt to isolate.

TABLE II

CYCLIC PRODUCTS

R	TYPE	M.P., °C.	CYCLIZATION METHOD	YIELD, %	ANALYSES[a], N	
					Calc'd	Found
4-CH_3	IV	270 dec.	A	73	15.90	15.73
			B	50		
5-CH_3	IV	300 dec.[b]	A	78	15.90	15.86
6-CH_3	III	300 dec.[b]	B	5	15.90	15.74
			A	0		
			C	trace		
5-Cl	IV	310 dec.[b]	C	91	14.30	13.98
			A	trace		
			B	0		
5-Br	IV	310 dec.[b]	C	82	11.60	11.77
5-I	[c]					
6-NH_2	III	325 dec.[b]	B	100	23.70	24.01
6-NHAc	III	325 dec.[b]	B	85	19.15	18.98
6-OC_2H_5	III	325 dec.[b]	B	92	13.59	13.48

[a] Microanalyses by Clark Microanalytical Laboratory, Urbana, Ill. [b] Decomposed slowly without melting when held at this temperature. [c] Starting materials decomposed in each method of cyclization.

products were established by the easy hydrolysis of Type IV and the stability to hydrolysis of Type III. Cyclizations were carried out in the absence of solvent (Method A), using diphenyl ether as a solvent (Method B), and employing a new sublimation-cyclization technique (Method C). Method C gave, on a semi-

micro scale, high yields of cyclic products with the haloaminopyridines (R=5-chloro or 5-bromo), contrary to Kucherova's report that these could not be cyclized. The results of these reactions are reported in Tables I and II.

As in the previously reported cyclization of ethyl 2-pyridylaminomethylenemalonates (3) the normal mode of ring closure involved the ring nitrogen of the imino form of the aminopyridine leading to the formation of a 2H-pyrido[1,2-a]-pyrimidine-2,4(3H)-dione (IV). Only when a strongly activating group was present in the 6-position of the pyridine ring did cyclization involve the 3-carbon atom to yield a 2,4-dihydroxy-1,8-naphthyridine (III). However, one significant difference appears between the results of the reaction with ethyl malonate herein reported and the earlier reported reaction of the methylenemalonate derivatives. In the latter reaction a good yield of a 1,8-naphthryidine was obtained when R = 6-methyl; in the reaction herein reported the yield of naphthyridine in this case was very low although no other cyclic product was obtained. We believe that this substantiates to some degree the earlier hypothesis (3), that for 1,8-naphthyridine formation by cyclization of a 2-aminopyridine derivative both activation of the 3-position and steric hindrance of the ring nitrogen by a 6-substituent are required. In the case of R = 6-methyl it seems probable that sufficient activation for the reaction with ethyl malonate is not supplied, although the activation is sufficient for the reaction with ethyl ethoxymethylenemalonate. In both cases the normal mode of cyclization at the ring nitrogen is completely prevented by steric hindrance.

EXPERIMENTAL

CYCLIZATION METHODS

Method A. Absence of a solvent. This procedure is a modification of the one used by Chichibabin (1). Equimolar quantities of the 2-aminopyridine and ethyl malonate were placed in a distilling flask connected to a water aspirator. The flask was heated in an oil-bath until the interior temperature reached 150° and was then evacuated to about 20 mm. pressure. Heating was continued until the interior temperature reached 210–220°. The solid reaction product was worked up as described below.

Method B. Use of a high-boiling solvent.[5] Equimolar quantities of the 2-aminopyridine and ethyl malonate were dissolved in about three times their weight of diphenyl ether. The solution was warmed slowly until the vigorous initial evolution of ethanol had ceased and was then heated under reflux at the boiling point for thirty minutes. After cooling the cyclic product was precipitated by the addition of three volumes of a crude heptane fraction at 15–20°. The product was purified by recrystallization from pyridine or a pyridine-ethanol mixture.

Method C. Sublimation of a non-cyclic product. The starting material, either of Type I or II, was placed on a microscope cover glass heated on the Fisher-Jones melting-point block. Over this was placed a beaker of ice-water with the bottom no more than 0.5 mm. from the surface of the cover glass. The block was held at 250–260° until all of the material had sublimed, usually several hours being required. The product was purified by resublimation. Because only about 0.1 g. could be handled this way an attempt was made to use a semi-micro sublimation apparatus (4) which allowed samples of 1.0 g. However, the yield was ex-

[5] A preliminary investigation of this method was made by Peter Dresel in connection with a Senior Research Project, Antioch College, 1947.

tremely low, about as much being obtained from 1.0 g. by this method as from 0.1 g. by the first method. This procedure worked well only if R = 5-chloro or 5-bromo although a trace of cyclic product was obtained when R = 6-methyl. With the other non-cyclic amides no sublimate was obtained and only tar resulted.

Separation of cyclic and non-cyclic products. If Method A was used for the cyclization the non-cyclic products could be extracted from the solid reaction product with boiling ether in which the cyclic products were insoluble. The mixture of I and II thus obtained could be separated by fractional crystallization from an ether-heptane solvent pair, II being considerably less soluble than I.

If Method B was used the filtrate from the separation of the cyclic products was diluted with an additional ten volumes of heptane and kept at 10° for several days. The mixture of I and II which crystallized was separated as above.

Structure proof of cyclic products. Approximately 0.5 g. of the cyclic product was dissolved in 5 ml. of 6 *N* hydrochloric acid. The solution was refluxed for fifteen hours, cooled, and neutralized with ice-cold 12 *N* aqueous sodium hydroxide solution. If the cyclic product was Type III it precipitated unchanged at this point and could be recovered quantitatively. If no precipitate was formed the solution was saturated with potassium carbonate and extracted with ether. Evaporation of the ether gave a 50–70% yield of the original 2-aminopyridine derivative from which the Type IV product was made. This was identified by mixture melting point with an authentic sample of the starting material.

SUMMARY

The reaction of several substituted 2-aminopyridines with ethyl malonate has been reported. It has been shown that two cyclic products may be obtained from this reaction, 1,8-naphthyridine derivatives being obtained as well as the previously reported pyridopyrimidine derivatives. The type of product obtained from a given 2-aminopyridine depends only on the substituents present in the pyridine ring.

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THE SYNTHESIS OF α,α-DISUBSTITUTED SUCCINIC ACIDS FROM ETHYL ALKYLIDENECYANOACETATES

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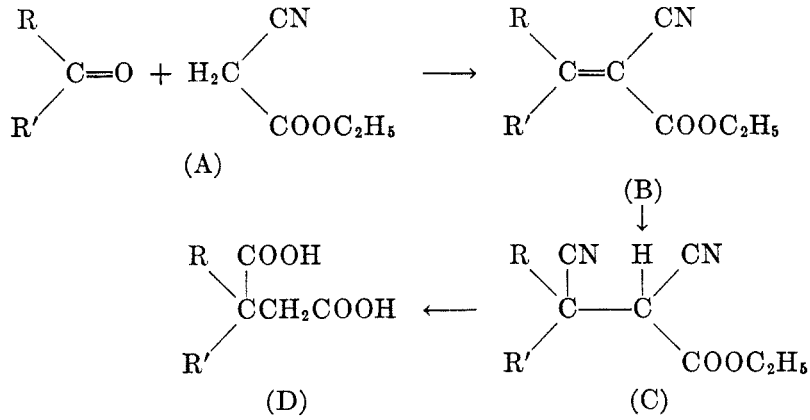
A number of investigators have prepared α-substituted succinic acids by the addition of hydrogen cyanide to alkylidenecyanoacetates (or alkylidenemalonates) followed by hydrolysis of the resulting nitrile. In the early work very few examples of α,α-disubstituted succinic acids appear, largely because the alkylidene compounds derived from ketones were difficultly accessible. The more recent studies of Cope and his associates (1, 2) have extended the number of alkylidenecyanoacetates that may be prepared from ketones by the Knoevenagel reaction.

The present paper reports further improvements in the application of the Knoevenagel reaction to ketones with ethyl cyanoacetate and describes the conversion of a variety of the alkylidene compounds (B) to α,α-disubstituted succinic acids (D).



The condensation of cyanoacetic acid and its esters with simple ketones has been reported by a number of the earlier investigators. In general, the usual conditions of the Knoevenagel reaction, employing basic catalysts such as piperidine, diethylamine or other amines, were effective. Cope (1) found more recently that with simple ketones better yields could be obtained using catalysts such as acetamide or the acetate salts of amines such as piperidine, diethylamine or ammonia. The maximum yield was obtained when the reaction was carried out in the presence of acetic acid and an inert, water-insoluble solvent that aided in the removal of water by distillation. In a later paper, Cope and associates (2) describe the condensation of cyanoacetic ester with a variety of ketones including aliphatic, alicyclic or mixed aromatic-aliphatic types. Furthermore, they were able to obtain reaction with benzophenone, the first example of the condensation

of an aromatic ketone with a cyanoacetate. Heretofore, the Knoevenagel reaction with diaryl ketones had been unsuccessful, in fact, it was said to be impossible according to the proposed mechanism (3).

When we attempted to prepare ethyl alkylidenecyanoacetates from higher molecular weight dialkyl and aryl alkyl ketones or diaryl ketones by the available methods, poor yields were encountered in many cases. Particular difficulty was met in the case of substituted diaryl ketones. Using benzophenone as a prototype, a study was made of the effect of catalyst, solvent, time, and temperature on the yield obtained in the Knoevenagel reaction. Ethyl cyanoacetate, benzophenone, acetic acid, and toluene were refluxed in the presence of various catalysts, with the continuous removal of water under the conditions described by Cope (2).

TABLE I

EFFECT OF CATALYST

$(C_6H_5)_2CO + H_2C(CN)COOC_2H_5 \rightarrow (C_6H_5)_2C{=}C(CN)COOC_2H_5$

CATALYST	REACTION TIME, HOURS	YIELD, %
None	8	0
Sodium acetate	2	0
Ammonium sulfate	2	0
Piperidine	4	0
Triethylamine	3	0
Acetamide	2	0
Heptamide	2	0
Ethylenediamine	15	18
Ammonium acetate	8	42

Ethyl cyanoacetate (0.6 mole), benzophenone (0.5 mole), acetic acid (0.5 mole), toluene (100 ml.), and catalyst (0.1 mole) were refluxed under the conditions of Cope's (2) method B. Where no product was obtained, no water separated.

From Table I it appears that of the previously recommended catalysts, only ethylenediamine and ammonium acetate gave any product and only the latter gave a good yield. In contrast to Cope's (1) observation in the case of simple aliphatic ketones, acetamide was not a catalyst for benzophenone.

Several different solvents have been reported useful in aiding the removal of water by distillation from the reaction mixture; among these are toluene (4), benzene (1, 2), and chloroform (5). In the present study, using benzophenone as the ketone and ammonium acetate as the catalyst, the solvent was varied. Benzene, cyclohexane, toluene, and xylene were investigated. In general, the reaction rate, as indicated by the formation of water, increased and the yield of alkylidene ester decreased with an increase in the boiling point of the solvent. However, it is difficult to compare the results, because at higher temperatures ammonium acetate dehydrates more rapidly to acetamide, which is not a catalyst for the reaction. In reactions where the condensation is very slow, it is obvious

that the catalyst will have completely decomposed long before the reaction is complete. In order to get a better comparison of the solvents it was necessary to add the ammonium acetate catalyst in small portions at frequent intervals until further addition gave no more reaction. The effect of the portionwise addition of catalyst when benzene was used as a solvent is illustrated in Table II. With a single addition only 66% yield was obtained while multiple addition gave yields as high as 84%. Using the multiple addition technique the effect of solvent was determined as recorded in Table II.

These data obtained with benzophenone, and those obtained with other ketones using benzene and toluene (*cf.* Table III), indicate that benzene is the best solvent. When the ammonium acetate catalyst was added portionwise at short intervals, with benzene as a solvent, the optimum yields were obtained. Under these conditions, ketones such as benzophenone, that previously gave

TABLE II

EFFECT OF SOLVENT

SOLVENT	AMMONIUM ACETATE		TOTAL TIME, HOURS	YIELD, %
	Total, G.	Number of Additions		
Cyclohexane	19	11	50	30
Benzene	7.7	1	18	66
Benzene	10	4	42.5	84
Benzene	20	14	32	80
Toluene	16	8	13.5	42
Xylene	20	10	8.5	35

Ethyl cyanoacetate (0.6 mole), benzophenone (0.5 mole), acetic acid (0.4 mole), and the solvent (100 ml.) were refluxed and the ammonium acetate catalyst added either all at once or in divided, equal portions at regular intervals until no more reaction occurred.

moderate yields, gave excellent yields (increased from 66% to 84%). Ketones that gave poor yields, such as 2,4′-dichlorobenzophenone or phenyl 2-thienyl ketone, now gave moderate yields. Furthermore, ketones said to be completely unreactive (2) such as camphor and pinacolone have yielded reasonable quantities of the ethyl alkylidenecyanoacetate derivative, 37% and 13% respectively. Recently, Cope and Field (7) have successfully used our method in condensing 2-allyl-1-indanone with ethyl cyanoacetate.

In general, the reactions proceeded without the formation of significant quantities of by-products. In a few cases of relatively inert ketones, *i.e.* those requiring a long reaction time and large quantities of catalyst, considerable amounts of high-boiling, polymeric materials were formed. In the case of 4,4′-dichlorobenzophenone, a 13% yield of the amide, $(p\text{-Cl—}C_6H_4)_2C{=}C(CN)CONH_2$, was isolated in addition to 43.5% of the expected ethyl di-(*p*-chlorophenyl)methylenecyanoacetate. With *o*-hydroxyhexanophenone, the product isolated was not ethyl 1-(*o*-hydroxyphenyl)hexylidenecyanoacetate but a cyclized product, 3-cy-

TABLE III

Ethyl Alkylidenecyanoacetates

$$RR'CO\ (A) + H_2C(CN)COOC_2H_5 \rightarrow RR'C{=}C(CN)COOC_2H_5\ (B)$$

NUMBER	KETONE (A)	METHOD	REACTION TIME, HRS.	YIELD, %	B.P., °C.	MM.	ETHYL ALKYLIDENECYANOACETATE (B)				
							M.P., °C. (uncor.)	n_D^{25}	FORMULA	N	
										Calc'd	Found
I	Diamyl	B1	11	70[a]	136–138	1	—	—	—	—	—
II	Dinonyl	B2	3.5	47	184–185	2	—	1.4673	$C_{24}H_{43}NO_2$	3.71	3.69
		A2	32.5	79							
III	Phenyl methyl	A2	46	71[b]	134–135	2	—	1.5468	—	—	—
IV	Phenyl ethyl	B1	3	41	138–140	2	—	1.5353	—	—	—
		A1	32	78[c]							
V	Phenyl amyl	B3	3	39	161–163	2	—	1.5239	—	—	—
		A1	32	87[d]							
VI	Phenyl heptyl	B2	4.5	52	170–177	0.08	—	1.5173	$C_{19}H_{25}NO_2$	4.68	4.78
		A1	42	86							
VII	Phenyl hendecyl	B2	6	22	182–185	2	—	1.5073	$C_{23}H_{33}NO_2$	3.94	4.02
		A1	24	68							
VIII	Phenyl 2-cyclohexylethyl	B2	4	52	174–177	1	—	1.5371	$C_{21}H_{25}NO_2$	4.50	4.51
		A1	32.5	75							
IX	Phenyl 5-cyclohexylpentyl	B2	6.5	29	190–195	0.1	—	1.5260	$C_{23}H_{31}NO_2$	3.96	3.83
		A1	26.5	67							
X	*p*-Butylphenyl hexyl	B2	4	14	180–185	1	—	1.5159	$C_{22}H_{31}NO_2$	4.10	4.09
		A1	52	34[e]							
XI	*p*-Hydroxyphenyl ethyl	A1	45	45	185–188	0.1	92–93.5[f]	—	$C_{14}H_{15}NO_3$	5.71	5.72
XII	*o*-Hydroxyphenyl pentyl	B3	11	28[g]	188–190	0.4	94–95	—	[g]	—	—
		A1	80	64							
XIII	Di-(β-phenethyl)	B2	4	68	184–187	0.1	—	1.5565	$C_{22}H_{23}NO_2$	4.20	4.20
		A1	10	73							
XIV	Diphenyl	B4	13.5	41.7	175–182	1	95–97	—	—	—	—
		A1	42.5	84[h]							
XV	Phenyl *p*-chlorophenyl	A1	42.5	81.7	160–180	0.15	110–111[i]	—	$C_{18}H_{14}ClNO_2$	4.49	4.45

XVI	Di-(*p*-chlorophenyl)	B3	6.5	31.5	185–192	0.13	88–89[k]	—	$C_{18}H_{12}Cl_2NO_2$	4.05	4.05
		A1	51	43.5 (56.5)[j]							
XVII	*o*-Chlorophenyl *p*-chlorophenyl	B3	6.3	4.3	190–195	0.18	105–106[m]	—	$C_{18}H_{12}Cl_2NO_2$	4.05	4.01
		A1	92	46							
XVIII	Phenyl *p*-methoxyphenyl	A1	32	75	187	0.075	—	[n]	$C_{19}H_{17}NO_3$[p]	4.56	4.37
XIX	Phenyl 2-thienyl	B3	5	8.8	185–188	2	77–78[q]	—	$C_{16}H_{13}NO_2S$[q]	4.94	4.93
		A1	47	53							
XX	Fluorenone	A1	22	87	194–196	0.09	58–60	—	$C_{18}H_{13}NO_2$[r]	5.09	5.09
XXI	Camphor	A2	69	37	121–122	0.05	86–87[s]	—	$C_{15}H_{21}NO_2$[t]	5.66	5.67
XXII	Pinacolone	A2	80.5	13.2	127–130	12	—	1.4680	$C_{11}H_{17}NO_2$[u]	7.17	7.19

[a] Cope (2) reports 87% yield using benzene as a solvent. [b] Cope (2) reports 69% yield. [c] Cope (2) reports 73% yield. [d] Cope (2) reports 75% yield. [e] A very small run was made in this case, thus the yield recorded may not be an accurate value. [f] The distilled material was purified by recrystallization from aqueous methanol, then hexane. *Anal.* Calc'd: C, 68.55; H, 6.17. Found: C, 68.74; H, 6.23. [g] The product is not the expected cyanoester but appears to be the cyclized derivative 3-cyano-4-pentylcoumarin. The distilled material was purified by recrystallization from hexane. *Anal.* Calc'd for $C_{15}H_{15}NO_2$: C, 74.66; H, 6.27; N, 5.81. Found: C, 74.84; H, 5.92; N, 5.75. [h] Cope (2) reports 66% yield. The distilled material can be further purified by recrystallization from *n*-heptane. [i] The distilled material was recrystallized first from ethanol, then from *n*-hexane. [j] In addition to 43.5% of the alkylidenecyanoacetic ester, there was isolated 13% of a substance which appeared to be the corresponding amide $(p\text{-}ClC_6H_4)_2C{=}C(CN)CONH_2$, m.p. 189–191°. *Anal.* Calc'd for $C_{16}H_{10}Cl_2N_2O$: C, 60.59; H, 3.18; N, 8.83. Found: C, 60.41; H, 3.01; N, 8.81. [k] The product was purified by distillation followed by recrystallization from heptane. [m] The distilled material was purified by recrystallization from ethanol. [n] This material is too viscous at 25° for refractive index determination. [p] Calc'd: C, 74.27; H, 5.58. Found: C, 74.32; H, 8.75. [q] Purification of the distilled product was effected by recrystallization from cyclohexane. *Anal.* Calc'd: C, 67.82; H, 4.63. Found: C, 67.92; H, 4.69. [r] Calc'd: C, 78.52; H, 4.76. Found: C, 78.49; H, 4.84. [s] The distilled product was purified by repeated recrystallizations from ethanol-water. [t] Calc'd: C, 72.84; H, 8.56. Found: C, 72.99; H, 8.66. [u] Calc'd: C, 67.66; H, 8.78. Found: C, 67.35; H, 8.75.

TABLE IV

α,α-Disubstituted Succinic Acids and Anhydrides

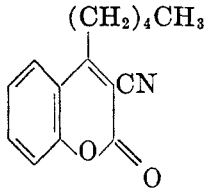
$$RR'C{=}C(CN)COOC_2H_5 \rightarrow RR'C(CN)CH(CN)COOC_2H_5 \rightarrow HOOCCRR'CH_2COOH \rightarrow \underset{\text{(E)}}{COCRR'CH_2CO}$$

(B) (C) (D)

(B)	R	R'	Yield, % Acid (D)	Yield, % Anh. (E)	B.P., °C	mm.	M.P., °C. (uncor.)	n_D^{25}	Formula	Analyses Calc'd C	Calc'd H	Found C	Found H
I	*n*-Amyl	*n*-Amyl	—	63	134–135	1.5	—	1.4537	$C_{14}H_{24}O_3$	69.96	10.07	69.91	10.14
II	*n*-Nonyl	*n*-Nonyl	—	41	186–192	1	—	1.4625	$C_{22}H_{40}O_3$	74.95	11.44	75.19	11.76
IV	Phenyl	Ethyl	77[a]	—	—	—	149–150	—	$C_{12}H_{14}O_4$	64.85	6.35	65.02	6.51
V	Phenyl	*n*-Amyl	—	65	162	1	—	1.5159	$C_{15}H_{18}O_3$	73.15	7.37	73.11	7.47
VI	Phenyl	*n*-Heptyl	—	56	170–172	2	—	1.5081	$C_{17}H_{22}O_3$	74.42	8.08	74.43	8.18
VII	Phenyl	*n*-Hendecyl	—	48	193–196	1–2	—	1.5010	$C_{21}H_{30}O_3$	76.32	9.15	76.36	9.37
VIII	Phenyl	2-Cyclohexylethyl	—	52	185–188	1–2	—	1.5301	$C_{18}H_{22}O_3$	75.49	7.74	75.47	7.82
IX	Phenyl	5-Cyclohexylpentyl	—	45	210	1–2	—	1.5210	$C_{21}H_{28}O_3$	76.79	8.59	76.78	8.86
X	*p*-(*n*-Butyl)phenyl	*n*-Hexyl	—	54	178–180	1–2	95–98[b]	1.5055[c]	$C_{20}H_{28}O_3$	75.91	8.92	75.85	9.02
XIV	Phenyl	Phenyl[d]	80	[e]	—	—	175[d]	—	$C_{16}H_{14}O_4$	71.10	5.22	71.13	5.34
XIII	2-Phenethyl	2-Phenethyl	16	—	—	—	155–156[f]	—	$C_{20}H_{22}O_4$	73.60	6.80	73.75	6.85
XV	Phenyl	*p*-Chlorophenyl	82	—	—	—	187–188[f]	—	$C_{16}H_{13}ClO_4$[g]	63.06	4.30	63.19	4.48
XVII	*p*-Chlorophenyl	*o*-Chlorophenyl	47	—	—	—	195–196[f]	—	$C_{16}H_{12}Cl_2O_4$[h]	56.66	3.56	56.70	3.72
XVI	*p*-Chlorophenyl	*p*-Chlorophenyl	76	—	—	—	188–189[f]	—	$C_{16}H_{12}Cl_2O_4$[i]	56.66	3.56	56.88	3.73

[a] Purification was carried out by recrystallization from water. [b] This material solidified only after long standing. [c] The refractive index was taken on the supercooled liquid. [d] α,α-Diphenylsuccinic acid, prepared by another method, has been reported by Salmon-Legagneur (15). He reported that with slow heating it melted at 170° with the formation of the anhydride, while in a preheated bath the minimum instantaneous m.p. was 197–199°. The sample prepared in the present work melted at 175° when placed in a bath preheated to 165° and heated at a rate of 1° per 10 sec. In a bath held at 175° it melted in 70 to 75 sec. [e] α,α-Diphenylsuccinic anhydride, m.p. 90.5–91.5° was prepared by warming the corresponding acid with thionyl chloride; yield, 95%. *Anal.* Calc'd for $C_{16}H_{12}O_3$: C, 76.18; H, 4.80%. Found: C, 76.43; H, 5.01%. Salmon-Legagneur (15) reported the synthesis of this compound by the action of acetyl chloride on the succinic acid, m.p., 90–91°. [f] Purification of this compound was effected by recrystallization from a mixture of acetic acid and water. [g] *Anal.* Calc'd: Cl, 11.64. Found: Cl, 11.52. [h] *Anal.* Calc'd: Cl, 20.91. Found: Cl, 20.68. [i] *Anal.* Calc'd: Cl, 20.91. Found: Cl, 20.60.

ano-4-pentylcoumarin (XII). No product was isolated when the reaction was carried out with xanthone; when anthrone was used no nitrogenous product was isolated.



(XII)

In 1896 Bredt and Kallen (8) reported the synthesis of α-monosubstituted succinic acids by a method involving the hydrolysis of the hydrogen cyanide addition product of ethyl alkylidenemalonates. Shortly thereafter Lapworth (9) showed that alkylidenecyanoacetic acid salts could be used in a similar manner to give substituted succinic acids. Higson and Thorpe (10) found the reaction to be more generally applicable when the sodium derivative of ethyl cyanoacetate was condensed with cyanohydrins of aldehydes or ketones followed by conversion to the dicyano derivative and finally hydrolysis to the succinic acid. Later Lapworth (11, 12) improved his method by employing the alkylidenecyanoacetic ester rather than the salt. Other than α,α-dimethyl- (10), α-methyl-α-ethyl- (10), α,α-diethyl- (13), α,α-diphenyl- (14) and α,α-pentamethylene-succinic acids (11), few α,α-disubstituted succinic acids have been reported in the earlier literature. More recently Birch and Robinson (4) have synthesized α-methyl-α-hexylsuccinic acid and Ray and Bhattacharyya (14) have prepared α-ethyl-α-decylsuccinic acid by a combination of the methods of Cope (2) and Lapworth (9, 11, 12).

In the present work the conversion of the ethyl alkylidenecyanoacetates (B) to the ethyl β,β-disubstituted-α,β-dicyanopropionates (C) by Lapworth's method was rapid and nearly quantitative. Earlier experience in these laboratories[1] had shown that the hydrolysis of these dicyano derivatives using hydrochloric acid [according to Lapworth (9)] or sulfuric acid [described by Ray and Bhattacharyya (14)] often gave unsatisfactory results. Much better results were obtained using the method of Birch and Robinson (4) who employed a mixture of sulfuric acid, acetic acid, and water. However, even under these conditions, products were obtained which contained nitrogenous impurities, probably the succinamic acid derivatives. When the acid hydrolysis was followed by an alkaline hydrolysis, pure succinic acids resulted. Since in many cases, the α,α-disubstituted succinic acids were oils, it was found convenient to convert them to the corresponding anhydrides which then could be purified by distillation (*cf.* Table IV).

[1] The early work in these laboratories on the preparation of ethyl diphenylmethylenecyanoacetate and its conversion to α,α-diphenylsuccinic acid was carried out by Floyd Todd.

EXPERIMENTAL[2]

Ethyl alkylidenecyanoacetates. For comparative purposes, two different methods and several variations of each method were employed in the synthesis of the ethyl alkylidenecyanoacetates. These methods may be summarized as follows: Method A—benzene as a solvent, (A-1) multiple addition of ammonium acetate catalyst, (A-2) increased quantities of ethyl cyanoacetate, solvents, and catalyst for slowly reacting ketones. Method B—toluene as a solvent and ammonium acetate added in (B-1) one portion, (B-2) two portions, (B-3) three portions, and (B-4) multiple portions. A summary of the runs made by these methods appears in Table III.

Method A-1. Ethyl cyanoacetate (135.7 g., 1.2 moles), the ketone (1.0 mole), acetic acid (48 g., 0.8 mole), and benzene (200 ml.) were placed in a flask attached to a modified Dean and Stark (2, 6) constant water-separator. The mixture was vigorously refluxed and the ammonium acetate catalyst (19–62 g., 0.25–0.8 mole) added in small portions (4-g. portions for the rapid reactions and 3-g. portions for the slow reactions) at 3–4-hour intervals. Before each addition of catalyst, the water layer was removed from the separator. The reaction was considered to be complete when the rate of water formation reached a small constant value following each addition of catalyst. Usually acetamide crystallized from the aqueous phase. Care was taken to avoid excessive quantities of catalyst (*i.e.*, 1–2 moles). When this precaution was not observed considerable polymeric material was produced. Heating was continued for several hours after the last addition of catalyst. The total reaction time varied from 10–92 hours. The mixture was allowed to cool, washed with water (three 300-ml. portions), and dried over sodium sulfate. The solvent was removed by distillation and the residue fractionated; both operations were carried out at reduced pressure. In the case of a solid product further purification was carried out by recrystallization from an appropriate solvent.

Method A-2. Ethyl cyanoacetate (226.2 g., 2.0 mole), the ketone (1.0 mole), glacial acetic acid (96 g., 1.6 mole), benzene (400 ml.), and ammonium acetate (57.8–92.5 g., 0.75–1.2 moles) were allowed to react as in Method A-1. The catalyst was again added portionwise. This modification was especially advantageous with very inert ketones which requires long reaction times and large quantities of catalyst.

Method B-1. Ethyl cyanoacetate (135.7 g., 1.2 moles), the ketone (1.0 mole), acetic acid (48 g., 0.8 mole), and toluene (200 ml.) were allowed to react using the same apparatus as for Method A-1. The ammonium acetate (15.4 g., 0.2 mole) was added in one portion and refluxing continued until one hour after water ceased to separate. The product was isolated as in Method A-1.

Method B-2. The reaction was carried out as in Method B-1 except the ammonium acetate (19–27 g., 0.25–0.35 mole) was added in two equal portions; the second portion was added as soon as water ceased to separate following the initial addition.

Method B-3. The reaction was carried out the same as Method B-2 except the catalyst (19–58 g., 0.25–0.75 mole) was added in three portions.

Method B-4. The reaction was carried out as in B-1 except that a portion (approximately 4 g.) of catalyst (38.5 g., 0.5 mole) was added whenever the water ceased to separate.

Ethyl α,β-dicyano-β,β-disubstituted propionates. All of the ethyl alkylidenecyanoacetates (B) were converted to the ethyl α,β-dicyano-β,β-disubstituted propionates (C) in a similar fashion. A typical example is described below. In general, the products were viscous oils that failed to crystallize, therefore they were not purified and identified but used directly in the hydrolysis step (D).

Ethyl α,β-dicyano-β,β-diphenylpropionate. Ethyl diphenylmethylenecyanoacetate (118.5 g., 0.428 mole) was dissolved in warm ethanol (180 ml.) and treated with a solution of potassium cyanide (58.5 g., 0.9 mole) in water (180 ml.). The clear yellow solution that resulted

[2] Microanalyses by Mr. K. B. Streeter, Mrs. Thelma Buchanan, Miss Ruth Lynch, and Miss Joyce Pyett.

was heated on a steam-bath, with stirring for fifteen minutes. The solution was cooled and acidified with excess concentrated hydrochloric acid. The product separated, nearly quantitatively, as a viscous oil which solidified on cooling overnight. Recrystallization from aqueous ethanol gave 116.5 g. (90%) of white crystals, m.p. 89–91°.

Anal. Calc'd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.21.
Found: C, 74.94; H, 5.29; N, 9.20.

α,α-Disubstituted succinic acids. The succinic acids were prepared in a manner similar to that described for α,α-diphenylsuccinic acid. In the cases where the products were oils they were converted to the anhydrides and purified in that form (*C.f.* Table IV).

α,α-Diphenylsuccinic acid. Ethyl α,β-dicyano-β,β-diphenylpropionate (116.3 g., 0.382 mole) was added to a solution of sulfuric acid (475 g.), glacial acetic acid (380 g.), and water (95 ml.) and the mixture heated gently until the initial vigorous evolution of carbon dioxide subsided. Then the solution was refluxed for twelve hours, cooled, and poured onto ice (1 kgm.). The oil that separated soon solidified. After removing by filtration and washing with water, the solid was refluxed for 72 hours with 20% potassium hydroxide (350 ml.). After cooling, the solution was treated with decolorizing carbon and filtered. The filtrate was made acid to Congo Red paper with concentrated hydrochloric acid. The oil that separated solidified on stirring. The solid was removed by filtration, washed with water, and dried; yield, 100 g. (97%). The crude material was recrystallized twice from a mixture of acetic acid and water. The yield of pure material was 82.4 g. (80%), m.p. 175° (see Note[d], Table IV).

α,α-Disubstituted succinic anhydrides. The succinic anhydrides were all prepared in a manner similar to that described for α-phenyl-α-(2-cyclohexylethyl)succinic anhydride. Table IV gives a summary of the results.

α-Phenyl-α-(2-cyclohexylethyl)succinic anhydride. Ethyl 1-phenyl-3-cyclohexylpropylidenecyanoacetate (61 g., 0.196 mole) was dissolved in ethanol (80 ml.) and treated with a solution of potassium cyanide (25.5 g., 0.392 mole) in water (80 ml.). The orange solution was heated, with stirring, on a steam-bath for fifteen minutes, then cooled, diluted with water (100 ml.), and acidified with excess concentrated hydrochloric acid. The oily layer was extracted with benzene (three 75-ml. portions) and the combined extracts washed with water. The benzene was removed by distillation at reduced pressure. The residual oil (66 g., 99%) was ethyl 2,3-dicyano-5-cyclohexyl-3-phenylpentanoate. This material was added to a solution composed of concentrated sulfuric acid (248 g.), glacial acetic acid (262 g.), and water (50 ml.). The mixture was refluxed for 15 hours and then poured onto crushed ice (640 g.). The oily layer was removed by extraction with benzene (three 100-ml. portions). The benzene was removed from the combined extracts at reduced pressure. The residual oil was treated with 20% potassium hydroxide (185 ml.) and the resulting solution refluxed for 72 hours. After cooling, the solution was treated with decolorizing carbon, filtered, and the filtrate acidified with excess hydrochloric acid. The oily succinic acid derivative was removed by extraction with benzene (three 100-ml. portions), the extract washed with water, and dried over magnesium sulfate. After removal of the benzene by distillation at reduced pressure, a waxy solid remained; yield, 59.6 g. (94%), m.p. 100–110°.

The crude α-phenyl-α-(2-cyclohexylethyl)succinic acid was refluxed with acetyl chloride (75 ml.) for two hours. The excess acetyl chloride was removed by distillation and the residue fractionated under reduced pressure. The yield of material boiling at 184–188° at 1–2 mm. was 30.4 g. (54%). Refractionation gave 29.3 g. (52%) of material boiling at 185–188° at 1–2 mm.

SUMMARY

Ammonium acetate was found to be a satisfactory catalyst for the Knoevenagel reaction involving diaryl ketones and certain hindered ketones with ethyl cyanocetate. The yields of ethyl alkylidenecyanoacetates were improved by the portionwise addition of catalyst at frequent intervals.

Camphor and pinacolone, ketones that failed to react under conditions used previously, gave the corresponding alkylidene derivative.

A variety of the ethyl alkylidenecyanoacetates were converted to the corresponding α,α-disubstituted succinic acids by the addition of hydrogen cyanide followed by hydrolysis. Many of the succinic acids were converted to the corresponding α,α-disubstituted succinic anhydrides.

GLENOLDEN, PA.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF G. D. SEARLE AND COMPANY]

THE KNOEVENAGEL CONDENSATION OF 3,4,5-TRIMETHOXYBENZALDEHYDE WITH *p*-METHOXYPHENYLNITROMETHANE

KURT RORIG

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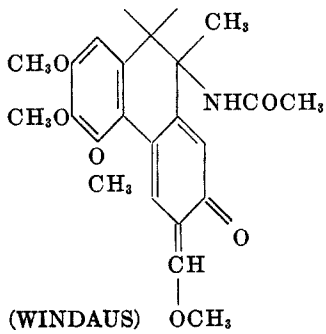
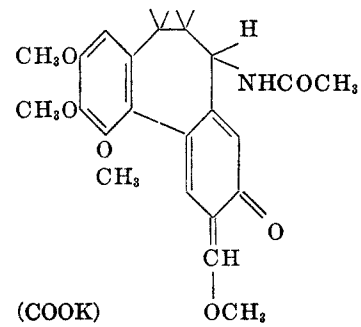
Although recent work on colchicine has not yet resulted in an unequivocal and generally accepted structural formula (1, 2, 3), the structure originally proposed by Windaus (4) definitely seems inadequate. Curiously enough, however, Lettré (5) found that the mitosis-inhibiting properties of certain simple analogs, *e.g.* I, predicated upon the Windaus formula are very similar to those exhibited by colchicine and its degradation products, whereas those analogs, *e.g.* II, based on the Cook formula, do not show this mitotic poisoning property.

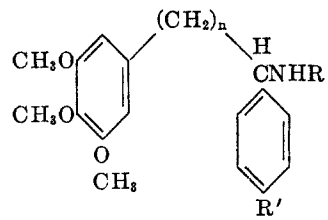
COLCHICINE FORMULAS



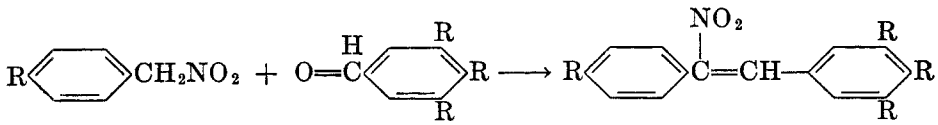
(WINDAUS)



(COOK)

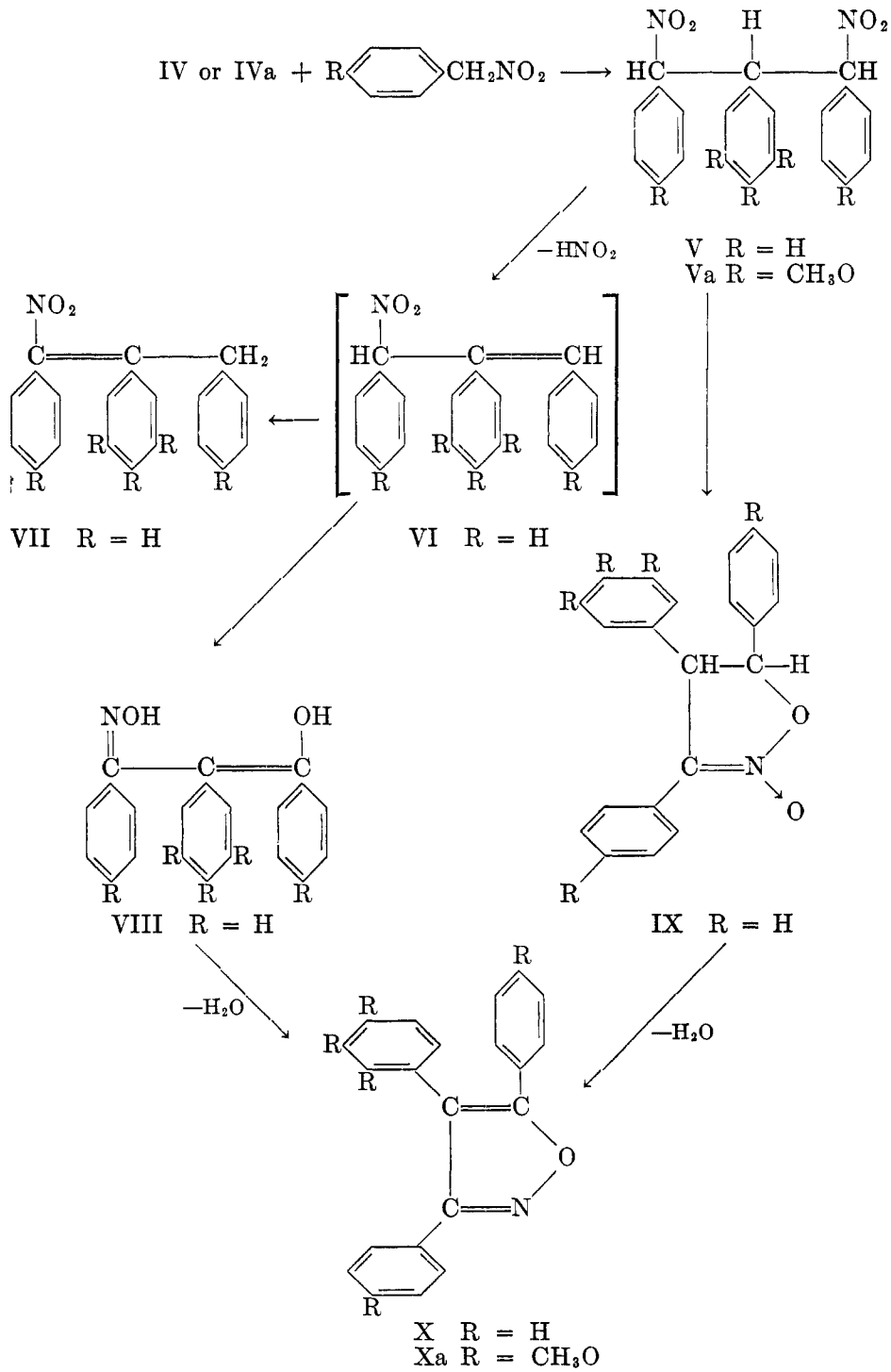


I R = H or Ac; R′ = H; n = 1
II R = H or Ac; R′ = OCH_3; n = 2
III R = H; R′ = OCH_3; n = 1



R = H or CH_3O

IV R = H
IVa R = CH_3O


IV or IVa + R
CH2NO2
NO2
H
NO2
HC
C
CH
R
R
R
R
R
R
−HNO2
V R = H
Va R = CH3O
NO2
C
C
CH2
NO2
HC
C
CH
VII R = H
VI R = H
R
R R
R
CH—C—H
O
C
N
O
R
NOH
OH
C
C
C
IX R = H
VIII R = H
−H2O
−H2O
R
R
R
C
C
O
C
N
R
X R = H
Xa R = CH3O

α-(*p*-Anisyl)-β-(3,4,5-trimethoxyphenyl)ethylamine (III) has now been prepared by the catalytic reduction (Pd-C) of 3′,4,4′,5′-tetramethoxy-α-nitrostilbene and tested as a mitosis-inhibitor. The required α-nitrostilbene IVa was prepared by the Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde with *p*-methoxyphenylnitromethane.

In addition to IVa there were formed in small amounts three other compounds: the dinitropropane[1] (Va), the isoxazole (Xa), and a compound of empirical formula $C_{26}H_{27}NO_7$ (XI). This is in accord with the formation of their unmethylated analogs from phenylnitromethane and benzaldehyde as reported by Heim (6). His compound $C_{21}H_{17}NO_2$, corresponding to our pentamethoxy analog (XI), was regarded by Heim and others (7) as having the nitropropene structure (VII). These workers further thought the isomeric nitropropene (VI) to be an intermediate in the formation of the isoxazole (X) from the nitrostilbene (IV) and phenylnitromethane *via* the path V → VI → VIII → X.

Kohler and Barret (8), however, found as a by-product from this condensation a compound $C_{21}H_{17}NO_2$ differing from that of Heim. This was shown to have the isoxazoline oxide structure (IX). Since IX was obtained also by the condensation of the nitrostilbene (IV) with phenylnitromethane in the presence of sodium methoxide, and was readily transformed into the isoxazole (X) by an excess of sodium methoxide, IX rather than VI was considered an intermediate in the formation of X as a by-product from the Knoevenagel condensation. By using ammonia with a trace of water as the Knoevenagel catalyst, Worrall (9) was able to obtain yet a third entity of formula $C_{21}H_{17}NO_2$, easily transformed into the isoxazole (X), which had all the characteristics expected of the enol-oxime (VIII). This compound had previously been postulated as an intermediate by Heim (6) but had not been isolated by him. Which of these three structures VII, VIII, or IX, if any, shall be regarded as analogous to our compound $C_{26}H_{27}NO_7$ is as yet uncertain. Our compound is not a bright yellow as was Heim's analog, nor is it soluble in aqueous alkali as demanded by Worrall's structure (9). Ruggli and Hegedus (10) have isolated an enol-oxime, which they regard as analogous to Worrall's, from *o*-nitrobenzaldehyde and phenylnitromethane. This compound is soluble in dilute base from which it is reprecipitated unchanged by acid.

It seems, however, that our compound $C_{26}H_{27}NO_7$ was formed *after* the isoxazole Xa and is therefore not a precursor of Xa. It is hoped soon to resume work which will yield the correct structural formula of $C_{26}H_{27}NO_7$ and afford further insight into the reaction mechanism.

Using the single-coverslip method (11) of tissue culture to test for inhibition of multiplication of embryonic chicken heart fibroblasts, it was found[2] that colchicine inhibited growth when present at a concentration of 0.001 mg. per ml. of chicken plasma, whereas 0.3 mg. of III per ml. of plasma was required

[1] Reichert and Hoffman, *Arch. Pharm.*, **274**, 217 (1936), have reported the formation of an analogous dinitropropane from phenylnitromethane and 3,4,5-trimethoxybenzaldehyde.

[2] We are greatly indebted to Dr. James Clampit of these laboratories for this report on the growth-inhibiting properties.

to inhibit growth of these cells. Oddly enough, the α-nitrostilbene (IVa) was more potent than its hydrogenation product III, inhibiting growth at a concentration of 0.03 mg. per ml. of plasma. Compounds Va and Xa were too water-insoluble to permit testing.

EXPERIMENTAL[3]

3,4,5-Trimethoxybenzaldehyde. This material was prepared in 56–79% yield by the Rosenmund reduction (12) of 3,4,5-trimethoxybenzoyl chloride with 5% palladium catalyst supported on barium sulfate (13). No catalyst poison was used but the yields of aldehyde improved as the catalyst was re-used a second and a third time.

p-Methoxyphenylnitromethane. Sodium *p*-methoxyphenyl-*aci*-nitroacetonitrile, obtained in 65% yield from homoanisonitrile (14) and methyl nitrate, was hydrolyzed and decarboxylated according to the general procedure of Meisenheimer and Weibezahn (7) to give a 60% yield of crude *p*-methoxyphenylnitromethane. This undistilled product was not further purified since it usually decomposed violently when small quantities (10 g.) were distilled.

Knoevenagel condensation. Gaseous methylamine was bubbled for one minute into a solution of 58.5 g. (0.3 mole) of trimethoxybenzaldehyde and 50 g. (0.3 mole) of *p*-methoxyphenylnitromethane in 170 ml. of 95% ethanol. After overnight standing at room temperature had yielded no crystals, the mixture was scratched and cooled in the refrigerator for three hours. Thereupon 40 g. of canary-yellow crystals melting at 129–132° were obtained (crop A). Two recrystallizations from absolute ethanol followed by two recrystallizations from a benzene-petroleum ether mixture gave an analytical sample of 3′,4,4′,5′-tetramethoxy-α-nitrostilbene (IVa) melting at 133–134°. [Lit. m.p. 137° (5c)].

Anal. Calc'd for $C_{18}H_{19}NO_6$: CH_3O, 35.95. Found: CH_3O, 35.88, 35.84.

The reaction mixture filtrate, reduced two-thirds in volume by distillation of ethanol *in vacuo*, deposited 6.3 g. of lemon-yellow crystals, m.p. 150–153° (crop B). This, when extracted with hot absolute ethanol, left a residue of 0.5 g. of white crystalline *1,3-di-(p-anisyl)-2-(3′,4′,5′-trimethoxyphenyl)-1,3-dinitropropane* (Va), m.p. 235–237°.

Anal. Calc'd for $C_{26}H_{28}N_2O_9$: C, 60.93; H, 5.51; N, 5.47; CH_3O, 30.28.
Found: C, 61.0; H, 5.52; N, 5.37; CH_3O, 30.22.

The alcohol-soluble portion of crop B was recrystallized from 120 ml. of 80% ethanol to give 4.63 g. of white *3,5-di-(p-anisyl)-4-(3′,4′,5′-trimethoxyphenyl)isoxazole* (Xa), m.p. 156–158°. A thrice-recrystallized analytical sample melted at 158–159°.

Anal. Calc'd for $C_{26}H_{25}NO_6$: C, 69.78; H, 5.63; N, 3.13; CH_3O, 34.68.
Found: C, 69.3; H, 5.67; N, 3.05; CH_3O, 34.62.

A third crop (crop C) of oily, yellow crystals was obtained from the reaction filtrate after it had stood for four months at 5°. By triturating this crystalline sludge with hot ethanol, 0.35 g. of faintly yellow crystals, m.p. 165–167°, was obtained as an insoluble residue. The ethanolic solution from this trituration deposited 2.7 g. of a white solid, m.p. 70–85°, upon dilution with water. Since the melting point of this material was not improved by recrystallization from a variety of solvents, it was not investigated further. A mixture melting point of the above product melting at 165–167° with *isoxazole*, m.p. 158–159°, was 138–150°.

Anal. Calc'd for $C_{26}H_{27}NO_7$: C, 67.08; H, 5.89; N, 3.01; CH_3O, 33.33.
Found: C, 66.51; H, 5.86; N, 2.85; CH_3O, 33.58.

α-(p-Anisyl)-β-(3,4,5-trimethoxyphenyl)ethylamine hydrochloride. Catalytic reduction of the nitrostilbene (IVa) was done according to the directions of McPhee, *et al.* (15). Ten grams of 3′,4,4′,5′-tetramethoxy-α-nitrostilbene, 0.6 g. of palladium chloride, and 4 g. of acid-washed "Darco G-60" charcoal took up the required amount of hydrogen in 2.5 hours of shaking at 50°. After filtration and evaporation of the solvent, the free amine was taken up in 30 ml. of absolute ethanol containing 1.5 g. of anhydrous hydrogen chloride. Warming,

[3] All melting points are uncorrected. The analyses were done in these laboratories by Dr. Robert Dillon and his staff.

adding absolute ether to incipient cloudiness, and cooling gave 5.0 g. of the desired hydrochloride, m.p. 214–217°. A sample twice recrystallized from ethanol-ether melted at 216–218°. A second crop from the original mother liquor weighed 1.6 g., m.p. 190–202°.

Anal. Calc'd for $C_{18}H_{24}ClNO_4$: N, 3.96; Cl, 10.02; CH_3O, 35.08.
Found: N, 3.85; Cl, 9.65; CH_3O, 35.30.

SUMMARY

The Knoevenagel condensation of 3,4,5-trimethoxybenzaldehyde with *p*-methoxyphenylnitromethane has been utilized to prepare 3′,4,4′,5′-tetramethoxy-α-nitrostilbene. Three additional products of this reaction have been isolated and the possible modes of their formation discussed.

Hydrogenation of the above α-nitrostilbene has given α-(*p*-anisyl)-β-(3,4,5-trimethoxyphenyl)ethylamine, an open chain analog of Windaus' colchicine formula.

The growth-inhibitory properties of the above compounds are given.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY,
MICHIGAN STATE COLLEGE]

ORIENTATION IN THE PHOSPHORIC ACID-CATALYZED ALKYLATION OF ORTHO-CRESOL[1, 2]

HAROLD HART AND E. A. HAGLUND

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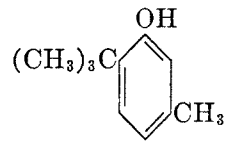
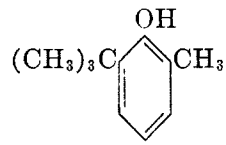
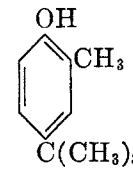
In connection with a research program on the *ortho*-alkylphenols and their derivatives (1) it was of interest to reinvestigate the orientation described by Chichibabin (2) when *o*-cresol was alkylated with *tert*-butyl alcohol in the presence of phosphoric acid. A careful examination of the product obtained when *m*-cresol was similarly alkylated showed that the *tert*-butyl group entered the ring *ortho* to the hydroxyl and *para* to the methyl, yielding



Chichibabin, reasoning by analogy, assumed that the product obtained from *o*-cresol, *tert*-butyl alcohol, and phosphoric acid was 6-*tert*-butyl-*o*-cresol (I).



I



II

Other workers have claimed that when zinc chloride (3) or aluminum chloride (4) was used as the catalyst, the product was 4-*tert*-butyl-*o*-cresol (II). If phosphoric acid acts uniquely to give *ortho* alkylation, then this behavior is worthy of further investigation; if not, the error[3] should be corrected.

Structure I claimed by Chichibabin is one which belongs to the class of compounds known as partially hindered phenols (5, 6). Such substances are known to be insoluble in 10% aqueous alkali, whereas Chichibabin isolated his product *via* extraction with dilute aqueous alkali. Furthermore, it has been shown (1) that *o*-*tert*-butylphenol readily rearranges to the *para* isomer in the presence of 100% phosphoric acid. It was believed, therefore, the Chichibabin's product had, in fact, structure II.

The hydrogenation of I has been reported (7) but its synthesis was not given. The properties of two *tert*-butyl-*o*-cresols of undetermined structure have also been reported (8).

[1] The material herein presented is taken from the M.S. thesis of Edwin A. Haglund, Michigan State College, August 1949.

[2] Presented before the Organic Division at the Atlantic City meeting of the American Chemical Society, September 1949.

[3] See, for example, Heilbron, *Dictionary of Organic Compounds*, Oxford University Press, New York, N. Y., 1943, Vol. I, p. 284, which ascribes to 6-*tert*-butyl-*o*-cresol the properties and method of preparation described by Chichibabin.

An authentic sample of I was synthesized according to the scheme which had been used previously (1) to prepare *o-tert*-butylphenol. Reduction of III was

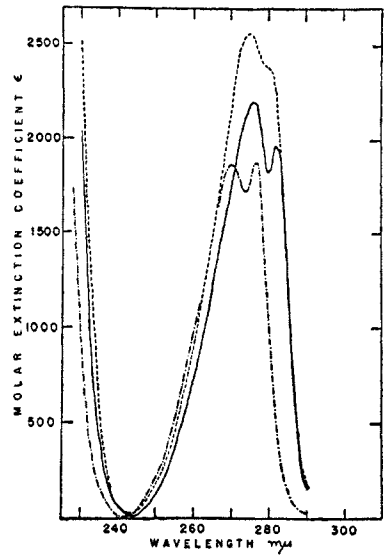
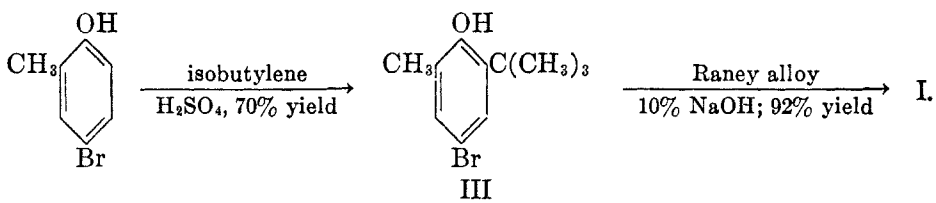


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA: ———, 2.35×10^{-4} *M* 4-*tert*-butyl-*o*-cresol (II); —·—·—, 2.67×10^{-4} *M* 6-*tert*-butyl-*o*-cresol (I); - - - -, 2.37×10^{-4} *M* 4, 6-di-*tert*-butyl-*o*-cresol; all in cyclohexane solvent.

carried out in an alkaline medium, thus avoiding migration of the *tert*-butyl group.



The boiling point of I was about 10° below that of the product obtained by alkylation of *o*-cresol according to Chichibabin's precedure. Furthermore, I was insoluble in 10% sodium hydroxide and did not give the characteristic phenol test with ferric chloride. No derivative could be prepared by the conventional methods [save the bromo derivative (III)] whereas the alkylation product of Chichibabin readily yielded a crystalline aryloxyacetic acid. That I was a partially hindered phenol and not an ether was indicated by a positive reaction in the sensitive spot test for phenols with phosphomolybdic acid and ammonium hydroxide (9) and the fact that its ultraviolet absorption spectrum (Figure 1) was very similar to that of phenol. Furthermore, under the conditions used to prepare III, any ether, if formed, would have rearranged (10) to the alkyl phenol.

That the product obtained by the alkylation of *o*-cresol was the 4-isomer (II) was indicated by the facts that (a) compound I, when treated with either

sulfuric or phosphoric acid, rearranged to give a product in all respects identical with the alkylation product and (b) its absorption spectrum (Figure 1) shows the shift of about 6 mμ toward the longer wavelengths characteristic of *para*-alkylphenols (1). This point is further illustrated in Table I, in which the similar positions of the peaks in the spectra of unsubstituted and *ortho*-alkylphenols are contrasted with the spectra of the *para*-alkylphenols. It is to be noted that 4,6-di-*tert*-butyl-*o*-cresol also exhibits this shift (Figure 1) although the peaks

TABLE I

MAXIMA IN THE ULTRAVIOLET ABSORPTION SPECTRA OF SOME PHENOLS

	PEAK 1		PEAK 2		REF.
	mμ	ε	mμ	ε	
Phenol	271	2130	278	1847	1
o-Cresol	271	2140	278	2040	11
o-*tert*-Butylphenol	271	2014	278	2018	1
6-*tert*-Butyl-*o*-cresol (I)	270	1865	277	1876	Fig. 1
p-Cresol	278	2180	284	1860	11
p-*tert*-Butylphenol	277	2130	283	2054	1
Alkylation product (II) (4-*tert*-Butyl-*o*-cresol)	276	2200	282	1957	Fig. 1
4,6-Di-*tert*-butyl-*o*-cresol	275	2557	(280)	2384	Fig. 1

are broader and overlap, as one would expect of the more highly substituted compound. Thus, sterically hindering the hydroxyl group does not appreciably effect this spectral shift.

It is concluded, therefore, that the alkylation of *o*-cresol according to the procedure of Chichibabin leads to a product with structure II.

EXPERIMENTAL

4-Bromo-6-tert-butyl-o-cresol (III). A solution of 140 g. (0.75 mole) of 4-bromo-*o*-cresol (m.p. 63–64°, 4-bromo-2-methylphenoxyacetic acid) m.p. 122–123°) in 200 cc. of benzene was alkylated with isobutylene and 5 cc. of concentrated sulfuric acid at 65° using a procedure similar to that of Stillson, Sawyer, and Hunt (5). It was necessary to use an excess of isobutylene (about 1.4 moles) and a reaction time of about five hours in order to obtain maximum yields. Under these conditions, 128 g. (70.0%) of III were obtained, b.p. 130–135° at 11 mm.; recrystallized from petroleum ether, m.p. 49–50°.

Anal. Calc'd for $C_{11}H_{15}BrO$: Br, 32.89. Found: Br, 32.75 (Parr).

The compound was insoluble in 10% aqueous sodium hydroxide and did not yield a phenoxyacetic acid derivative by the usual procedure.

6-tert-Butyl-o-cresol (I). When 11.1 g. (0.0457 mole) of III was treated with 30 g. of Raney nickel-aluminum alloy and 300 cc. of 10% sodium hydroxide according to the procedure of Schwenk, *et. al.* (12) and Hart (1) it yielded 6.9 g. (92.0%) of I, b.p. 225–227° at 740 mm.

Anal.[4] Calc'd for $C_{11}H_{16}O$: C, 80.3; H, 9.80.
Found: C, 80.34; H, 10.08.

I was insoluble in 10% aqueous sodium hydroxide and gave a negative color test with

[4] This analysis was performed by the Clark Microanalytical Laboratory, Urbana, Illinois. The other analyses were performed by E.A.H.

ferric chloride. With phosphomolybdic acid and ammonium hydroxide, a blue color appeared (9).

Alkylation of o-cresol. *o*-Cresol (54 g.) was treated with a total of 200 g. of 100% phosphoric acid and 40 g. of *tert*-butyl alcohol for eight hours at 60–65° according to the procedure of Chichibabin (2). Instead of using Chichibabin's tedious procedure of isolation of the sodium phenoxide, the reaction mixture was poured into 2 liters of water and extracted with ether. Extraction of the ether layer with 10% sodium hydroxide, acidification, extraction with ether, drying over calcium chloride, removal of the solvent, and distillation of the product yielded 52 g. (63.4%) of alkylation product, [4-*tert*-butyl-*o*-cresol (II)] b.p. 235–237° at 740 mm. Treatment with chloroacetic acid yielded the 2-methyl-4-*tert*-butylphenoxyacetic acid, m.p. 101.5–102.0°.

Anal. Calc'd for $C_{13}H_{18}O_3$: Neut. equiv., 222. Found: Neut. equiv., 221.5.

The alkylation product gave a positive ferric chloride test and a positive phenol spot test (9).

Rearrangement of I. The homogenous mixture of one cc. of I with five drops of concentrated sulfuric acid was warmed gently for five minutes, then poured on ice, and extracted with petroleum ether. After washing with sodium carbonate and evaporation of the solvent, a liquid remained which was soluble in 2% aqueous sodium hydroxide and yielded a phenoxyacetic acid derivative, m.p. 99–100°; mixture with the same derivative of the alkylation product, m.p. 97–100°.

Two cc. of I treated with 100% phosphoric acid at 65–70° for eight hours, with constant stirring, also yielded some II (phenoxyacetic acid derivative, m.p. 97–100°) as well as some unchanged I.

The ultraviolet absorption spectra were determined with a Beckman spectrophotometer, model DU, using 1-cm. quartz cells. The cyclohexane solvent was freed of benzene by passage through silica gel, followed by fractionation.

SUMMARY

1. The product obtained from the phosphoric acid-catalyzed alkylation of *o*-cresol with *tert*-butyl alcohol is 4-*tert*-butyl-*o*-cresol and not 6-*tert*-butyl-*o*-cresol as stated in the literature.

2. The chemical properties and absorption spectra of these compounds are discussed.

EAST LANSING, MICH.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

SULFONES. I. THE ISOMERIC X,X'-DIAMINODIPHENYL SULFONES

B. R. BAKER, ARTHUR F. KADISH, AND MERLE V. QUERRY

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In order to determine the relationship of the structure to chemotherapeutic activity in 4,4'-diaminodiphenyl sulfone, the effect of the positions of the amino groups on activity was undertaken. There are six possible isomers of diaminodiphenyl sulfone having one amino group in each ring. Of these, three have been described in the literature, namely, 2,4'-diaminodiphenyl sulfone (1), 3,3'-diaminodiphenyl sulfone (2) and, of course, 4,4'-diaminodiphenyl sulfone. Two of the remaining three isomers have one amino group in the 3-position. The easiest method of introducing an amino group in this position appeared to be by nitration of the proper sulfone, a *meta*-directing group (3), followed by reduction. Thus, nitration of 4-nitrodiphenyl sulfone and 2-nitrodiphenyl sulfone would be expected to lead to 3,4'-dinitro- and 2,3'-dinitro-diphenyl sulfone, respectively. Reduction with stannous chloride in hydrochloric acid gave the corresponding diamines. The last isomer, 2,2'-diaminodiphenyl sulfone was obtained by simultaneous reduction and hydrolysis of the known 2-acetamino-2'-nitrodiphenyl sulfone (4).

Of the six isomers only 4,4'-diaminodiphenyl sulfone showed chemotherapeutic activity.[1]

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

2,3'-Dinitrodiphenyl sulfone. 2-Nitrodiphenyl sulfone was obtained in 78% yield, m.p. 138–141°, by the condensation of sodium benzenesulfinate and *o*-chloronitrobenzene in a mixture of ethylene glycol and Carbitol at 160° for fifteen hours.

Ullmann and Pasdermadjian (5) have recorded a yield of 88% of product, m.p. 147.5°, when the reaction was carried out in alcohol in a sealed tube at 160°.

To a mixture of 23 g. of 2-nitrodiphenyl sulfone and 80 cc. of concentrated sulfuric acid was added dropwise over a period of ten minutes 40 cc. of nitric acid ($d = 1.42$). The temperature was maintained at 55–60° by occasional cooling. After being stirred at 55–60° for fifteen minutes more, the mixture was poured on ice. The product was washed thoroughly with water, and heated to boiling with alcohol, then cooled, to remove impurities; yield, 24.1 g. (90%), m.p. 168–171°. Recrystallization from acetic acid gave cream-colored crystals, m.p. 173–175°.

Anal. Calc'd for $C_{12}H_8N_2O_6S$: C, 46.6; H, 2.6; N, 9.1.
Found: C; 46.7; H, 2.9; N, 9.6.

3,4'-Dinitrodiphenyl sulfone. 4-Nitrodiphenyl sulfone was obtained in 46% yield, m.p. 140–142°, by the condensation of sodium benzenesulfinate and *p*-chloronitrobenzene in boiling Carbitol (six hours) containing a little sodium iodide. Ullmann and Pasdermadjian (5) have recorded a m.p. of 143° when the reaction was run in alcohol at 160° in a sealed tube.

[1] The biological studies will be reported elsewhere.

Nitration in the same manner as described for 2,3′-dinitrodiphenyl sulfone resulted in a 96% yield of product, m.p. 174–179°. Recrystallization from acetic acid gave orange crystals, m.p. 182–184°.

Anal. Calc'd for $C_{12}H_8N_2O_6S$: C, 46.6; H, 2.6; N, 9.1.
Found: C, 46.8; H, 3.6; N, 9.2.

3,4′-Diaminodiphenyl sulfone. To a solution of 156 g. of stannous chloride dihydrate in 156 cc. of concentrated hydrochloric acid was added 24.3 g. of 3,4′-dinitrodiphenyl sulfone. The mixture was warmed gently on the steam-bath to initiate the reaction which was then controlled by cooling in an ice-bath. In about two minutes the reaction had subsided and most of the nitro sulfone had dissolved. After being heated on the steam-bath for two hours, the solution was poured into 170 g. of sodium hydroxide in 170 cc. of water diluted with excess ice. The solid was collected on a sintered-glass funnel. An ethyl acetate solution of the solid was clarified with Norit, diluted with an equal volume of benzene, and petroleum ether was added to incipient crystallization; yield, 14.1 g. (72%) of white crystals, m.p. 129–131°. Recrystallization from the same solvents raised the m.p. to 131.5–133°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 58.5; H, 5.2; N, 11.4.

2,3′-Diaminodiphenyl sulfone. Reduction of 2,3′-dinitrodiphenyl sulfone was carried out the same as in the preceding experiment in 67% yield, m.p. 118–120°. Recrystallization from benzene gave white crystals, m.p. 124–126°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2S$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 57.7; H, 5.0; N, 11.7.

3,3′-Diaminodiphenyl sulfone was prepared in the same way from 3,3′-dinitrodiphenyl sulfone (6) in 40% yield, m.p. 168–170°. Catalytic reduction in acetic acid with Adams' catalyst gave a 36% yield, m.p. 158–163°.

Marchak, *et al.* (2) record a yield of 70% and m.p. 168–169°, using ammonium sulfide as the reducing agent.

2,2′-Diaminodiphenyl sulfone. 2-Nitro-2-aminodiphenyl sulfide was prepared from *o*-chloronitrobenzene and sodium sulfide in 50% yield according to Lantz (7). The amine was acetylated, then oxidized with hydrogen peroxide to 2-acetamino-2′-nitrodiphenyl sulfone in 64% yield essentially according to the method of Evans and Smiles (4). From 24.6 g. of the sulfone, 78 g. of stannous chloride dihydrate, and 78 cc. of conc'd hydrochloric acid was obtained 17.1 g. (90%) of 2,2′-diaminodiphenyl sulfone, m.p. 143–145°, in the same way as described for 3,4′-diaminodiphenyl sulfone except that the crude product was purified by recrystallization from alcohol-water. The analytical sample formed white crystals, m.p. 146–147°.

Anal. Calc'd for $C_{12}H_{12}N_2O_2S$: C, 58.1; H, 4.8; N, 11.3.
Found: C, 57.8; H, 5.2; N, 11.1.

SUMMARY

Syntheses of three unknown isomers of 4,4′-diaminodiphenyl sulfone have been described.

PEARL RIVER, NEW YORK

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

SULFONES. II. DERIVATIVES OF 4,4′-DIAMINODIPHENYL SULFONE

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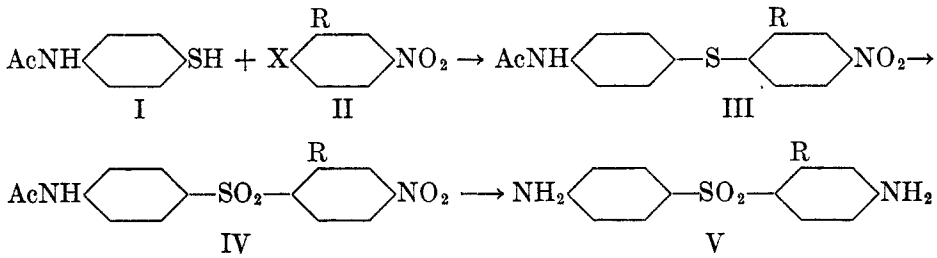
Since 4,4′-diaminodiphenyl sulfone is the only diaminodiphenyl sulfone which has chemotherapeutic activity (1), a number of C and N derivatives of it have been synthesized in order to determine the effect on the activity.[1]

4,4′-Diaminodiphenyl sulfones were prepared with substituents in the 2-position, namely: amino, chloro, sulfamyl, carbamyl, and methyl. The 2-amino derivative was synthesized by the condensation of *p*-acetaminobenzenesulfinic acid with 2,4-dinitrochlorobenzene followed by reduction of the nitro groups and hydrolysis. The remainder were synthesized by the condensation of the appropriately substituted *p*-nitrohalobenzene (II) with *p*-acetaminothiophenol (I) to the sulfides, III, then oxidation to the sulfones, IV. Reduction of the nitro group and hydrolysis gave the desired diamines, V. Similarly, 4-amino-1-naphthyl 4-aminophenyl sulfone[2] was prepared starting with 1-iodo-4-nitronaphthalene.



Nitration of 4-acetamino-4′-nitrodiphenyl sulfone led to 3,4′-dinitro-4-acetaminodiphenyl sulfone. After removal of the acetyl group, the nitro groups were reduced with stannous chloride to form 3,4,4′-triaminodiphenyl sulfone.

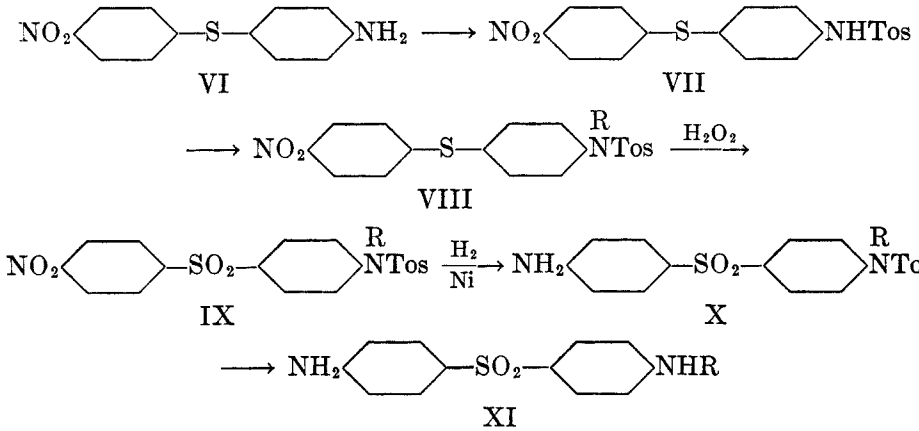
Since it seemed desirable to synthesize a number of N-alkyl derivatives, a general method was sought. 4-Amino-4′-nitrodiphenyl sulfide (VI) (7) was converted to the tosylamide, VII, with *p*-toluenesulfonyl chloride in pyridine. The amide, VII, was smoothly alkylated in Methyl Cellosolve with 10% aqueous potassium hydroxide and a variety of alkyl halides[3] including *n*- and isopropyl iodide, allyl bromide, octyl bromide, lauryl bromide, cetyl iodide, benzyl chloride, *p*-nitrobenzyl chloride, and α-chloroacetanilide to VIII. No difficulty was encountered in the sequence VIII → X.

[1] The biological studies will be reported elsewhere.

[2] Since the completion of this work the preparation of this sulfone by a different method has been described (11).

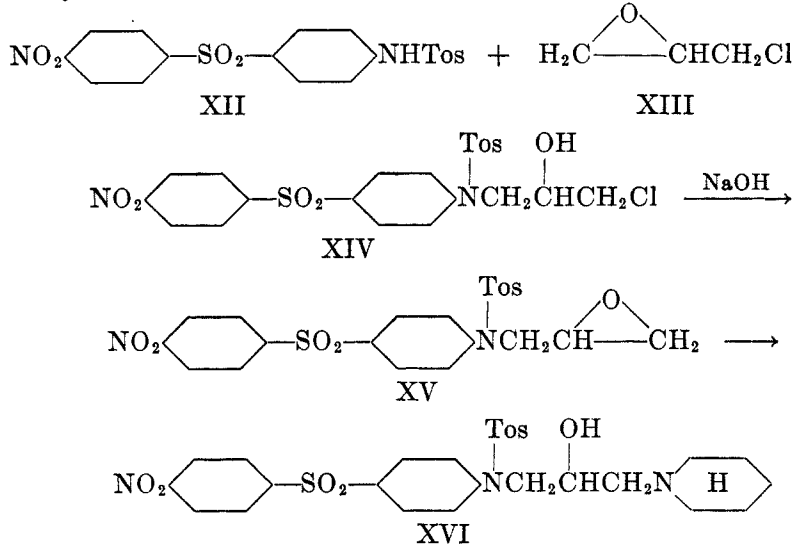
[3] Attempts to alkylate 4-tosylamino-4′-acetamino (or nitro) diphenyl sulfone with *n*-propyl iodide under similar conditions led to mixtures and much of the unalkylated sulfonamide could be recovered.

Acid hydrolysis of X to XI proceeded smoothly except in the cases of R = isopropyl, benzyl, and *p*-aminobenzyl. The latter two groups were rapidly cleaved to the corresponding alkyl chloride. 4-Amino-4′-benzylaminodiphenyl



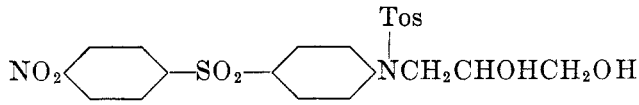
sulfone was then synthesized by condensation of benzaldehyde with 4-acetamino-4′-aminodiphenyl sulfone and catalytic reduction of the anil followed by hydrolysis of the acetyl group.

4-Tosylamino-4′-nitrodiphenyl sulfone (XII) readily condensed with epichlorohydrin (XIII) to form the chlorohydrin, XIV, in excellent yield according



to the method of Oehle and Haesler (2). With sodium hydroxide in Methyl Cellosolve, the chlorohydrin was converted to the oxide, XV. The latter, with piperidine, gave the amino alcohol, XVI. Catalytic reduction of the nitro group and hydrolysis of the sulfonamide linkage gave 4-(β-hydroxy-γ-piperidinopropylamino)-4′-aminodiphenyl sulfone.

Attempts to open the oxide ring of XV to the glycol, XVII, under a variety of conditions were unsuccessful. However, XVII could be prepared by the direct condensation of glycidol with the sulfone, XII, or by condensation of glycidol



XVII

with the sulfide, VII, followed by oxidation to the sulfone with hydrogen peroxide. The nitro group of XVII was smoothly reduced catalytically, but the 4-(β,γ-dihydroxypropylamino)-4′-aminodiphenyl sulfone obtained on hydrolysis under a variety of conditions could not be induced to crystallize.

Only one disubstituted 4,4′-diaminodiphenyl sulfone was synthesized, namely the 2,2′-dichloro derivative. This compound was prepared in the same manner as the 2-monochloro derivative. Oxidation of the intermediate 2,2′-dichloro-4-acetamino-4-nitrodiphenyl sulfide with hydrogen peroxide in acetic acid gave a mixture which was predominantly the sulfoxide. The oxidation was successfully carried out by the use of potassium permanganate in dilute acetic acid.

It is interesting to note that hydrogen peroxide oxidation of diphenyl sulfides unsubstituted in either 2-position takes place smoothly at 50° in excellent yield. With one substituent *ortho* to the sulfide linkage, the peroxide oxidation is incomplete at 50° and is finished by heating on the steam-bath. However, the yields are considerably lower than with the non-*ortho* substituted sulfides. As noted above, with groups in both the 2 and 2′-positions, hydrogen peroxide oxidation fails completely as a preparative method.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

2,4-Dinitro-4′-acetaminodiphenyl sulfone. To a solution of 40 g. of *p*-acetaminobenzenesulfinic acid in 200 cc. of alcohol containing 8 g. of reagent sodium hydroxide in 8 cc. of water was added 42 g. of 2,4-dinitrochlorobenzene. The mixture was refluxed for thirty minutes, during which the product separated. The mixture was cooled, the solid was removed and washed successively with alcohol, ether, and water; yield, 68 g. (93%), m.p. 222–225°. Recrystallization from Methyl Cellosolve afforded yellow crystals, m.p. 226–227°.

Anal. Calc'd for $C_{14}H_{11}N_3O_7S$: N, 11.5. Found: N, 11.7.

2,4,4′-Triaminodiphenyl sulfone. A mixture of 250 g. of stannous chloride dihydrate in 500 cc. of concentrated hydrochloric and 25 g. of 2,4-dinitro-4′-acetaminodiphenyl sulfone was stirred for fifteen minutes maintaining the temperature at 20–23° by occasional cooling. At the end of this time the tin complex separated; the mixture was diluted with 500 cc. of water, then heated on the steam-bath for thirty minutes after the temperature reached 85°. The product was isolated in the same manner as described for 3,4′-diaminodiphenyl sulfone (1), except that alcohol-water was used for purification; yield, 12.8 g. (71%), m.p. 118°, resolidifies and remelts at 150°. Recrystallization from dilute alcohol did not change the m.p.

Anal. Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0.
Found: C, 54.5; H, 5.2; N, 16.1.

p-Acetaminothiophenol. A mixture of 344 g. of *p*-chloronitrobenzene, 1290 g. of sodium sulfide monohydrate, and 5.7 l. of water was refluxed for seven hours. Some insoluble oil was removed by washing the solution with benzene. The solution was cooled to 7° with stirring in an ice-bath and treated with 700 cc. of acetic anhydride in one portion. After being stirred in the ice-bath for thirty minutes during which the temperature rose to 21° then subsided, the *p*-acetylthioacetanilide was removed by filtration and washed with water; weight, 398 g., m.p. 125–130°.

The crude acetyl derivative was refluxed on the steam-bath with 1200 cc. of alcohol and 196 g. of sodium hydroxide in 1900 cc. of water for seventy-five minutes. The solution was concentrated *in vacuo* to cloudiness, diluted to about 4 l. with water, and cooled to 5°. The insoluble material was removed by filtration through Celite and the filtrate acidified. The product was washed with water; yield, 196 g. (54%), m.p. 148–150°. In other runs the yields were consistently 54–57%.

The thiophenol was also prepared by reduction of 4,4′-dinitrodiphenyl disulfide with stannous chloride, acetylation of the tin complex, and reprecipitation of the product from alkaline solution. Several reprecipitations were necessary to remove the tin; yield, 36%, m.p. 140–147°. Reduction of acetylsulfanilyl chloride with zinc according to Zincke and Jörg (3) gave inconsistent results. The highest yield obtained was 53%. Very frequently, for no explainable reason, no thiophenol was obtained and sometimes 4,4′-diacetaminodiphenyl disulfide was isolated. Zincke and Jörg (3) give the m.p. of *p*-acetaminothiophenol as 140–145°.

2-Methyl-4-nitro-4′-acetaminodiphenyl sulfide. 2-Methyl-4-nitroiodobenzene was prepared in 71% yield, m.p. 100–103°, from 2-methyl-4-nitroaniline according to the general procedure of Hodgson and Walker (4).

To a solution of 45 g. of *p*-acetaminothiophenol in 360 cc. of alcohol containing 10.8 g. of reagent sodium hydroxide in 11 cc. of water was added 72 g. of 2-methyl-4-nitroiodobenzene. After being refluxed for one hour on the steam-bath, the solution was cooled in an ice-bath. The product was collected and washed with cold alcohol until no more color was removed; yield, 63.5 g. (77%), m.p. 120° (dec.). For analysis a sample was recrystallized from 95% alcohol, yellow crystals of unchanged m.p. The sulfide could not be crystallized from anhydrous solvents and appeared to be a hydrate.

Anal. Calc'd for $C_{15}H_{14}N_2O_3S \cdot H_2O$: C, 56.3; H, 5.0; N, 8.8.
Found: C, 56.5; H, 5.4; N, 8.8.

Similarly, the condensation of 1-iodo-4-nitronaphthalene (4) with *p*-acetaminothiophenol gave a 77% yield of *4-nitro-1-naphthyl 4-acetaminophenyl sulfide*, m.p. 206–208°.

Anal. Calc'd for $C_{18}H_{14}N_2O_3S$: C, 63.9; H, 4.1; N, 8.3.
Found: C, 64.3; H, 4.7; N, 8.1.

2-Carbamyl-4-nitro-4′-acetaminodiphenyl sulfide. To a warm solution of 36 g. of *p*-acetaminothiophenol in 940 cc. of 50% alcohol containing 8.8 g. of reagent sodium hydroxide was added a hot solution of 47 g. of 2-chloro-5-nitrobenzamide (5) in 470 cc. of alcohol in portions over a period of five minutes. After standing for fifteen minutes, the product was washed successively with alcohol and water; yield, 66 g. (93%) m.p. 262–264°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 264–266°.

Anal. Calc'd for $C_{15}H_{13}N_3O_4S$: N, 12.7. Found: N, 12.6.

2-Sulfamyl-4-nitro-4′-acetaminodiphenyl sulfide. This compound was prepared from 2-chloro-5-nitrobenzenesulfonamide (6) in the same manner as the corresponding 2-methyl compound. The crude product was filtered from the hot reaction mixture and leached with boiling alcohol; yield, 80%, m.p. 258–263°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 266–268°.

Anal. Calc'd for $C_{14}H_{13}N_3O_5S_2$: C, 45.8; H, 3.6; N, 11.4.
Found: C, 45.9; H, 4.0; N, 11.5.

2-Chloro-4-amino-4′-nitrodiphenyl sulfide. A mixture of 75 g. of 3,4-dichloronitrobenzene, 245 g. of sodium sulfide nonahydrate, and 615 cc. of water was refluxed for nineteen hours. After the addition of 62 g. of *p*-nitrochlorobenzene, refluxing was continued for fifteen

hours longer. The insoluble product was recrystallized from alcohol; yield, 59.3 g. (54%), m.p. 145–147°. Recrystallization from alcohol gave orange crystals, m.p. 146–148°.

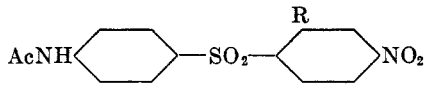
Anal. Calc'd for $C_{12}H_9ClN_2O_2S$: N, 10.0. Found: N, 9.8.

The procedure is patterned after that of Lantz for 4-amino-4'-nitrodiphenyl sulfide (7).

2-Methyl-4-nitro-4'-acetaminodiphenyl sulfone. A mixture of 63.5 g. of the corresponding sulfide, 550 cc. of acetic acid, and 150 cc. of 30% hydrogen peroxide was stirred in a bath at 50° for three hours, then heated on the steam-bath for two hours. The solution was evaporated to dryness *in vacuo* and the residue crystallized from alcohol. Additional compounds prepared in a similar manner are listed in table I.

2-Sulfamyl-4-amino-4'-acetaminodiphenyl sulfone. A mixture of 43.5 g. of 2-sulfamyl-4-nitro-4'-acetaminodiphenyl sulfone, 150 cc. of Cellosolve, and one teaspoon of Raney nickel was shaken with hydrogen at 2–3 atmospheres for 24 hours when reduction was complete. The mixture was heated on the steam-bath to dissolve the product, then filtered.

TABLE I



R	YIELD	M.P., °C.	SOLVENT	ANALYSES					
				Calc'd			Found		
				C	H	N	C	H	N
CH_3	80	160–163	Alc.			8.4			8.3
SO_2NH_2	78[a]	235–237	[b]			10.5			10.1
$CONH_2$	69[f]	254–256	[b]	49.7	3.6	11.6	49.4	3.7	11.5
Cl[g]	88[c]	[d]	Alc.	47.4	3.1	7.9	46.7	3.4	7.8
[e]	93[c]	199–200	Alc.	58.4	3.8	7.6	58.3	3.6	7.1

[a] The condensation of 2-chloro-5-nitrobenzenesulfonamide with sodium *p*-acetaminobenzenesulfinate in dilute alcohol (8) gave a product melting 80° low which was difficult to purify. [b] Methyl Cellosolve-water. [c] The product was isolated by dilution of the reaction mixture with water. [d] Partially melts at 115–120°, resolidifies and remelts at 178–180°. [e] 4-Nitro-1-naphthyl 4-acetaminophenyl sulfone. [f] Attempts to prepare this compound by the direct condensation of 2-chloro-5-nitrobenzamide and sodium *p*-acetaminobenzenesulfinate in dilute alcohol were unsuccessful. [g] The 2-chloro-4'-amino-4-nitrodiphenyl sulfide was acetylated with acetic anhydride in acetic acid, then hydrogen peroxide was added for the oxidation.

Dilution with alcohol gave 28 g. (70%) of product, m.p. 220–223°. Recrystallization of a sample from a large volume of alcohol gave nearly white crystals, m.p. 227–229°.

Anal. Calc'd for $C_{14}H_{15}N_3O_5S_2$: N, 11.4. Found: N, 11.6.

2-Sulfamyl-4,4'-diaminodiphenyl sulfone. A mixture of 28 g. of 2-sulfamyl-4-amino-4'-acetaminodiphenyl sulfone and 280 cc. of 6 *N* hydrochloric acid was refluxed for fifteen minutes. The solution was poured on ice and a slight excess of ammonia water. After acidification with acetic acid, the product was collected; yield, 21.5 g. (88%), m.p. 207–210° dec. Admixture with a sample prepared by an alternative method (8) gave no depression in m.p.

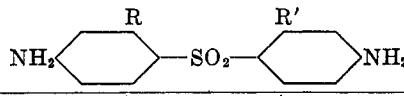
2-Carbamyl-4,4'-diaminodiphenyl sulfone. 2-Carbamyl-4-nitro-4'-acetaminodiphenyl sulfone (48 g.) was hydrogenated in Methyl Cellosolve in the same manner as described for the corresponding 2-sulfamyl derivative. The product crystallized out during reduction and could not be separated from the catalyst by the use of organic solvents. The solvent

was decanted, the precipitate was cooled with 250 cc. of water and then it was treated cautiously with 250 cc. of concentrated hydrochloric acid. After most of the nickel had dissolved, the mixture was refluxed for ten minutes and filtered hot. The filtrate was poured into ice and excess ammonia. The crude product was dissolved in 1 *N* hydrochloric acid, the solution was clarified with Norit, and again made basic with ammonia; yield, 27 g. (70%), m.p. 250° dec. This compound is insoluble in all the common organic solvents. For analysis a sample was continuously extracted with acetone for eight hours. The product was collected from the extract by filtration, white crystals, m.p. 250–252°.

Anal. Calc'd for $C_{13}H_{13}N_3O_3S$: C, 53.6; H, 4.5.
Found: C, 53.7; H, 4.6.

2,2'-Dichloro-4-amino-4'-nitrodiphenyl sulfide. From 100 g. of 3,4-dichloronitrobenzene, 100 g. of sodium sulfide nonahydrate, and 1500 cc. of water followed by 100 g. more of 3,4-

TABLE II



R	R'	YIELD[a]	M.P., °C.	SOLVENT	ANALYSES					
					Calc'd			Found		
					C	H	N	C	H	N
CH_3	H	65	150–153	Alc.	59.6	5.4	10.7	59.6	5.6	10.7
Cl	H	68	118–120	EtAc-C_6H_6	59.8[b]	4.7	7.8	59.8	5.0	7.5
[c]	H	84	261–262	Alc.	64.4	4.7	9.4	64.3	5.4	9.3
Cl	Cl	83	255–257	[d]			8.8			9.0

[a] These compounds were prepared by stannous chloride reduction of the corresponding nitro compounds (IV) in the same way as described for 2-nitro-2'-acetaminodiphenyl sulfone (1). [b] This compound is solvated with one molecule of benzene of crystallization. [c] 4-Amino-1-naphthyl 4-aminophenyl sulfone. The literature (11) records a m.p. of 265° for the compound prepared in a different manner. [d] Methyl Cellosolve and alcohol.

dichloronitrobenzene, was obtained 108 g. (66%) of orange crystals from alcohol, m.p. 136–138° in the same manner as described for 2-chloro-4-amino-4'-nitrodiphenyl sulfide.

Anal. Calc'd for $C_{12}H_8Cl_2N_2O_2S$: C, 45.7; H, 2.5; N, 8.9.
Found: C, 46.0; H, 3.1; N, 9.0.

The *acetyl* derivative formed hydrated yellow crystals from 95% alcohol, m.p. 133–135° dec.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2O_3S \cdot H_2O$: C, 44.8; H, 3.3; N, 7.6.
Found: C, 45.1; H, 3.5; N, 7.7.

2,2'-Dichloro-4-acetamino-4'-nitrodiphenyl sulfone. A solution of 20 g. of 2,2'-dichloro-4-amino-4'-nitrodiphenyl sulfide in 80 cc. of acetic acid and 9 cc. of acetic anhydride was heated on the steam-bath for thirty minutes, then it was diluted with 120 cc. of acetic acid. The solution was treated at 40–50° with 26 g. of potassium permanganate dissolved in 200 cc. of water in portions. After standing for thirty minutes, the manganese dioxide was dissolved by the addition of sodium bisulfite. After dilution with water, the product was collected; yield, 20.5 g. (82%), m.p. 181–184°. Recrystallization from alcohol gave white crystals, m.p. 182–184°.

Anal. Calc'd for $C_{14}H_{10}Cl_2N_2O_5S$: C, 43.2; H, 2.6; N, 7.2.
Found: C, 43.0; H, 3.3; N, 7.4.

3,4'-Dinitro-4-acetaminodiphenyl sulfone. 4-Acetamino-4'-nitrodiphenyl sulfone was

prepared according to Ferry, Buck, and Baltzly (9b) except that *p*-acetaminobenzenesulfinic acid and *p*-nitrochlorobenzene were condensed directly in the presence of the theoretical amount of sodium hydroxide. The over-all yield was the same.

To a stirred mixture of 50 g. of this sulfone and 200 cc. of concentrated sulfuric acid was added with ice-cooling 100 cc. of nitric acid (d = 1.42) at such a rate that the temperature was 10–15° (fifteen minutes). After removal of the ice-bath, the mixture was stirred for fifteen minutes longer, then poured on ice. The crude product was washed well with water, then leached with hot alcohol and recrystallized from Methyl Cellosolve; yield, 39 g. (68%) of yellow crystals, m.p. 194–195°.

Anal. Calc'd for $C_{14}H_{11}N_3O_7S$: N, 11.5. Found: N, 11.5.

3,4'-Dinitro-4-aminodiphenyl sulfone. A mixture of 38.8 g. of 3,4'-dinitro-4-acetaminodiphenyl sulfone, 388 cc. of 6 *N* hydrochloric acid, and 388 cc. of alcohol was refluxed for one hour, then cooled; yield, 32.8 g. (96%), m.p. 227–231°. Recrystallization from Methyl Cellosolve-water gave yellow crystals, m.p. 230–232°.

Anal. Calc'd for $C_{12}H_9N_3O_6S$: C, 44.6; H, 2.8; N, 13.0.
Found: C, 44.9; H, 3.3; N, 13.5.

3,4,4'-Triaminodiphenyl sulfone. To a solution of 330 g. of stannous chloride dihydrate in 660 cc. of concentrated hydrochloric acid and 620 cc. of alcohol was added 32.8 g. of 3,4'-dinitro-4-aminodiphenyl sulfone. The mixture was stirred for 75 minutes. At the end of twenty minutes solution had taken place and the temperature had risen to 60°. The solution was poured into 730 g. of sodium hydroxide in 730 cc. of water and excess ice. The solid was collected on a sintered-glass funnel. The filtrate was extracted with 800 cc. of butanol. The solid was dissolved in the butanol extract by warming on the steam-bath. After clarification withNorit, the solution was concentrated to about 400 cc. *in vacuo*, then cooled; yield, 18.6 g. (62%), m.p. 132–134°. Recrystallization from butanol gave nearly white crystals of the same m.p.

Anal. Calc'd for $C_{12}H_{13}N_3O_2S$: C, 54.8; H, 5.0; N, 16.0.
Found: C, 55.2; H, 5.4; N, 15.9.

4-Tosylamino-4'-nitrodiphenyl sulfide (VII). A solution of 310 g. of *p*-toluenesulfonyl chloride and 387 g. of 4-amino-4'-nitrodiphenyl sulfide (7) in 1220 cc. of reagent pyridine was allowed to stand for three hours. The mixture was warmed to dissolve the separated product. It was diluted with 2.4 l. of alcohol and 1.1 l. of water, then cooled in an ice-bath. The product was washed with water; yield, 572 g., m.p. 150–154°. From the filtrate was isolated an additional 43 g. (total 97%) of product, m.p. 148–152°. Recrystallization of a sample from alcohol gave yellow crystals, m.p. 154–155°.

Anal. Calc'd for $C_{19}H_{16}N_2O_4S_2$: C, 57.0; H, 4.0; N, 7.0.
Found: C, 57.1; H, 4.0; N, 7.0.

4-(N-Tosyl-n-propylamino)-4'-nitrodiphenyl sulfide (VIII). A mixture of 10 g. of 4-tosylamino-4'-nitrodiphenyl sulfide (VII), 14 cc. of 10% potassium hydroxide, 100 cc. of Methyl Cellosolve, and 2.5 cc. of *n*-propyl iodide was refluxed until the color changed from orange to yellow (two hours). The solution was then neutral. After the addition of 3.2 cc. of 10% potassium hydroxide and 0.6 cc. of *n*-propyl iodide, the solution was again refluxed until the color changed from orange to yellow (two hours). Water was added to turbidity and the solution was cooled in an ice-bath. The yellow product was collected and washed with cold 50% alcohol.

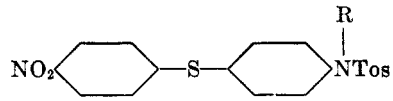
Similar alkylations are listed in Table III.

4-(N-Tosyl-n-propylamino)-4'-nitrodiphenyl sulfone (IX). A mixture of 37.5 g. of corresponding sulfide (VIII), 470 cc. of acetic acid, and 90 cc. of 30% hydrogen peroxide was stirred in a bath at 50° for three hours. The product was isolated by dilution with water. Similar oxidations are listed in Table IV.

4-(N-Tosyl-n-propylamino)-4'-aminodiphenyl sulfone (X). A mixture of 39.2 g. of the corresponding nitro sulfone (IX) and 150 cc. of Methyl Cellosolve was shaken with hydrogen at 2–3 atm. at 60–70° in the presence of Raney nickel until reduction was complete. The mixture was then heated on the steam-bath and enough Methyl Cellosolve was added

to dissolve the product which had separated. The filtered solution was diluted with water to turbidity and cooled. Similar reductions are listed in Table V.

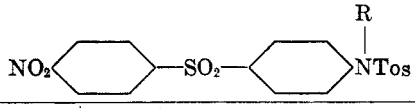
TABLE III



R[a]	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	91	112–113			5.9			5.7
iso-C_3H_7-	64[b]	150–151	59.8	5.0	6.3	59.6	5.5	5.9
CH_2=$CHCH_2$-	96	91–93	60.0	4.6	6.4	60.3	4.8	6.4
$C_6H_5CH_2$-	87	121–122	63.7	4.5	5.7	63.6	4.8	5.6
p-$NO_2C_6H_4CH_2$-	65	187–190	58.3	4.0	7.8	57.9	4.2	7.8
-$CH_2CONHC_6H_5$	56	185–187	60.8	4.4	7.9	60.7	4.7	7.8

[a] R = octyl, lauryl, and cetyl were oils which were carried to the next step without further purification. Numbers 1, 2, and 3 were recrystallized from alcohol. Numbers 4, 5, and 6 were recrystallized from Methyl Cellosolve-water. [b] The crude yield, m.p. 124–126°. Considerable loss was entailed in purification.

TABLE IV



R	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	98	156–158[c]			5.9			5.7
iso-C_3H_7-	44[a]	199–203[d]	55.7	4.7	5.9	55.8	5.0	5.6
CH_2=$CHCH_2$-	94	145–147[c]			5.9			5.7
C_8H_{17}-	84[b]	118–120[c]	59.7	5.9		59.6	5.9	
$C_{12}H_{25}$-	94[b]	100–102[e]	62.0	6.7	4.7	62.2	7.2	4.6
$C_{16}H_{33}$-	99[b]	96–98[e]			4.3			4.0
$C_6H_5CH_2$-	97	195–197[d]	59.8	4.3	5.4	60.2	4.7	5.4
p-$NO_2C_6H_5CH_2$-	92	183–185[d]	55.1	3.7	7.4	55.5	4.2	7.4
$HOCH_2CHOHCH_2$-	91	170–172[c]			5.5			5.3
H	90	174–176[c]			6.5			6.6

[a] The oxidation was carried out on crude sulfide, m.p. 124–126°. [b] Over-all yield including alkylation step. [c] Recrystallized from alcohol. [d] Recrystallized from Methyl Cellosolve-water. [e] Recrystallized from benzene-petroleum ether. These compounds were waxy solids.

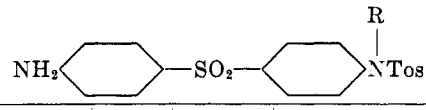
4-(N-Tosyl-N-allylamino)-4'-aminodiphenyl sulfone. To a solution of 18 g. of stannous chloride dihydrate in 18 cc. of concentrated hydrochloric was added 50 cc. of acetic acid

and 10 g. of the corresponding nitro sulfone (IX). The mixture was heated on the steam-bath for thirty minutes, then concentrated *in vacuo* until a solid began to separate. An excess of 40% sodium hydroxide and ice was added. The solid was dissolved in hot Methyl Cellosolve, the solution was clarified with Norit, then diluted with water to turbidity and cooled. The white crystals melted at 193–195°; yield, 7.1 g. (76%).

Anal. Calc'd for $C_{22}H_{22}N_2O_4S_2$: C, 59.7; H, 5.0; N, 6.3.
Found: C, 59.4; H, 5.6; N, 5.9.

4-(N-Tosyl-γ-chloro-β-hydroxypropylamino)-4'-nitrodiphenyl sulfone (XIV). A mixture of 47.4 g. of XII, 0.35 cc. of pyridine, and 14.2 cc. of epichlorohydrin was heated on the steam-bath for one hour. The oil was heated with alcohol when it crystallized. After cool-

TABLE V



R	YIELD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
n-C_3H_7-	96	221–222[d]	59.5	5.5	6.3	59.2	5.2	6.3
iso-C_3H_7-	65	243–245[d]	59.5	5.5	6.3	59.0	5.6	6.0
C_8H_{17}-	99	88–90[e]			5.5			5.7
$C_{12}H_{25}$-	93	90–92[f]	65.2	7.4	4.9	65.2	7.7	4.9
$C_{16}H_{33}$-	94	48–50[f]	67.2	8.0	4.5	67.4	8.0	4.9
$C_6H_5CH_2$-	65	202–204[d]			5.7			5.7
p-$NH_2C_6H_4CH_2$-	72	125–127[e]			8.3			8.3
$HOCH_2CHOHCH_2$-	92	[b]			5.9			6.2
$C_5H_{10}NCH_2CHOHCH_2$-	66	75–78[c]	61.8	6.2	7.2	61.5	6.8	7.3
[a]	90	236–238						

[a] Reduction of 4-nitro-4'-acetaminodiphenyl sulfone. This method was found superior to the stannous chloride reduction described by Raiziss, *et al.* (9a). They record m.p. 242–243° and crude yield, 66%. [b] Melts at 165°, resolidifies and remelts at 185° when crystallized from alcohol. [c] Contains one-half molecule benzene of crystallization. Other solvents give an oil. Also obtained in 86% yield by stannous chloride reduction. [d] Recrystallized from Methyl Cellosolve. [e] Recrystallized from alcohol. [f] Recrystallized from benzene.

ing, the mixture was filtered and the product washed with alcohol; yield, 47.5 g. (85%), of yellow crystals, m.p. 165–167°.

Anal. Calc'd for $C_{22}H_{21}ClN_2O_7S_2$: N, 5.3. Found: N, 5.2.

4-(N-Tosyl-β,γ-oxidopropylamino)-4'-nitrodiphenyl sulfone (XV). To a solution of 46 g. of XIV in 460 cc. of Methyl Cellosolve containing a trace of phenolphthalein and heated on the steam-bath was added a 10% solution of reagent sodium hydroxide in Methyl Cellosolve over a period of ten minutes until a permanent color was obtained (35 cc.). The mixture was heated five minutes more, then diluted with water; yield, 33.3 g. (76%), m.p. 137–140°. Recrystallization from Methyl Cellosolve-water gave nearly white crystals, m.p. 147–149°.

Anal. Calc'd for $C_{22}H_{20}N_2O_7S_2$: C, 54.2; H, 4.1.
Found: C, 54.4; H, 4.5.

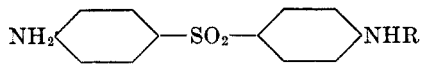
4-(N-Tosyl-β-hydroxy-γ-piperidinopropylamino)-4'-nitrodiphenyl sulfone (XVI). A mixture of 40 g. of XV and 40 cc. of piperidine was heated on the steam-bath to 80° with mix-

ing when the reaction proceeded with heat evolution and formation of a brown solution. After five minutes, during which time the temperature was not allowed to go above 100°, the oil was dissolved in alcohol and diluted with an equal volume of ether. After being cooled, the mixture was filtered and the product washed with alcohol-ether; yield, 37.5 g. (80%) of yellow crystals, m.p. 139–140°.

Anal. Calc'd for $C_{27}H_{31}N_3O_7S_2$: N, 7.3. Found: N, 7.7.

4-(N-Tosyl-β,γ-dihydroxypropylamino)-4'-nitrodiphenyl sulfide. A mixture of 10 g. of VII, 0.1 cc. of pyridine, and 2.5 cc. of glycidol (10) was heated on the steam-bath with mixing for thirty minutes. The temperature was maintained at 99–105° by removing the tube from the steam-bath when necessary. The oil was crystallized from dilute alcohol; yield, 9.2 g. (78%), m.p. 110–115°. Recrystallization from benzene gave yellow crystals, m.p. 120–122°.

TABLE VI



R	METHOD*	TIME (hours)	YIELD, %	M.P., °C.	SOLVENT	ANALYSES					
						Calc'd			Found		
						C	H	N	C	H	N
n-C_3H_7-	A	2	96	200–202[d]	Me Cell.-H_2O	62.2	6.2	9.7	62.2	6.6	9.7
	B[c]	20	80								
CH_2=$CHCH_2$-	B	2	80	154–156[d]	Alc.-H_2O			9.7			9.3
C_8H_{17}-	B	18	95	184–186[a]	MeOH-Et_2O	55.6	7.0	6.5	55.2	7.5	6.5
$C_{12}H_{25}$-	B	2	80	165–167	Alc.	69.2	8.7	6.7	68.9	9.4	6.8
$C_{16}H_{33}$-	A	17	86	159–161	Me Cell.-Alc.	71.2	9.4	5.9	71.0	9.0	6.0
$CH_2OHCHOHCH_2$-	C	3	81	[b]							
$C_5H_{10}NCH_2CHOHCH_2$-	C	2.5	78	150–155	Alc.-H_2O	61.7	7.0	10.8	62.0	7.4	10.8

* (A) Concentrated sulfuric acid (2 cc./g.) at room temperature. Poured on ice and excess ammonium hydroxide; (B) Refluxed with 15 cc. of 9 *N* HCl per g.; worked up as in A; (C) Refluxed with 10 cc. of 9 *N* H_2SO_4 per g., worked up as in A. [a] The dihydrochloride, which crystallized from the reaction mixture. [b] Light colored oil which could not be crystallized. [c] The corresponding isopropyl compound could not be prepared by any of the three methods. [d] This compound has been mentioned in the biological literature a number of times (13), but no description of its preparation or chemical properties has appeared.

Anal. Calc'd for $C_{22}H_{22}N_2O_6S$: C, 55.7; H, 4.7; N, 5.9.
Found: C, 55.6; H, 5.0; N, 5.9.

Glycidol could also be condensed with the sulfone, XII, in the same manner, but the yields were only 40–50% and in one run the reaction got out of control with a rise in temperature to 150° and the formation of a black tar.

4-Acetamino-4'-benzylaminodiphenyl sulfone. A mixture of 29 g. of 4-acetamino-4'-aminodiphenyl sulfone, 20 cc. of benzaldehyde, 2 g. of anhydrous sodium acetate, and 150 cc. of Methyl Cellosolve was heated on the steam-bath for thirty minutes with occasional shaking. The solution was hydrogenated at 2–3 atm. using 400 mg. of palladium chloride as a catalyst until a 20% excess of hydrogen was absorbed (100 minutes). The product, mixed with catalyst, was collected and recrystallized from Methyl Cellosolve; yield, 11 g. (29%), m.p. 230–240°. Further recrystallization gave buff-colored crystals, m.p. 242–247°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3S$: N, 7.4. Found: N, 7.1.

4-Benzylamino-4'-aminodiphenyl sulfone. A mixture of 8 g. of 4-acetamino-4'-benzylaminodiphenyl sulfone and 80 cc. of, 6 *N* hydrochloric acid was refluxed for ten minutes, the solution was clarified by filtration and the filtrate added to excess ammonia water and ice.

After standing overnight to complete crystallization, the product was recrystallized from alcohol-water; yield, 5.3 g. (75%), m.p. 172–174°. Further recrystallization gave buff crystals, m.p. 175–177° (uncorr.).

Anal. Calc'd for $C_{19}H_{18}N_2O_2S$: C, 67.4; H, 5.4; N, 8.3.
Found: C, 67.7; H, 6.1; N, 8.6.

After this work was completed, Jackson (12) prepared this compound in another manner and reported the m.p. 188.5–189° (corr.).

SUMMARY

Eight N-substituted and seven C-substituted derivatives of 4,4′-diaminodiphenyl sulfone have been synthesized by general methods for chemotherapeutic testing.

PEARL RIVER, N. Y.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

SULFONES. III. 4-AMINOPHENYL ALKYL SULFONES

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It has been observed by Fourneau and co-workers (1) that 4-aminophenyl methyl sulfone has chemotherapeutic activity and that activity decreased as the length of the aliphatic side chain was increased. A number of 4-aminophenyl alkyl sulfones with functional groups in the alkyl residue have now been synthesized in order to determine their effect on activity.[1]

Condensation of sodium 4-acetaminobenzenesulfinate with ethylene chlorohydrin resulted in 4-acetaminophenyl β-hydroxyethyl sulfone. The hydroxyl group was converted to the *p*-toluenesulfonic ester with *p*-toluenesulfonyl chloride in pyridine. The tosylate group was very reactive and was readily replaced by such amines as diethylamine, piperidine or N-carbethoxypiperazine. The tosylate group also reacted smoothly with potassium phthalimide or sodium iodide to give 4-acetaminophenyl β-phthalimidoethyl sulfone and 4-acetaminophenyl β-iodoethyl sulfone, respectively. In all the above compounds the acetyl group was removed by short hydrolysis with boiling hydrochloric acid.

Similarly, by the condensation of sodium 4-acetaminobenzenesulfinate with propyl iodide, allyl bromide, octyl bromide, lauryl bromide, 4-nitrobenzyl chloride, 6-bromo-1-phthalimidohexane,β -bromopropionic acid, and ethyl α-bromocaproate followed by reduction and/or hydrolysis additional alkyl sulfones were synthesized.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

4-Acetaminophenyl β-hydroxyethyl sulfone. To a solution of 140 g. of 4-acetaminobenzenesulfinic acid in 540 cc. of water containing 36 g. of reagent sodium hydroxide was added 108 cc. of ethylene chlorohydrin. After being heated on the steam-bath for three hours, the solution was cooled in an ice-bath and the product collected on a filter. The filtrate and water washings were made just alkaline with 10% sodium hydroxide and heated on the steam-bath for three hours, 10% alkali being added at intervals to keep the solution barely alkaline; total yield, 118 g. (54%), m.p. 187–190°. Recrystallization of a sample from methanol-acetone gave white crystals, m.p. 192–193°.

Anal. Calc'd for $C_{10}H_{13}NO_4S$: C 49, 3; H, 5.4; N, 5.8.
Found: C, 49.0; H, 5.9; N, 6.0.

4-Acetaminophenyl β-(p-toluenesulfonyloxy)ethyl sulfone. To an ice-cold solution of 203 g. of *p*-toluenesulfonyl chloride in 950 cc. of reagent pyridine was added 225 g. of 4-acetaminophenyl β-hydroxyethyl sulfone. After two hours at 0°, the mixture was poured into a large volume of ice-water; yield, 290 g. (79%), m.p. 100–103°. Recrystallization from alcohol gave white crystals, m.p. 105–107°.

Anal. Calc'd for $C_{17}H_{19}NO_6S_2$: N, 3.5. Found: N, 3.4.

4-Acetaminophenyl β-piperidinoethyl sulfone. To 35 g. of the above tosyl sulfone was

[1] The biological studies will be reported elsewhere.

added 22 cc. of piperidine. Considerable heat was evolved. After being heated on the steam-bath for two hours, the oil was treated with water when it quickly solidified; yield, 28.7 g. (99%), of a hydrate, m.p. 110° (gas evolution). Recrystallization from benzene gave anhydrous white crystals, m.p. 121–123°.

Anal. Calc'd for $C_{15}H_{22}N_2O_3S$: N, 9.0. Found: N, 9.1.

Similarly *4-acetaminophenyl β-diethylaminoethyl sulfone* was prepared in 99% yield, m.p. 100–102° from water.

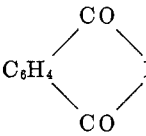
Anal. Calc'd for $C_{14}H_{22}N_2O_3S$: N, 9.4. Found: N, 9.3.

Walker (2) has synthesized this compound in a different manner and recorded that it formed a hydrate, m.p. 94–96°.

By condensation of the tosylate with N-carbethoxypiperazine in boiling alcohol for one hour a 92% yield of *4-acetaminophenyl β-(N-carbethoxypiperazinoethyl) sulfone* was ob-

TABLE I

CH_3CONH–C$_6$H$_4$–SO_2R

R	REFLUX (hours)	YIELD %	M.P. °C.	ANALYSES					
				Calc'd			Found		
				C	H	N	C	H	N
n-C_3H_7-[f]	2	64	125–127[a]	54.8	6.3	5.8	54.5	6.5	6.1
CH_2=$CHCH_2$-[e]	½	67	113–115[a]			5.8			5.5
	20	87	175–177[c]			6.5			6.7
$-CH_2CH_2COOH$	17	42	182–183[d]	48.7	4.8	5.2	48.6	5.3	5.1
$-CH_2C_6H_4NO_2$	⅙	70	246–250[c]			8.4			8.2
$C_4H_9CHCO_2Et$ |	2.5	67	102–104[b]	56.3	6.8	4.1	55.7	6.8	4.4

[a] Recrystallized from ethyl acetate-petroleum ether. [b] Recrystallized from dilute alcohol. [c] Recrystallized from Methyl Cellosolve-water. [d] Reaction run in water, acidified, and product recrystallized from water. [e] This compound has been recently reported to melt at 98–100° (4). [f] Recently reported (6) to melt at 129°.

tained by evaporation of the solvent, solution in water and basification with 10% sodium hydroxide; white crystals from ethyl acetate-petroleum ether, m.p. 127–128°.

Anal. Calc'd for $C_{17}H_{25}N_3O_5S$: N, 11.0. Found: N, 11.0.

4-Acetaminophenyl β-phthalimidoethyl sulfone. A mixture of 5 g. of 4-acetaminophenyl β-(*p*-toluenesulfonyloxy)ethyl sulfone, 2.5 g. of potassium phthalimide, and 5 cc. of *n*-propyl alcohol was heated on the steam-bath for one hour. Dilution with water gave 4.5 g. (96%) of product, m.p. 216–221°.

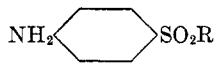
Goldberg (3) has recorded a m.p. of 228–230° for this compound prepared in a different manner.

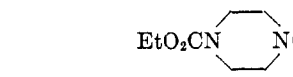
4-Acetaminophenyl β-iodoethyl sulfone. A mixture of 50 g. of 4-acetaminophenyl β-(*p*-toluenesulfonyloxy)ethyl sulfone, 38 g. of sodium iodide, and 380 cc. of acetone was refluxed for fifteen hours during which time sodium *p*-toluenesulfonate separated. The mixture was poured into about four volumes of water containing some sodium bisulfite. The product was collected; yield, 38.5 g. (87%), m.p. 188–190°. Recrystallization from acetone gave white crystals, m.p. 192–193°.

Anal. Calc'd for $C_{10}H_{12}INO_3S$: N, 4.0. Found: N, 3.9.

4-Acetaminophenyl n-propyl sulfone. To a solution of 2.0 g. of reagent sodium hydroxide in 2 cc. of water was added 50 cc. of alcohol and 10 g. of *p*-acetaminobenzenesulfinic acid. The solution was refluxed with 7.5 cc. of *n*-propyl iodide. Dilution with water gave an oil which was extracted with ethyl acetate. The extracts, washed with aqueous sodium bicarbonate and dried with magnesium sulfate, were evaporated to dryness *in vacuo* and the residue triturated with benzene. Other compounds prepared similarly are listed in Table I.

TABLE II



R	METHOD	M.P., °C.	ANALYSES					
			Calc'd			Found		
			C	H	N	C	H	N
$HOCH_2CH_2$-	B	210–213 dec.[i]			5.9			6.0
$Et_2NCH_2CH_2$-[e]	C	102–104[j]	56.3	7.9	10.9	56.5	7.8	10.4
$C_5H_{10}NCH_2CH_2$-	C	127–129[j]	58.3	7.5	10.4	58.3	6.6	10.8
	C	96–98 dec.[a]	50.2	7.0	11.7	50.6	7.1	11.4
$NH_2CH_2CH_2$-	D	235–238 dec.[b]						
ICH_2CH_2-	A[c]	206–208 dec.[k]			4.0			4.4
$CH_3CH_2CH_2$-[f]	A	215–217 dec.[l]			6.0			6.3
CH_2=$CHCH_2$-[g]	A	212–213 dec.[l]	46.3	5.2	6.0	46.7	5.4	6.2
n-C_8H_{17}-[h]	E	96–98[k]	62.4	8.6	5.2	63.0	8.8	5.3
n-$C_{12}H_{25}$-	E	105–107[k]			4.3			4.5
$NH_2(CH_2)_6$-	D	217–220 dec.[l]			8.5			9.0
$-CH_2CH_2COOH$[f]	A	222–224 dec.[m]	40.7	4.6	5.5	41.1	4.7	5.3
$-CH_2C_6H_4NH_2$	[d]	215–216 dec.[n]	59.6	5.4	10.7	59.9	5.8	10.6
C_4H_9-$CHCOOEt$	F	148–150 dec.[o]	50.2	6.6	4.2	50.5	6.3	4.5
CH_3-	A	236–237 dec.[m]			6.8			6.9

[a] Monohydrate from water. [b] Obtained in 95% yield by modification of the procedure of Goldberg (3) who recorded a m.p. of 238–240°. [c] An equal volume of alcohol was used to aid solubility during the hydrolysis which required one hour. [d] The nitro group was reduced with simultaneous removal of the acetyl group using stannous chloride and the free base isolated as previously described for similar compounds in paper I of this series. [e] Walker (2) has described the dihydrochloride of this compound. [f] The free base has been synthesized in a different manner (5). [g] The free base has been described (4). [h] Smirnova (6) reported a m.p. of 197–198°, a probable misprint. [i] Methanol-ethyl acetate. [j] Benzene. [k] Methanol. [l] Methanol-ether. [m] 12 *N* Hydrochloric acid. [n] Aqueous Methyl Cellosolve. [o] Chloroform-ether.

4-Aminophenyl alkyl sulfones. The acetyl group was removed by boiling with 10 cc./g. of 6 *N* hydrochloric acid for fifteen minutes. The compounds obtained are listed in Table II. The yields were 80–95% with the following modifications in procedure.

A. The hydrochloride crystallized on cooling the reaction mixture.

B. The reaction mixture was evaporated to dryness *in vacuo* and the hydrochloride salt triturated with acetone.

C. The reaction mixture was evaporated to dryness *in vacuo*, the residue was dissolved in water and poured into an excess of ammonia water and ice. The free base was collected.

D. The acetyl and phthalyl groups were removed by boiling with 10 *N* hydrochloric acid for twelve hours. The phthalic acid was removed after cooling and the filtrate was worked up as in B.

E. The crude non-crystalline acetyl derivative was hydrolyzed by boiling with 10 cc. of 6 *N* hydrochloric acid and 5 cc. of alcohol per gram. The hydrochloride separated on cooling. It was dissolved in Methyl Cellosolve, made basic with ammonia water, and diluted with water.

F. The acetyl group was removed by refluxing with absolute ethanol saturated with hydrogen chloride for ninety minutes. Solvent was removed *in vacuo* and the residue crystallized from chloroform-ether.

SUMMARY

Fifteen 4-aminophenyl alkyl sulfones have been synthesized for chemotherapeutic testing.

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[CONTRIBUTION FROM THE LEDERLE LABORATORIES DIVISION, AMERICAN CYANAMID CO.]

SULFONES. IV. α,β-UNSATURATED 4-AMINOPHENYL SULFONES

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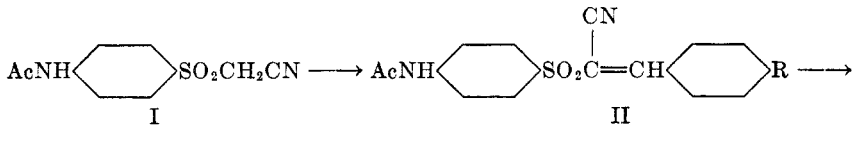
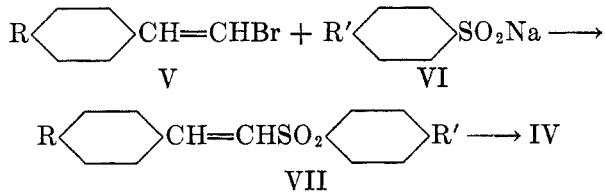
α,β-Unsaturated ketones have been shown by Geiger and Conn (1) to have antibiotic activity, attributed to the ease with which the double bond added thiols. Since the sulfone group can also activate a double bond towards addition of thiols (2), it seemed of interest to synthesize some α,β-unsaturated sulfones in order to examine their possible chemotherapeutic activity.[1]

Condensation of benzaldehyde, 4-acetaminobenzaldehyde or 4-hydroxybenzaldehyde with 4-acetaminobenzenesulfonylacetonitrile (I)[2] led to the unsaturated



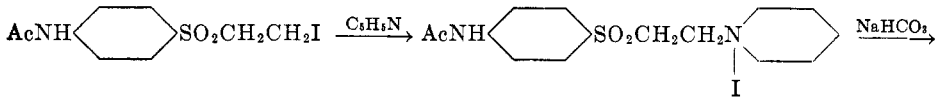
sulfones, II. Short acid hydrolysis removed the acetyl group with the formation of III, but extended hydrolysis to remove the cyano group to form IV led to regeneration of the aldehyde by cleavage.

Compounds of type IV were successfully synthesized by the condensation of β-bromostyrene or 4-nitro-β-bromostyrene (V) with sodium benzenesulfinate or sodium 4-acetaminobenzenesulfinate (VI), forming VII, followed by reduction and/or hydrolysis.

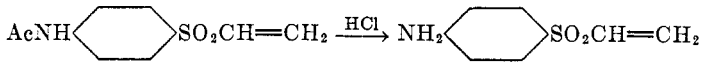


[1] The biological studies will be reported elsewhere. [2] This method is a modification of that used by Tröger and Prochnow (3) for the condensation of phenylsulfonylacetonitrile with aromatic aldehydes. 4-Acetaminophenylsulfonylacetamide, 4-acetaminophenylsulfonylacetic acid or its ethyl ester would not condense with benzaldehyde under a variety of conditions. However, salicylaldehyde readily condensed with ethyl 4-acetaminophenylsulfonylacetate in the presence of piperidine to form 3-(*p*-acetaminophenylsulfonyl)coumarin in excellent yield. Methyl β-(carbomethoxymethylsulfonyl)propionate reacted in the same manner. A similar condensation between ethyl phenylsulfonylacetate and salicylaldehyde has been described by Tröger and Lux (4).

When 4-acetaminophenyl β-iodoethyl sulfone (VIII) (5) was refluxed in pyridine, a pyridinium iodide (IX) formed. Stirred with aqueous sodium bicarbonate, the pyridinium iodide eliminated pyridine to yield 4-acetaminophenyl



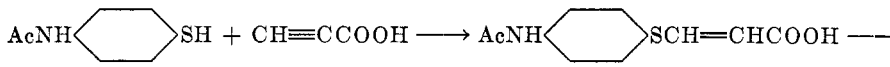
VIII IX



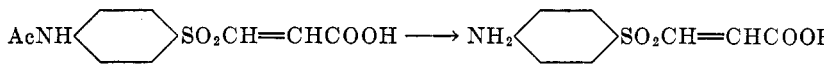
X XI

vinyl sulfone (X). Short acid hydrolysis gave the desired unsaturated sulfone XI.

Although 4-acetaminobenzenesulfinic acid did not add to propiolic acid in basic solution, 4-acetaminothiophenol (XII) rapidly reacted to give XIII in excellent yield. The thio acid, XIII, was smoothly oxidized with hydrogen peroxide to the sulfonylacrylic acid, XIV, which was hydrolyzed to the amino acid, XV. Since the benzylamide of XV was also desired it was obtained from the benzylamide of β-(4-acetaminophenylthio)acrylic acid (XIII) by oxidation, then short acid hydrolysis.



XII XIII



XIV XV

4-Acetaminothiophenol also added to the triple bond of acetylene dicarboxylic acid or its ethyl ester. Saponification of the ester gave an acid, lower-melting, but isomeric to that obtained by direct addition of the thiophenol to acetylene dicarboxylic acid. The lower-melting acid is assumed to be 4-acetaminophenylthiomaleic acid and the higher-melting acid the corresponding derivative of fumaric acid. Neither thioacid nor the ester yielded an isolatable sulfone on oxidation with hydrogen peroxide under conditions which smoothly oxidized β-(4-acetaminophenylthio)acrylic acid (XIII) to its sulfone, XIV.

Acknowledgment. The authors wish to thank Mr. Louis Brancone and his staff for the microanalyses.

EXPERIMENTAL

4-Acetaminophenylsulfonylacetonitrile (I). A mixture of 52 g. of 4-acetaminobenzenesulfinic acid, 250 cc. of alcohol, 60 cc. of water, and 18 cc. of concentrated ammonia water was heated to boiling to complete solution. After the addition of 15.6 cc. of chloroacetonitrile, the solution was refluxed for fifteen hours during which part of the product separated. The cooled mixture was filtered and the product washed with alcohol, then water; yield, 41.5 g. (67%), m.p. 265–267°. The average yield was 62% in six runs.

Walker (6) recorded the m.p. 263–264° and yield of 92% for this compound using the sodium salt in 75% alcohol. We were not able to isolate any of the product by this procedure.

Ethyl 4-acetaminophenylsulfonylacetate. A mixture of 20 g. of 4-acetaminobenzenesulfinic acid, 100 cc. of alcohol, 13 cc. of ethyl chloroacetate, and a solution of 4 g. of reagent sodium hydroxide in 4 cc. of water was refluxed for two hours, then diluted to turbidity with water and cooled in an ice-bath; yield, 20.5 g. (72%), m.p. 122–125°. Recrystallization from dilute alcohol gave white crystals, m.p. 124–125°.

Anal. Calc'd for $C_{12}H_{15}NO_5S$: C, 50.5; H, 5.3; N, 4.9.
Found: C, 50.1; H, 5.3; N, 5.2.

Goldberg and Besley (7) have described a less convenient procedure for preparing this compound. They employed the anhydrous sodium sulfinate in xylene and obtained a yield of 70%, m.p. 122–124°.

4-Acetaminophenylsulfonylacetic acid. To a mixture of 35 g. of 4-acetaminobenzensulfinic acid, 19 g. of chloroacetic acid, and 150 cc. of water was added cautiously 20.2 g. of anhydrous sodium carbonate. After being heated on the steam-bath for three hours, the solution was cooled and acidified; yield, 42.7 g. (95%), m.p. 214–216° dec. Recrystallization of a sample from water gave white crystals, m.p. 215–216° dec.

Anal. Calc'd for $C_{10}H_{11}NO_5S$: N, 5.4. Found: N, 5.6.

Goldberg and Besley (7) obtained a yield of 53%, m.p. 206–208°d., with the use of sodium hydroxide as the base for condensation, whereas Walker (6) employed the less convenient sodium 4-acetaminobenzenesulfinate and obtained an 80% yield, m.p. 216–217°d.

α-(4-Acetaminophenylsulfonyl)cinnamonitrile (II, R = H). A mixture of 7.5 g. of 4-acetaminophenylsulfonylacetonitrile, 3.3 cc. of benzaldehyde, 150 cc. of alcohol, 70 cc. of water, and 0.75 cc. of piperidine was heated on the steam-bath until solution took place, then it was allowed to stand one hour. Dilution with water gave 7.4 g. (73%) of white crystals, m.p. 189°. Recrystallization from dilute alcohol raised the m.p. to 193°.

Anal. Calc'd for $C_{17}H_{14}N_2O_3S$: C, 62.6; H, 4.3; N, 8.6.
Found: C, 62.7; H, 4.7; N 8.7.

Similarly, *4-acetamino-α-(4-acetaminophenylsulfonyl)cinnamonitrile* (II, R = AcNH) was prepared in 57% yield from 4-acetaminobenzaldehyde (8); white crystals from dilute alcohol, m.p. 266–267°.

Anal. Calc'd for $C_{19}H_{17}N_3O_4S$: C, 59.6; H, 4.5; N, 11.0.
Found: C, 59.3; H, 4.2; N, 10.8.

Also, *4-hydroxy-α-(4-acetaminophenylsulfonyl)cinnamonitrile* (II, R = OH) was prepared in 82% yield, m.p. 247–255°. Recrystallization from dilute alcohol raised the m.p. to 276–277°.

Anal. Calc'd for $C_{17}H_{14}N_2O_4S$: C, 59.7; H, 4.1.
Found: C, 60.0; H, 4.5.

α-(4-Aminophenylsulfonyl)cinnamonitrile (III, R = H). A mixture of 30 g. of α-(4-acetaminophenylsulfonyl)cinnamonitrile (II, R = H), 90 cc. of water, 150 cc. of acetic acid, and 60 cc. of concentrated sulfuric acid was refluxed for twenty minutes, then cooled and poured into ice and excess ammonia. The crude product was recrystallized from 50% alcohol; yield, 22 g. (85%), m.p. 145–147°. Further recrystallization raised the m.p. to 146–147°.

Anal. Calc'd for $C_{15}H_{12}N_2O_2S$: C, 63.3; H, 4.3; N, 9.9.
Found: C, 63.4; H, 4.9; N, 9.6.

4-Amino-α-(4-aminophenylsulfonyl)cinnamonitrile (III, R = NH_2). From 35 g. of II (R = AcNH), 105 cc. of water, 175 cc. of acetic acid, and 70 cc. of concentrated sulfuric acid was obtained 23.2 g. (85%) of crude product, m.p. 198–201°, as in the preceding experiment. Recrystallization by solution in a mixture of alcohol and acetone, then dilution with water raised the m.p. to 206–207°.

Anal. Calc'd for $C_{15}H_{13}N_3O_2S$: N, 14.0. Found: N, 13.8.

4-Hydroxy-α-(4-aminophenylsulfonyl)cinnamonitrile (III, R = OH). A mixture of 30 g. of II (R = OH), 90 cc. of water, 150 cc. of acetic acid, and 60 cc. of conc'd sulfuric acid was refluxed exactly five minutes. The cooled solution was poured on excess ice and 400 cc.

of 28% ammonia water. The mixture was acidified with acetic acid, the product collected and washed with water. Recrystallization from dilute alcohol gave 20.5 g. (81%) of solid, m.p. 200–203°. Further recrystallization from dilute alcohol raised the m.p. to 203–205°.

Anal. Calc'd for $C_{15}H_{12}N_2O_3S$: C, 60.0; H, 4.0; N, 9.3.
Found: C, 60.4; H, 4.0; N, 9.6.

A longer reflux period led to mixtures.

Methyl β-(carbomethoxymethylsulfonyl)propionate. To a stirred solution of 95 g. of methyl β-(carbomethoxymethylthio)propionate, prepared in 97% yield according to a procedure described for the corresponding ethyl ester (9), in 500 cc. of acetic acid was added dropwise a solution of 230 g. of potassium permanganate in 2300 cc. of water over a period of thirty minutes maintaining the temperature just below 50° by adequate cooling. The manganese dioxide was dissolved by the addition of sodium bisulfite. The oil was removed by two extractions with ethyl acetate. Washed with aqueous sodium bicarbonate and water, the combined extracts were evaporated to dryness *in vacuo*. The residual oil solidified on standing, m.p. 53–57°; yield, 93.6 g. (85%). Recrystallization from heptane-benzene gave white crystals, m.p. 55–56°.

Anal. Calc'd for $C_7H_{12}O_6S$: C, 37.5; H, 5.4.
Found: C, 38.2; H, 5.8.

3-(β-Carbomethoxyethylsulfonyl)coumarin. To a mixture of 10 g. of methyl β-(carbomethoxymethylsulfonyl)propionate and 5.3 cc. of salicylaldehyde cooled to 0° in an ice-salt bath was added 0.5 cc. of piperidine. After five hours at 3°, the solid was triturated with alcohol; yield, 11.5 g. (87%), m.p. 153–156°. Recrystallization from alcohol raised the m.p. to 154–155°.

Anal. Calc'd for $C_{13}H_{12}O_6S$: C, 52.7; H, 4.1.
Found: C, 52.9; H, 3.7.

Attempts to convert this compound to 2-hydroxy-ω-(β-carboxyethylsulfonyl)styrene according to the procedure used by Tröger and Bolte (10) for a similar compound were unsuccessful

3-(β-Carboxyethylsulfonyl)coumarin. To a solution of 12 g. of the above ester in 25 cc. of acetic acid was added 120 cc. of 50% sulfuric acid. After being heated on the steam-bath for thirty minutes during which time part of the product separated, the mixture was diluted with ice and water; yield, 10.7 g. (94%) of white crystals, m.p. 195–196°. Recrystallization from methanol did not change the m.p.

Anal. Calc'd for $C_{12}H_{10}O_6S$: C, 51.1; H, 3.5.
Found: C, 51.6; H, 3.3.

Similarly, *3-(β-carbomethoxyethylsulfonyl)-7-hydroxycoumarin* was prepared from 2,4-dihydroxybenzaldehyde in 15% yield, m.p. 210–212°. Hydrolysis gave 3-(β-carboxyethylsulfonyl)-7-hydroxycoumarin in 79% yield, m.p. 243–245°d. Recrystallization from dilute alcohol raised the m.p. to 246–247°d.

Anal. Calc'd for $C_{12}H_{10}O_7S$: C, 48.3; H, 3.4.
Found: C, 48.7; H, 3.9.

3-(4-Acetaminophenylsulfonyl)coumarin. A hot solution of 5.8 g. of ethyl 4-acetaminophenylsulfonylacetate and 2.6 cc. of salicylaldehyde in 25 cc. of absolute alcohol was cooled to 25° and treated with 0.6 cc. of piperidine. In a few minutes a solid began to separate. After one hour the solid was washed with alcohol; yield, 7.5 g. (100%), m.p. 270–276°. Recrystallization from pyridine raised the m.p. to 275–277°.

Anal. Calc'd for $C_{17}H_{13}NO_5S$: C, 59.5; H, 3.8; N, 4.1.
Found: C, 59.7; H, 4.5; N, 4.6.

3-(4-Aminophenylsulfonyl)coumarin. A mixture of 24 g. of the preceding acetyl derivative, 120 cc. of acetic acid, and 120 cc. of 50% sulfuric acid was heated on the steam-bath for fifty minutes during which time solution took place and a solid separated. The mixture was poured on ice and 480 cc. of 28% ammonia water. After digestion on the steam-bath for thirty minutes, the mixture was cooled, the product was collected and washed with water;

yield, 19.5 g. (93%), m.p. 203–205°. Recrystallization from dilute acetone raised the m.p. to 208–210°.

Anal. Calc'd for $C_{15}H_{11}NO_4S$: N, 4.6. Found: N, 4.4.

4-Acetaminophenyl ω-styryl sulfone. A mixture of 50 g. of 4-acetaminobenzenesulfinic acid, 49 g. of ω-bromostyrene, 150 cc. of Methyl Cellosolve, 50 cc. of water, 2.5 g. of sodium iodide, and 14 g. of anhydrous sodium carbonate was refluxed for thirty hours, then diluted with several volumes of water and extracted twice with ethyl acetate. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. The residue was crystallized from benzene-heptane; yield, 33 g., m.p. 140–158°. Recrystallization from dilute alcohol gave 23.5 g. (31%) of product, m.p. 162–165°. Further recrystallization from dilute alcohol raised the m.p. to 168–170°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: C, 63.8; H, 5.0; N, 4.7.
Found: C, 63.7; H, 5.8; N, 4.70.

4-Nitro-ω-styryl 4'-acetaminophenyl sulfone. A mixture of 29.5 g. of a crude mixture of *cis* and *trans* isomers of 4-nitro-ω-bromostyrene (11), 27 g. of 4-acetaminobenzenesulfinic acid, 195 cc. of alcohol, 52 cc. of water, and 7.7 g. of anhydrous sodium carbonate was refluxed 25 hours. The mixture was cooled, the product was collected, and washed well with alcohol; yield, 11.4 g. (24%), m.p. 243–246°. For analysis a sample was recrystallized from Methyl Cellosolve-water, m.p. 244–245°.

Anal. Calc'd for $C_{16}H_{14}N_2O_5S$: N, 7.8. Found: N, 8.0.

4-Nitro-ω-styryl phenyl sulfone was obtained in a similar manner using 55 g. of crude 4-nitro-ω-bromostyrene and 20 g. of sodium benzenesulfinate; yield, 17%, m.p. 158–161°. Recrystallization from 1:1 alcohol-Methyl Cellosolve narrowed the m.p. to 158–160°.

Anal. Calc'd for $C_{14}H_{11}NO_4S$: C, 58.2; H, 3.8; N, 4.8.
Found: C, 57.7; H, 4.6; N, 5.0.

4-Amino-ω-styryl 4'-acetaminophenyl sulfone. A mixture of 41 g. of 4-nitro-ω-styryl 4'-acetaminophenyl sulfone, 82 g. of iron powder, 1 l. of alcohol, 165 cc. of water, and 8 cc. of concentrated hydrochloric acid was refluxed with stirring for three hours. The hot mixture was filtered through Celite, the filtrate was evaporated to dryness *in vacuo*, and the residue crystallized from dilute alcohol; yield, 30 g. (80%), m.p. 160–165°. Further recrystallization from ethyl acetate-heptane raised the m.p. to 173–175°.

Anal. Calc'd for $C_{16}H_{16}N_2O_3S$: C, 60.7; H, 5.1; N, 8.9.
Found: C, 60.7; H, 5.2; N, 8.8.

4-Amino-ω-styryl phenyl sulfone hydrochloride was prepared in the same way from 4-nitro-ω-styryl phenyl sulfone except that the product was isolated as the hydrochloride from 6 *N* hydrochloric acid in 25% yield, m.p. 220° dec.

Anal. Calc'd for $C_{14}H_{14}ClNO_2S$: N, 4.7. Found: N, 4.9.

ω-Styryl 4-aminophenyl sulfone. A mixture of 38.5 g. of 4-acetaminophenyl ω-styryl sulfone, 117 cc. of water, 78 cc. of concentrated sulfuric acid, and 195 cc. of acetic acid was refluxed for twenty minutes, then cooled and poured into ice and 600 cc. of 28% ammonia water. The crude product (32 g., m.p. 147–150°) was recrystallized from alcohol; yield, 26 g. (79%), m.p. 158–160°.

Anal. Calc'd for $C_{14}H_{13}NO_2S$: C, 64.8; H, 5.0; N, 5.4.
Found: C, 65.0; H, 5.3; N, 5.2.

Similarly, hydrolysis of 4-aminostyryl 4'-acetaminophenyl sulfone gave *4-aminostyryl 4'-aminophenyl sulfone* in 61% yield, m.p. 155–158°. Recrystallization from dilute alcohol raised the m.p. to 160–161°.

Anal. Calc'd for $C_{14}H_{14}N_2O_2S$: C, 61.4; H, 5.2; N, 10.2.
Found: C, 61.1; H, 5.1; N, 10.5.

4-Acetaminophenyl vinyl sulfone (X). A solution of 172.5 g. of 4-acetaminophenyl β-iodoethyl sulfone (VIII) (5) in 530 cc. of reagent pyridine was refluxed for three hours, then evaporated to dryness *in vacuo*. The residue was dissolved in hot water, filtered from a little insoluble material, then cooled in an ice-bath. The pyridinium iodide (IX) was washed with ice water; yield, 193 g. (88%), m.p. 108–110°.

A mixture of 100 g. of the pyridinium iodide (IX), 2 l. of 8% sodium bicarbonate, and 1 l. of ethyl acetate was stirred for fifteen hours. The aqueous layer was separated and extracted once more with ethyl acetate. Dried with magnesium sulfate, the combined extracts were evaporated to dryness *in vacuo*. Trituration of the residue with water gave 35.5 g. (71%) of product, m.p. 120–122°. Recrystallization from ethyl acetate-benzene-petroleum ether raised the m.p. to 122–123°.

Anal. Calc'd for $C_{10}H_{11}NO_3S$: C, 53.3; H, 4.9; N, 6.2.
Found: C, 53.1; H, 5.1; N, 6.3.

4-Aminophenyl vinyl sulfone (XI) *hydrochloride*. A mixture of 35.5 g. of 4-acetaminophenyl vinyl sulfone (X) and 355 cc. of 6 *N* hydrochloric acid was refluxed for twenty minutes. The solution was evaporated to dryness *in vacuo*. The residual hydrochloride, obtained in quantitative yield, m.p. 211–213°, was recrystallized from methanol-ethyl acetate, m.p. 212–213°.

Anal. Calc'd for $C_8H_{10}ClNO_2S$: C, 43.8; H, 4.6; N, 6.4.
Found: C, 43.8; H, 5.2; N, 6.6.

β-(4-Acetaminophenylthio)acrylic acid (XIII). To a suspension of 40 g. of 4-acetaminothiophenol (12) in 150 cc. of alcohol was added successively 20 g. of propiolic acid (13), 20 cc. of concentrated ammonium hydroxide, and 20 cc. of water. The mixture was heated on the steam-bath for five minutes, then diluted with several volumes of water and cooled. Some insoluble material was removed and the filtrate acidified; yield, 46 g. (82%), m.p. 198–202°d. Recrystallization from alcohol gave white crystals, m.p. 210–212°dec.

Anal. Calc'd for $C_{11}H_{11}NO_3S$: C, 55.7; H, 4.7; N, 5.9.
Found: C, 55.8; H, 4.6; N, 5.9.

β-(4-Acetaminophenylthio)-N-benzylacrylamide. To a suspension of 46 g. of the above acid (XIII) in 100 cc. of reagent ether containing 0.5 cc. of pyridine was added 92 cc. of thionyl chloride. The mixture was shaken for fifteen minutes during which time most of the acid dissolved and the acid chloride separated. The solid was washed with dry ether. The solvent-wet acid chloride was covered with 460 cc. of acetone and treated dropwise with stirring with 92 cc. of benzylamine in 100 cc. of acetone over a period of fifteen minutes, the temperature being maintained at 20–25° by ice-cooling. After being stirred for five minutes more, the mixture was diluted with dilute hydrochloric acid. The product was washed with water; yield, 46.5 g. (74%), m.p. 213–216°, suitable for the next step. Recrystallization from Methyl Cellosolve gave white crystals, m.p. 229–230°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2S$: N, 8.6. Found: N, 8.6.

The *anilide* was prepared in the same way and formed white crystals from dilute alcohol, m.p. 228–230°.

Anal. Calc'd for $C_{17}H_{16}N_2O_2S$: N, 9.0. Found: N, 9.2.

β-(4-Acetaminophenylsulfonyl)acrylic acid (XIV). A mixture of 41.5 g. of β-(4-acetaminophenylthio)acrylic acid (XIII), 540 cc. of acetic acid, and 96 cc. of 30% hydrogen peroxide was heated in a bath at 50° for three hours. The solution was evaporated to dryness *in vacuo* and the residue triturated with water. The hydrated solid was washed with water, and dissolved in ethyl acetate. The ethyl acetate solution, dried with magnesium sulfate, was diluted to turbidity with petroleum ether; yield, 28.6 g. (61%), m.p. 172–175°. For analysis a sample was twice recrystallized from ethyl acetate by the addition of sufficient acetone at the b.p. to cause solution, followed by concentration and cooling; white crystals, m.p. 174–176°.

Anal. Calc'd for $C_{11}H_{11}NO_5S$: N, 5.2. Found: N, 5.0.

The corresponding *benzylamide* was prepared in 87% yield, m.p. 174–177°, by oxidation in the same manner except that the residue remaining after evaporation of the reaction mixture was crystallized from dilute alcohol. Recrystallization from alcohol gave white crystals, m.p. 185–186°.

Anal. Calc'd for $C_{18}H_{18}N_2O_4S$: C, 60.4; H, 5.1; N, 7.8.
Found: C, 60.5; H, 5.7; N, 7.6.

β-(4-Aminophenylsulfonyl)acrylic acid (XV) *hydrochloride*. A solution of 2.0 g. of β-(4-

acetaminophenylsulfonyl)acrylic acid (XIV) and 20 cc. of 6 *N* hydrochloric acid was refluxed for five minutes when the product separated. The hydrochloride was washed with alcohol; yield, 1.0 g. (51%), m.p. 232–233°d. Recrystallization by solution in water and addition of an equal volume of concentrated hydrochloric acid gave white crystals of the same m.p.

Anal. Calc'd for $C_9H_{10}ClNO_4S$: C, 41.1; H, 3.8; N, 5.3.
Found: C, 41.0; H, 3.6; N, 5.4.

β-(4-Aminophenylsulfonyl)-N-benzylacrylamide and hydrochloride. A mixture of 10 g. of β-(4-acetaminophenylsulfonyl)-N-benzylacrylamide and 100 cc. of 6 *N* hydrochloric acid was refluxed for twenty minutes during which solution took place and the hydrochloride separated. The hydrochloride was washed with acetone; yield, 7 g. (82%), m.p. 200–204°d.

A hot filtered solution of a sample of the hydrochloride in 1 *N* hydrochloric acid was poured into excess dilute ammonia. The free base was recrystallized from acetone-water; white crystals, m.p. 213–215°.

Anal. Calc'd for $C_{16}H_{16}N_2O_3S$: C, 60.8; H, 5.1; N, 8.9.
Found: C, 60.8; H, 5.2; N, 8.7.

Ethyl (4-Acetaminophenylthio)maleate. To a mixture of 13 g. of 4-acetaminothiophenol (12) and 14.5 g. of ethyl acetylenedicarboxylate was added 65 cc. of alcohol. An exothermic reaction took place. The mixture was heated on the steam-bath until solution was complete, then it was diluted with water until the product began to separate. The mixture was cooled in an ice-bath, filtered, and the product washed with dilute alcohol; yield, 20 g. (80%), m.p. 128–133°. Recrystallization from alcohol gave yellow crystals, m.p. 140–141°.

Anal. Calc'd for $C_{16}H_{19}NO_5S$: C, 56.9; H, 5.7; N, 4.2.
Found: C, 57.0; H, 5.8; N, 4.2.

Attempts to oxidize the thio ether to the sulfone were unsuccessful; (a) chromic acid in acetic acid or (b) hydrogen peroxide in alcohol gave starting material and (c) hydrogen peroxide in acetic acid gave no identifiable product.

(4-Acetaminophenylthio)maleic acid. To a solution of 2.1 g. of sodium hydroxide in 75 cc. of 3-A alcohol[3] was added 5 g. of the preceding ester. The solution was refluxed for one hour during which a sodium salt separated. This salt was washed with 3-A alcohol, and dissolved in water. The solution was acidified with hydrochloric acid, saturated with salt, and extracted with ethyl acetate. The combined extracts, dried with magnesium sulfate, were evaporated to dryness *in vacuo*. The oily residue was crystallized from ethyl acetate-benzene; yield, 2.8 g. (67%), m.p. 145–146°dec. Recrystallization from the same solvents raised the m.p. to 150–152° dec.

Anal. Calc'd for $C_{12}H_{11}NO_5S$: N, 5.0. Found: N, 5.4.

(4-Acetylaminophenylthio)fumaric acid. To a solution of 2.5 g. of potassium hydrogen acetylenedicarboxylate in 20 cc. of water and 1.1 cc. of concentrated ammonium hydroxide was added 2.7 g. of 4-acetaminothiophenol, 10 cc. of alcohol, and 0.1 cc. of piperidine. The mixture was refluxed for fifteen minutes. Most of the alcohol was removed *in vacuo*, the remainder of the solution was diluted with water and acidified. The aqueous solution containing suspended oil was shaken with ethyl acetate and the insoluble material removed. The ethyl acetate layer was evaporated to dryness *in vacuo*. The gummy residue, covered with ethyl acetate-benzene, gradually solidified; yield, 2.7 g. (59%), m.p. 198–200°dec.

Recrystallization from acetone-petroleum ether raised the m.p. to 205–207°dec.

Anal. Calc'd for $C_{12}H_{11}NO_5S$: C, 51.3; H, 3.9; N, 5.0.
Found: C, 51.5; H, 4.2; N, 5.6.

SUMMARY

Twelve α,β-unsaturated sulfones, ten of which contain the 4-aminophenyl radical, have been synthesized for chemotherapeutic testing.

PEARL RIVER, NEW YORK

[3] Denatured ethyl alcohol.

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[CONTRIBUTION FROM THE TECHNICAL COMMAND ARMY CHEMICAL CENTER, MD.]

ALIPHATIC FLUORIDES. II. 1-HALOGENO-ω-FLUOROALKANES[1]

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The preparation of some members of the ω,ω′-difluoroalkane series from the corresponding dibromo- or dichloro-alkanes by halogen exchange with anhydrous potassium fluoride in glycol was recently described (1). In this reaction small quantities of 1-halogeno-ω-fluoroalkanes were obtained as by-products. It was expected that by proper alteration of the reaction conditions the fluorination of the dihalogenoalkanes could be stopped after exchange of one halogen atom thus leading to the formation of 1-halogeno-ω-fluoroalkanes as the main product of the reaction.

Synthesis of 1-halogeno-ω-fluoroalkanes. Complete substitution of the halogen of the dihalogenoalkanes by fluorine requires continuous removal of the low-boiling difluorides from the reaction mixture in order to maintain the necessary reaction temperature of 160–180° for the chlorides and 130–150° for the bromides. It was found that the first step of the fluorination takes place at a reasonable rate at lower temperatures. Satisfactory results were usually obtained at about 100° for replacement of bromine and approximately 130° for the exchange of one chlorine atom by fluorine. With the exception of 1-bromo-2-fluoroethane, 1-chloro-2-fluoroethane, and 1-chloro-3-fluoropropane the boiling points of the fluorohalogenoalkanes do not allow distillation of the reaction products from the mixture as the reaction proceeds. They are, therefore, best prepared by heating a mixture of the dihalogenoalkane, potassium fluoride, and ethylene glycol with vigorous stirring at the indicated temperatures for several hours with subsequent dilution of the reaction mixture with water and fractionation of the separated organic layer. The halogenofluoroalkanes are formed in about 20–40% yield together with 10–30% yields of the difluoroalkanes.

Formation of fluoroalkenes, which are obtained in traces as by-products of the preparation of the difluoroalkanes (1), was not observed. However, in all fluorinations with potassium fluoride in ethylene glycol, an appreciable amount of a high-boiling, fluorine-free by-product is formed. For example, in the preparation of *n*-amyl fluoride which was needed in this investigation for comparison of the relative reactivity of the primary-bound fluorine in alkyl fluoride and halogenofluoroalkane, this high-boiling by-product was isolated and identified as ethylene glycol mono-*n*-amyl ether. A solution of potassium fluoride in ethylene glycol reacts strongly basic behaving like alcoholic caustic. In competition with the ionic halogen-fluorine exchange a replacement of halogen by $HOCH_2CH_2O$— occurs to some extent, leading to the formation of glycol ethers. An equivalent amount of hydrogen ions is liberated, thus decreasing the alkalinity of the reaction mixture. If only a slight excess (10–20%) of potassium fluoride

[1] Presented in part before the Division of Industrial and Engineering Chemistry, American Chemical Society at the 116th meeting, Atlantic City, N. J., September 1949.

is used in the fluorination process, the reaction mixture soon becomes acid due to this side reaction. An ionic halogen-fluorine exchange alone should not render the reaction mixture acid. The formation of glycol ethers is believed to be responsible for the relatively low yields of fluorinated products.

The first four members of each of the bromo- and chloro-fluoroalkane series have been prepared. Data on the reaction temperature, reaction time, and yields of halogenofluoro- and difluoro-alkanes obtained in the fluorination of several dibromo- and dichloro-alkanes are listed in Table I. The three members of the series whose boiling points are considerably below the required reaction temperature are more favorably prepared from 2-fluoroethanol and 3-fluoropropanol, respectively. These two fluorinated alcohols are easily obtained from the corresponding chlorohydrins by the potassium fluoride-glycol method. The preparation of 3-fluoropropanol is described in detail in the experimental part

TABLE I

FLUORINATION OF DIHALOGENOALKANES

STARTING MATERIAL	REACTION TEMP., °C.	REACTION TIME, HOURS	YIELDS OF	
			Halogenofluoro-alkane, %	Difluoroalkane, %
$Br(CH_2)_2Br$	90	6	24	0
$Br(CH_2)_3Br$	80–100	7	31.0	10.2
$Br(CH_2)_4Br$	100–110	7	19.6	23.4
$Br(CH_2)_5Br$	100–110	6	31.4	25.0
$Cl(CH_2)_4Cl$	110	20	36.6	15.9
	125	20	34.2	29.3
$Cl(CH_2)_5Cl$	125	18	22.0	—
	130	7	38.5	14.1

of this paper; the 2-fluoroethanol was obtained according to directions previously given (2) and purified as described below.

1-Bromo-2-fluoroethane has been previously described in the literature (1, 3, 4). Physical data for 1-chloro-2-fluoroethane could not be found;[2] however, McCombie and Saunders have reported the preparation of this compound and its reaction with sodium phenoxide without giving experimental details (4). Therefore, it was included in Table II which lists the boiling points, densities, and refractive indices of several fluorinated compounds. The 1-halogeno-ω-fluoroalkanes are colorless liquids having a sweet odor which resembles that of the corresponding alkyl halides. They are stable to distillation at atmospheric pressure.

Reactivity of 1-halogeno-ω-fluoroalkanes. A comparison of the reactivity of the halogenofluoroalkanes towards alkaline reagents with that of the dihalogeno- and the difluoro-alkanes shows that in general the bromine or chlorine atom exhibits the same reactivity as in the di-bromides or -chlorides and that the fluorine is as unreactive as in the difluorides.

[2] Two recent articles on the preparation and properties of 1-chloro-2-fluoroethane came to the author's attention since this paper was submitted for publication (10, 11).

Alkyl fluorides are generally unable to form alkylmagnesium fluorides and only *n*-amyl fluoride has been reported (5) to yield pentane, decane, and *n*-amyl alcohol by prolonged refluxing with magnesium in ether and subsequent hydrolysis. Since the halogen atom in halogenofluoroalkanes was found to be of the same order of reactivity towards alkaline reagents, as that in alkyl halides, it was expected that bromofluoroalkanes would form ω-fluoroalkylmagnesium bromides with magnesium in ether. These Grignard reagents would be very valuable for further synthesis of organic fluorine derivatives. Although the bromofluoroalkanes react with magnesium in ether after initiation of the reaction with traces of iodine, no ω-fluoroalkylmagnesium bromides are formed, and treatment of the reaction mixture with ketone or phenyl isocyanate leads only to the formation of fluorine-free reaction products which have not been investigated further. Hydrolysis of a reaction product obtained from 1-bromo-5-fluoropentane and magnesium in ether and determination of fluoride ions in the hydrolysate showed

TABLE II

PHYSICAL CONSTANTS OF NEW COMPOUNDS

COMPOUND	B.P., °C.	d_4^{25}	d_4^{35}	n_D^{25}	MR_D [a]	AR_F [b]
$Cl(CH_2)_2F$	53.2	1.1675	—	1.3727	16.09	0.89
$Cl(CH_2)_3F$	82.1	1.0992	1.0862	1.3855 [c]	20.66	.84
$Br(CH_2)_4F$	134.2	1.4443	1.4298	1.4372	28.13	.79
$Br(CH_2)_5F$	162.0	1.3604	—	1.4406	32.79	.83
CH_3CO / $F(CH_2)_3$ > $CHCOOC_2H_5$	105.2 [d]	1.064	1.054	1.4237	—	-
$F(CH_2)_3CH(COOC_2H_5)_2$	122 [e]	1.0764	1.0663	1.4176	51.52	.91
$F(CH_2)_5CH(COOC_2H_5)_2$	142 [f]	1.0407	1.0314	1.4237	60.84	1.01
n-$C_5H_{11}F$	64.4	0.7852	0.7744	1.3569	25.14	.95

[a] MR_D is the molecular refraction for the sodium-D line calculated by the Lorentz-Lorenz equation. [b] AR_F is the atomic refraction for fluorine, computed by subtracting the increments for C (2.418), H (1.100), Cl (5.967), Br (8.865), O′ (1.1525), and O< (1.643) from MR_D. [c] at 27.2°. [d] 7 mm. [e] 11 mm. [f] 10 mm.

that over 60% of the organic-bound fluorine was present in the ionic state. Since a preferred attack of the metallic magnesium on the fluorine atom seems improbable, it appears as if the fluoroalkylmagnesium bromide formed in the first step of the reaction exchanges to a large extent its bromine for fluorine from unreacted bromofluoroalkane or fluoroalkylmagnesium bromide. This assumption is supported by the fact that by reaction of phenylmagnesium bromide with 1-bromo-5-fluoropentane or with *n*-hexyl fluoride in equimolar quantities, the fluorine is found quantitatively as fluoride ion upon hydrolysis of the reaction mixture, whereas the amount of bromide ions is only about 60% of the bromine present in the phenylmagnesium bromide. The phenylmagnesium fluoride formed by halogen exchange between the phenylmagnesium bromide and the alkyl fluoride apparently reacts to some extent with the alkyl bromide formed during the reaction to yield an alkyl benzene. The reaction of aliphatic-bound fluorine

with the Grignard reagent can be summarized as follows:

$$R—F + C_6H_5MgBr \rightarrow C_6H_5MgF + R—Br \rightarrow C_6H_5—R + MgBrF.$$

The reaction 1 mole of 1-bromo-5-fluoropentane with 1 gram-atom of metallic sodium in absolute ether has been investigated quantitatively. After 24 hours of refluxing, the hydrolysate of the reaction mixture contained as ions 34% of the bromine and 25% of the fluorine originally present in the bromofluoropentane.

With alkali phenoxides, diethyl sodium malonate, and ethyl sodium acetoacetate, the halogen atom of the halogenofluoroalkane exhibits its normal reactivity, whereas the fluorine is not or only slightly attacked by these reactants. The first four members of the 1-bromo-ω-fluoroalkane series have been treated with sodium β-naphthoxide, yielding the crystalline ω-fluoroalkyl β-naphthyl ethers. Diethyl 3-fluoropropyl- and 5-fluoropentyl-malonate were obtained in 52 and 74% yield, respectively, by malonic ester synthesis, and ethyl α-(3-

TABLE III

REACTIVITY OF ω,ω'-DIBROMO- AND 1-BROMO-ω-FLUOROALKANES

COMPOUND $X(CH_2)_nY$	1 *N* NaOEt			1 *N* KOH		
	X and Y = Br	X = Br and Y = F		X and Y = Br	X = Br and Y = F	
		Br^-	F^-		Br^-	F^-
n = 2	51[a]	45[a]	1[b]	50[c]	27[c]	2[e]
n = 3	85	82	0.5	70	31	0
n = 4	62	67	1.6	47	52	8
n = 5	58	57	0.5	37[d]	39	0
n-$C_5H_{11}Br$	–	47	–	–	23	–
n-$C_5H_{11}F$	–	–	trace	–	–	trace

[a] Percentage of bromine reacted after treatment of 0.01 mole of substance with 25 ml. of 1 *N* $NaOC_2H_5$ in ethanol at 35° for 4 hours. [b] Percentage of fluorine reacted under the same conditions as in [a]. [c] Percentage of bromine reacted after treatment of 0.01 mole of substance with 25 ml. of 1 *N* KOH in 70% ethanol at 35° for 5 hours. [d] In this run sufficient 95% ethanol (12.5 ml.) was added to obtain a homogeneous mixture. [e] Percentage of fluorine reacted under the same conditions as in [c].

fluoropropyl)acetoacetate in 53% yield from ethyl sodium acetoacetate and 1-bromo-3-fluoropropane. The physical data of these esters are listed in Table II.

The relative reactivities of the 1-bromo- and 1-chloro-ω-fluoroalkanes towards alkaline reagents are of interest for introducing ω-fluoroalkyl groups into organic molecules in reactions of the above-mentioned type. The halogenofluoroalkanes were therefore compared with the corresponding ω,ω'-dibromo- and dichloroalkanes on the basis of the percentage of reacted halogen after treatment with 1 *N* sodium ethoxide and 1 *N* 70% alcoholic KOH solutions as previously described for the difluoroalkanes (1). The reactions with the bromine derivatives were carried out at 35° for 4 and 5 hours, respectively, whereas the chlorine derivatives were treated with the same reagents at reflux temperature for 30 minutes. The results obtained are listed in Tables III and IV, in which the rela-

tive reactivities of *n*-amyl bromide, chloride, and fluoride have been included for comparison. The data show that the halogen in the dibromides and dichlorides exhibits a higher reactivity than in the corresponding *n*-amyl halides. The relatively large quantity of reacted halogen in the runs with the trimethylene derivatives and sodium ethoxide solution is probably due to a simultaneous dehydrohalogenation of the molecule competing with the normal substitution reaction, as was outlined in the first paper of this series. The halogenofluoroalkanes show a maximum reactivity at the C_3 derivatives for the bromine and chlorine, but the fluorine in these derivatives is very unreactive. 1,3-Difluoropropane was found to react to the extent of 11.6% of its fluorine by refluxing with 1 *N* NaOEt solution (1), but 1-bromo- and 1-chloro-3-fluoropropane react only to the extent of 0.5 and 0.7%, respectively, under the same conditions. In comparing the re-

TABLE IV

REACTIVITY OF ω,ω'-DICHLORO- AND 1-CHLORO-ω-FLUORO-ALKANES

COMPOUND $X(CH_2)_nY$	1 *N* NaOEt			1 *N* KOH		
	X and Y = Cl	X = Cl and Y = F		X and Y = Cl	X = Cl and Y = F	
		Cl^-	F^-		Cl^-	F^-
n = 2	49[a]	18[a]	11[b]	39[c]	6[c]	6[d]
n = 3	61	52	0.7	23	19	0
n = 4	36	36	0.7	20	33	4
n = 5	30	26	1.6	15	14	0
n-$C_5H_{11}Cl$	–	23	–	–	9	–
n-$C_5H_{11}F$	–	–	traces	–	–	trace

[a] Percentage of chlorine reacted after refluxing 0.01 mole of substance with 25 ml. of 1 *N* $NaOC_2H_5$ in ethanol for 30 minutes. [b] Percentage of fluorine reacted under the same conditions as in [a]. [c] Percentage of chlorine reacted after refluxing 0.01 mole of substance with 25 ml. of 1 *N* KOH in 70% ethanol for 30 minutes. [d] Percentage of fluorine reacted under the same conditions as in [c].

activities of the ethane derivatives, it is obvious that chlorine activates the fluorine on the adjacent carbon atom, since their reactivities are of the same order of magnitude, whereas bromine activates the neighboring fluorine only very slightly. The comparatively high reactivity of fluorine in the halogenofluorobutane derivatives towards KOH is presumably caused by the pronounced tendency of 4-fluorobutanol, formed by hydrolysis of the halogen, to eliminate hydrogen fluoride with ring closure to tetrahydrofuran (3c). The relatively high reactivity of the fluorine atom of 1-chloro-2-fluoroethane towards strong alkaline reagents makes the corresponding bromine derivative the preferred starting material for further synthetic reactions. 1-Bromo-2-fluoroethane retains the high reactivity of the bromine of an alkyl bromide without a pronounced increase in the reactivity of the fluorine over the normally low reactivity of primary fluorine. A number of interesting reactions using this reagent have been mentioned by McCombie and Saunders (4).

EXPERIMENTAL PART

Materials. The commercial, anhydrous potassium fluoride (Harshaw Chemical Co.) and the ethylene glycol (Du Pont) were dried before use as previously described (1).

ω,ω'-Dihalogenoalkanes. The dichloroalkanes, ethylene bromide, and trimethylene bromide used as starting materials were commercial products. 1,4-Dibromobutane and 1,5-dibromopentane were obtained by reaction of tetrahydrofuran and tetrahydropyran, respectively, with hydrobromic acid according to the directions given for the preparation of 1,5-dibromopentane (6).

Purification of 2-fluoroethanol. The 2-fluoroethanol was prepared by fluorination of ethylene chlorohydrin with potassium fluoride in glycol (2). The crude product obtained from several runs was distilled through a 40 x 1.5 cm. column packed with $\frac{1}{8}''$ single-turn glass-helices at a reflux ratio of about 20:1. The fraction b.p. 103.0–103.8° was collected and redistilled through the same column which was also used in each of the following distillations. The fraction b.p. 103.1–103.8° was collected and about 5 vol.% of concentrated sodium bisulfite solution added to remove small amounts of crotonaldehyde [b.p. 104.0° (7)] which is formed in traces during the preparation of the alcohol (3*a*). After 48 hours at room temperature, and filtration, an equal volume of methylene chloride was added. The water was then removed by continuous, azeotropic distillation (b.p. of CH_2Cl_2–H_2O azeotrope: 38°). After removal of the solvent, the fluoroethanol was filtered from a small amount of crystalline precipitate and then distilled three times, collecting the distillate at 103.1–103.3°. During the third fractionation a mid-cut was taken at 103.3° for analysis and determination of the physical constants: n_D^{25} 1.3633, d_4^{25} 1.1002.

Anal. Calc'd for C_2H_5FO: C, 37.5; H, 7.9.
Found: C, 37.7; H, 8.0.

Preparation of 3-fluoropropanol. A mixture of 378 g. (4 moles) of trimethylene chlorohydrin, 350 g. (6 moles) of potassium fluoride, and 500 g. of ethylene glycol was heated at 175–180° with vigorous stirring. During the reaction the product was continuously distilled off between 130 and 154°. After 5 hours 186.9 g. of a colorless liquid was collected. Distillation through a 40-cm., packed column yielded 155.6 g. (49.8% yield) of 3-fluoropropanol, b.p. 126–128°. The crude 3-fluoropropanol was distilled twice through the same column and a constant-boiling mid-cut taken at 127.8° [b.p. 127.5–128° (3*c*)] for analysis and determination of the physical constants: n_D^{25} 1.3771, d_4^{25} 1.0390.

Anal. Calc'd for C_3H_7FO: C, 46.1; H, 9.0; F, 24.3.
Found: C, 45.9; H, 8.9; F, 24.1.

Preparation of 1-bromo-2-fluoroethane. (a) A mixture of 376 g. (2 moles) of ethylene bromide, 232 g. (4 moles) of potassium fluoride, and 400 g. of ethylene glycol was heated at 90° for 6 hours with vigorous stirring in a 2-liter round-bottom flask to which was attached a condenser with a receiver and a Dry Ice-acetone cold trap. In the receiver 7.1 g. of a colorless distillate (b.p. 32–42°) was collected. The cold trap contained 21.1 g. of a low-boiling liquid. After standing overnight the reaction mixture was diluted with 1000 ml. of water. The heavy, organic layer (225.7 g.) was separated, combined with the distillate and the cold trap condensate, and dried with 20 g. of calcium chloride. Distillation through a 40-cm., packed column yielded 38.4 g. of vinyl bromide boiling at 16–18°, 32.6 g. of 1-bromo-2-fluoroethane boiling at 70–74°, and 169.4 g. of unreacted ethylene bromide. Based on the reacted ethylene bromide the yield of 1-bromo-2-fluoroethane was 24%.

(b) To a refluxing mixture of 192 g. (3 moles) of 2-fluoroethanol and 10 g. of red phosphorus, 160 g. (1 mole) of bromine was added dropwise over a period of 3 hours through a dropping-funnel reaching to the bottom of the reaction flask. The mixture was then refluxed for 3 hours. Toward the end of the reaction a slight evolution of hydrogen fluoride and etching of the glass apparatus was noticed. Distillation of the reaction mixture yielded 265.9 g. of a pale-orange liquid boiling from 71° to 132°. The distillate was washed twice with 200-ml. portions of water and finally with sodium bicarbonate solution. The heavy, colorless layer was separated and dried with calcium chloride. Distillation through a 40-cm.

column yielded 129.4 g. of 1-bromo-2-fluoroethane boiling at 71–72°; yield based on bromine, 51%.

Preparation of 1-bromo-3-fluoropropane. (a) A mixture of 808 g. (4 moles) of trimethylene bromide, 350 g. (6 moles) of potassium fluoride, and 500 g. of ethylene glycol was heated with vigorous stirring at 80–100° for 7 hours. After 12 hrs., 1000 ml. of water was added to the reaction mixture. The heavy, organic layer was separated (490 g.) and dried with calcium chloride. Distillation through a 40-cm., packed column yielded after a forerun of 21.3 g. of trimethylene fluoride boiling at 41.0–41.2°, 113.4 g. of 1-bromo-3-fluoropropane boiling at 100–101.5°, and 283.4 g. of unreacted trimethylene bromide. The yield based on reacted starting material was 31.0%.

(b) To 100 g. of phosphorus tribromide ($\frac{1}{3}$ mole = 90.25 g.), cooled to −15° was added 78 g. (1 mole) of 3-fluoropropanol (b.p. 126–128°) in small portions in the course of 15 minutes. The temperature of the mixture was maintained between −5° and 0° until all of the fluoropropanol had been added. The reaction mixture was then allowed to warm to room temperature. After standing overnight it was refluxed for 1 hour and distilled. Between 100–114°, 146 g. of a colorless distillate was obtained, which was washed with 50 ml.

TABLE V

ANALYTICAL DATA OF NEW COMPOUNDS

COMPOUND	C		H		F	
	Calc'd	Found	Calc'd	Found	Calc'd	Found
$Cl(CH_2)_2F$	29.1	29.0	4.9	4.9	23.0	23.0
$Cl(CH_2)_3F$	37.3	37.3	6.3	6.1	19.7	19.7
$Br(CH_2)_4F$	31.0	30.9	5.2	5.2	12.3	12.2
$Br(CH_2)_5F$	35.5	35.7	6.0	6.1	11.2	11.3
$CH_3CO \atop F(CH_2)_3 > CHCOOC_2H_5$	56.8	56.7	8.0	7.9	10.0	9.9
$F(CH_2)_3CH(COOC_2H_5)_2$	54.5	54.6	7.8	7.9	8.6	8.6
$F(CH_2)_5CH(COOC_2H_5)_2$	58.1	57.8	8.5	8.4	7.7	7.6
n-$C_5H_{11}F$	66.6	66.6	12.3	12.4	21.1	21.0

of concentrated potassium carbonate solution and dried with calcium chloride. Distillation through a 40-cm., packed column gave 99.5 g. (70.6% yield) of 1-bromo-3-fluoropropane boiling at 100.5–101.5°. This material was used without further purification for the reactions with malonic and acetoacetic esters. For the quantitative measurements it was redistilled twice through a 40-cm., packed column and a mid-cut taken at 101.2° at 756 mm. [(b.p.$_{760}$ 101.4° (1)].

Preparation of 1-bromo-4-fluorobutane and 1-bromo-5-fluoropentane. These substances were prepared from the corresponding dibromoalkanes in essentially the same manner as described for 1-bromo-3-fluoropropane from trimethylene bromide. The reaction conditions and yields are listed in Table I, their physical data in Table II, and the analyses in Table V.

Reaction of 1-bromo-5-fluoropentane with phenylmagnesium bromide. To 4.23 g. (0.025 mole) of 1-bromo-5-fluoropentane was added a solution of 4.51 g. of phenylmagnesium bromide (0.025 mole, 4.53 g.) in 23.1 ml. of absolute ether. The mixture was refluxed for 20 hours and then hydrolyzed with 25 ml. of water and 100 ml. of 20% sulfuric acid. The aqueous layer was separated and after washing with 75 ml. of ether, aliquots were titrated for bromide and fluoride ions. *Found*: 0.49 g. F^-, 1.15 g. Br^-; Calc'd on charged bromofluoropentane: 0.48 g. F^-; on charged phenylmagnesium bromide: 1.99 g. Br^-.

Preparation of 1-chloro-2-fluoroethane. To 64 g. of 2-fluoroethanol was added dropwise in the course of 4 hours 131 g. (1.1 moles) of thionyl chloride, freshly distilled from linseed

oil. After the addition was completed the reaction mixture was refluxed for 5 hours and then distilled through a 25-cm., 3-step Vigreux column. At 50–53.5°, 87.0 g. of a pale yellow liquid consisting of chlorofluoroethane and some thionyl chloride was collected. In order to remove the thionyl chloride, 5 ml. of water was added and the mixture shaken frequently. After standing overnight, anhydrous potassium carbonate was added in small portions until the evolution of carbon dioxide ceased. After two hours at room temperature the colorless liquid was decanted from the salt and distilled through a 40-cm., packed column; at 52–53.5°, 57.3 g. (69.4% yield) of chlorofluoroethane was collected. To remove traces of moisture from the product, it was dried with 4 g. of potassium carbonate for 18 hours. Redistillation through a 40-cm. column yielded, after a small forerun at 53.0–53.2°, pure 1-chloro-2-fluoroethane boiling at 53.2°. Physical data and analyses are given in Tables II and V, respectively.

Preparation of 1-chloro-3-fluoropropane. (a) To 104 g. (0.5 mole) of PCl_5 was added dropwise 78 g. (1 mole) of 3-fluoropropanol in the course of 45 minutes. The extremely vigorous reaction was moderated by occasional cooling of the reaction flask in a Dry-Ice-acetone bath. After the addition of 3-fluoropropanol was completed and the PCl_5 had gone into solution, the mixture was allowed to warm to room temperature and was finally refluxed for 3 hours. Distillation yielded 53.8 g. of a colorless liquid boiling at 82–96°, which was fractionated through a 40-cm., packed column, yielding 43.6 g. of crude 1-chloro-3-fluoropropane boiling at 79–81°. For further purification the product was washed with potassium carbonate solution, dried with calcium chloride, and redistilled twice through a 40-cm. column. A constant boiling mid-cut was taken at 79.9°. Physical data and analyses are listed in Tables II and V, respectively.

(b) To 44 g. (0.37 mole) of refluxing thionyl chloride was added dropwise 26.0 g. (0.33 mole) of 3-fluoropropanol in the course of 2 hours. After refluxing this mixture for 24 hours, the excess thionyl chloride was hydrolyzed with 10 ml. of water. The crude reaction product was then washed with water and finally with sodium bicarbonate solution, dried with calcium chloride, and distilled through a 40-cm., packed column. At 79–81°, 26.0 g. (81.3% yield) of 1-chloro-3-fluoropropane was obtained.

Preparation of 1-chloro-4-fluorobutane and 1-chloro-5-fluoropentane. Both substances were prepared in the same way as described for the corresponding bromine derivatives. The reaction conditions and yields are given in Table I.

Preparation of ω-fluoroalkyl β-naphthyl ethers. The β-naphthyl ethers described were all prepared in the same manner. A mixture of 0.03 mole each of 1-bromo-ω-fluoroalkane, β-naphthol, and sodium hydroxide in 50 ml. of 95% ethanol was refluxed for 3–4 hours. The mixture was then poured into 150 ml. of water and made distinctly alkaline with sodium hydroxide. The naphthyl ethers separated as oils, which crystallized on cooling, and were recrystallized from methanol or ethanol until a constant melting point was obtained. A Fisher-Johns melting point apparatus was used for the determination of the melting points.

2-Fluoroethyl ether. White crystals from 95% ethanol, m.p. 47.7° (uncorr.).

Anal. Calc'd for $C_{12}H_{11}FO$: C, 75.8; H, 5.8.
Found: C, 75.9; H, 5.8.

3-Fluoropropyl ether. White micro-plates from methanol after decolorization with Norit, m.p. 28.1°.

Anal. Calc'd for $C_{13}H_{13}FO$: C, 76.5; H, 6.4.
Found: C, 76.4; H, 6.4.

4-Fluorobutyl ether. White, glistening platelets from 95% ethanol, m.p. 47.6°.

Anal. Calc'd for $C_{14}H_{15}FO$: C, 77.0; H, 6.9.
Found: C, 76.7; H, 6.9.

5-Fluoropentyl ether. White micro-plates from methanol, m.p. 31.0°.

Anal. Calc'd for $C_{15}H_{17}FO$: C, 77.6; H, 7.4.
Found: C, 77.3; H, 7.5.

Preparation of diethyl 3-fluoropropylmalonate. To a warm solution of 27 g. (0.5 mole) of 96% sodium methoxide in 250 ml. of absolute ethanol was added 82.0 g. (0.51 mole) of diethyl

malonate. To this solution was added 70.5 g. (0.5 mole) of 1-bromo-3-fluoropropane in the course of 10 minutes. The mixture was refluxed for 35 minutes, when it reacted neutral. The ethanol was distilled off and the residue taken up in 150 ml. of water. The upper, orange-yellow layer was separated and distilled through a 20-cm., packed column at reduced pressure. After a forerun of unreacted diethyl malonate, 56.9 g. (51.7% yield) of diethyl 3-fluoropropylmalonate was obtained, boiling at 124–127° at 13 mm. For analysis and determination of the physical constants the product was redistilled at 11 mm. and a mid-cut taken at 122°. The physical data and analyses are listed in the tables.

Preparation of diethyl 5-fluoropentylmalonate. The diethyl 5-fluoropentylmalonate was obtained from 1-bromo-5-fluoropentane in 74.3% yield using the same procedure as for the 3-fluoropropyl derivative. From the fraction boiling at 140–143° at 10 mm. pressure, a middle fraction was taken at 142° for analysis and determination of physical constants (Tables II and V).

Preparation of ethyl α-(3-fluoropropyl)acetoacetate. To a warm solution of 16.2 g. (0.3 mole) of sodium methoxide in 150 ml. of absolute ethanol was added 40 g. of ethyl acetoacetate and, after cooling to 45°, 42.3 g. (0.3 mole) of 1-bromo-3-fluoropropane. The mixture was refluxed for 6 hours, when it reacted neutral. The ethanol was removed *in vacuo* and the residue taken up in 60 ml. of water. The light, organic layer was diluted with 30 ml. of ether to facilitate separation. The ether was removed *in vacuo* and the residue, a yellow, oily liquid, was distilled through a 15-cm., packed column under reduced pressure. After a small forerun, 30.4 g. (53.2% yield) of ethyl α-(3-fluoropropyl)acetoacetate was obtained at 144–148° and 48 mm. The product was redistilled at 7 mm. and a mid-cut taken at 105.2° for analysis and determination of physical constants.

Preparation of n-amyl fluoride. A mixture of 290 g. (5 moles) of anhydrous potassium fluoride and 350 g. of ethylene glycol was heated to 120° with a mercury-seal stirrer, thermometer, dropping-funnel, and reflux still-head. *n*-Amyl bromide (453 g., 3 moles) was added dropwise in the course of 6 hours at such a rate that the reaction product distilled at 69–85°. The colorless distillate was treated with calcium chloride and sodium fluoride overnight, filtered, and distilled through a 40-cm., packed column. After a forerun of 12.1 g. of 1-pentene boiling at 40–45°, 136.3 g. (50.4%) of crude *n*-amyl fluoride boiling at 61–64.8° was obtained. For further purification the crude product was treated with bromine in order to remove small amounts of olefin still present. After one hour at room temperature, the pale-orange liquid was washed with 75 ml. of saturated sodium bicarbonate solution until it became colorless, and dried with calcium chloride overnight. It was distilled three times through a 40-cm. column. The pure substance boiled at 64.4° at 766 mm. This is somewhat higher than the boiling points reported in the literature: 62.8° (5); 62–63° (8). The physical constants were, therefore, determined and are included in Table II.

The contents of the reactor was diluted with 600 ml. of water. A pale-yellow, light layer separated, which was washed with 150 ml. of water and dried with silica-gel. Distillation through a 40-cm. column yielded a colorless liquid of pleasant fruity odor boiling at 70–72° and 8 mm. The substance was redistilled twice under reduced pressure through the same column: 68.5–69° at 6 mm. and 63.7–64.0° at 3 mm.; n_D^{25} 1.4229, d_4^{25} 0.8908; MR_D, Calc'd 37.69; Found 37.78.

Anal. Calc'd for $C_7H_{15}O_2$: C, 63.6; H, 12.2.
Found: C, 63.5; H, 12.2.

ACKNOWLEDGMENT

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SUMMARY

The first four members of each of the series of 1-bromo- and 1-chloro-ω-fluoroalkanes have been prepared. The physical properties, if not reported previously, have been tabulated and their chemical reactions are reported.

The reactivity of the halogen atoms in these compounds towards alkaline reagents is essentially the same as in the corresponding ω,ω'-dihalogenoalkanes; their fluorine atom exhibits the chemical stability of primary-bound fluorine.

The bromofluoroalkanes do not form fluoroalkylmagnesium bromides, and react with metallic sodium with simultaneous elimination of bromine and fluorine.

The ω-fluoroalkyl β-naphthyl ethers of the general formula $F(CH_2)_n—O—C_{10}H_7$ (n = 2, 3, 4, 5), diethyl 3-fluoropropyl- and 5-fluoropentyl malonate, and ethyl α-(3-fluoropropyl)acetoacetate have been synthesized.

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[CONTRIBUTION FROM THE ENDOCRINOLOGY SECTION, NATIONAL CANCER INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

THE PREPARATION OF SOME SUBSTITUTED GLYCOLS BY ELECTROLYTIC REDUCTION

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In the course of our biological work it was necessary to prepare the glycols of *p*-hydroxyacetophenone, β-acetylpyridine, and *p*-dimethylaminobenzaldehyde. The first glycol had previously been prepared by Tutin, *et al.*, (6) using sodium amalgam as the reducing agent. However, an oil was obtained from which the pinacol was isolated and no yields were reported. The preparation of this compound has now been successfully carried out by the use of electrolytic reduction at controlled cathode potential.

Klingel (4) described the preparation of *p*-hydroxyacetophenone by hydrolysis of the diazonium salt of *p*-aminoacetophenone. Unfortunately the details of the procedure were not given and these had to be developed and are reported here.

As 3,3-*bis*-(*p*-hydroxyphenyl)-2-butanone was needed for other purposes it was prepared from the pinacol by a pinacol-pinacolone type rearrangement using acetic anhydride as the reagent.

The preparation of the pinacol of β-acetylpyridine was also accomplished by electrolytic reduction with resulting satisfactory yields of the pinacol.

Rousset (5) reduced *p*-dimethylaminobenzaldehyde with sodium amalgam and obtained a solid, m.p. 155° which was a mixture of the two isomeric glycols. Clemo and Smith (3) repeated this work under modified conditions and were able to isolate the two forms of the glycol. One form had m.p. 178° and the other form which predominated had m.p. 113°. Their attempts to prepare the glycol by electrolytic reduction resulted in a 5% yield of the high-melting glycol.

By using an aqueous-alcoholic potassium hydroxide solution of the aldehyde and performing the reduction at a constant cathode potential, an over-all yield of 97% of both forms of the glycol was obtained; the ratio was approximately 1:1.5.

EXPERIMENTAL[1]

p.-Hydroxyacetophenone. One hundred fifty grams of *p*-aminoacetophenone was dissolved in 2 l. of water containing 282 ml. of concentrated hydrochloric acid. The mixture was cooled to 0° and a solution of 79 g. of sodium nitrite in 240 ml. of water was slowly added. The temperature was not permitted to rise above 5°. The solution was boiled for one-half hour and then refrigerated overnight. The yellow crystals were purified from water using a small quantity of Norit. Yield 98.9 g. (65.5%), m.p. 106–107° (4).

2,3-Bis-(p-hydroxyphenyl)-2,3-butanediol. The apparatus used for the preparation of this compound by electrolytic reduction was recently described (2). Essentially, this apparatus will give automatically controlled impressed potential to secure constant cathode potential.

The cathode chamber consisted of a 150-ml. beaker, with a mercury cathode at the bottom. An alundum crucible 8 cm. high by 3 cm. in diameter served as an anode chamber. A

[1] All melting points reported are uncorrected.

smooth sheet of platinum bent to encircle the inner surface of the crucible was the anode. A standard calomel reference electrode was placed against the cathode. A glass-enclosed magnet in conjunction with a magnetic stirrer was used to agitate the solution during reduction.

The catholyte consisted of 6 g. of *p*-hydroxyacetophenone in 50 ml. of 2 *N* sodium hydroxide. The anolyte was a 2 *N* sodium hydroxide solution. At a cathode potential of −2.2 volts, the initial current was 3.5 amperes. The electrolysis was allowed to proceed for twenty minutes at a temperature of 35° under a nitrogen atmosphere. The catholyte was chilled and made acid with dilute hydrochloric acid, the precipitate was washed with water, then lightly with 50% ethanol, ether, and dried; yield 4.6 g. (77%), m.p. 206–207°. Crystallization from ethanol gave colorless prisms, m.p. 209–210° (6).

The *tetraacetate* was prepared by dissolving 0.2 g. of the pinacol in 10 ml. of pyridine containing 1 ml. of acetic anhydride. After standing in the refrigerator for one week the contents were diluted with three volumes of water and allowed to crystallize. The collected crystals were washed with water and dried, m.p. 189–190° (6).

3,3-Bis-(p-hydroxyphenyl)-2-butanone. To a suspension of 2.6 g. of the above pinacol in 30 ml. of acetic anhydride was added a few drops of concentrated sulfuric acid. The mixture was shaken until all the pinacol was in solution and then poured on ice. The semi-solid ketone diacetate was washed a number of times with water by decantation. Fifty milliliters of 20% potassium hydroxide and 50 ml. of ethanol was added to the diacetate and the mixture heated on a steam-bath until all the alcohol had evaporated. The solution was chilled, made slightly acid and refrigerated overnight. The product was recrystallized from water to yield colorless platelets which turned white on drying, yield 1.95 g. (80%), m.p. 128–129° (1).

2,3-Bis-(β-pyridyl)-2,3-butanediol. The catholyte consisted of 6 g. of β-acetylpyridine in 1 ml. of concentrated hydrochloric acid and 49 ml. of distilled water. The anolyte was 0.5 ml. of concentrated hydrochloric acid and 24.5 ml. of water. The reduction was performed at a cathode potential of −1.8 volts against a standard calomel electrode. The initial current was 1.7 amperes for a cathode area of 22.9 cm.^{2}. The reduction was kept at 25°. The reaction was completed in about 50 minutes as indicated by the evolution of hydrogen at the cathode and a plateau of 0.69 amperes. The catholyte was distilled to dryness under reduced pressure at 25°, the residue triturated with a solution of 15 ml. of absolute ethanol and 10 ml. of ethyl acetate, and refrigerated. The filtered crystals were washed with a 50% solution of ethanol in ethyl acetate, yield 5.8 g. (73.4%). The *dihydrochloride* decomposes at about 244°.

The free *base* was prepared in almost quantitative yield by dissolving the dihydrochloride in water and making the solution slightly alkaline. The platelets which formed were recrystallized from water, m.p. 244–245° (dec).

Anal. Calc'd for $C_{14}H_{16}N_2O$: C, 68.83; H, 6.60.
Found C, 68.73; H, 6.81.

4,4-Bis-dimethylaminohydrobenzoin. A solution of 5 g. of *p*-dimethylaminobenzaldehyde, 38 ml. of ethanol, and 10% aqueous potassium hydroxide to make up a total volume of 75 ml. was placed in the cathode chamber. The anolyte consisted of equal parts of ethanol and aqueous potassium hydroxide.

At a cathode potential of −1.9 volts and a temperature of 35° the initial current was 3.3 amperes. Eight minutes after initiation of the reduction crystals appeared and at the end of 21 minutes a current plateau of 0.5 amperes had been reached which indicated completion of the reaction. The crystals were filtered and recrystallized from ethanol to give colorless prisms, yield 1.95 g. (39%), m.p. 178–179°.

The aqueous-alcoholic alkaline mother liquor was diluted with approximately an equal volume of water added portionwise with agitation. The crystals were collected, washed with water, and recrystallized from ethanol-petroleum ether (b.p. 65–85°) (1:9). A yield of 2.9 g. (58%) of colorless needles was obtained, m.p. 112–113°.

SUMMARY

The preparation of 2,3-bis-(*p*-hydroxyphenyl)-2,3-butanediol, 2,3-bis-(β-pyridyl)-2,3-butanediol, and 4,4-bis-dimethylaminohydrobenzoin in satisfactory yields by electrolytic reduction at constant cathode potential is described.

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SYNTHESES OF CYSTINE

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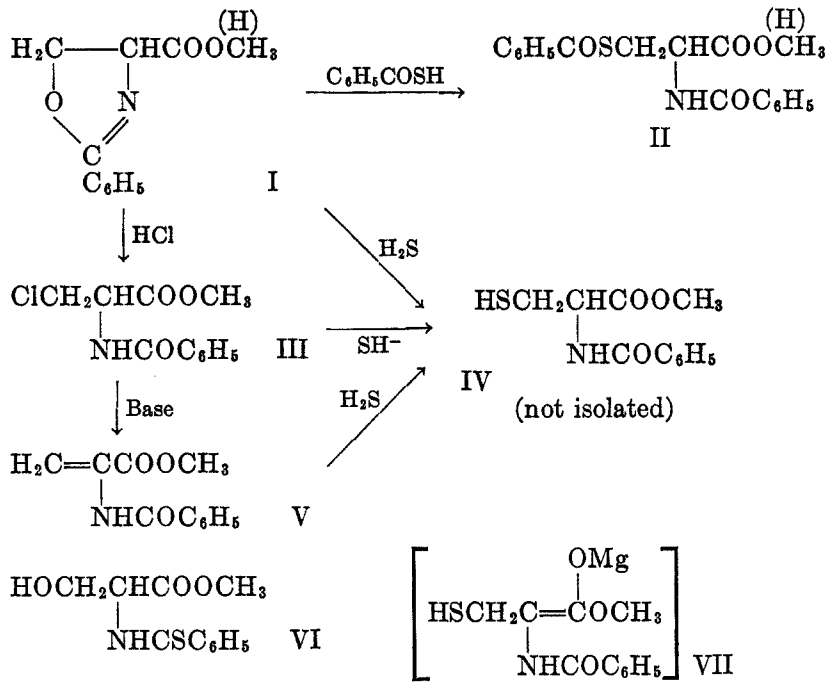
Previous syntheses of cystine designed for the use of isotopic sulfur have been based on the method of Wood and du Vigneaud (1), or on a modification of the procedure of Fischer and Raske (2), in which the benzyl group was used to protect the sulfide function. The routes to cystine described in this paper all depend on the initial transformation of serine into 2-phenyl-4-carboxymethyloxazoline (I). In the first example the hydrochloride salt of the oxazoline was rearranged to methyl α-benzamido-β-chloropropionate (III) and the chlorine replaced directly by the unprotected sulfhydryl group. The other useful method was based on rearrangement of the thiobenzoic acid salt of the oxazoline acid (I) to give N, S-dibenzolycysteine (II). The replacement reaction was useful only for the preparation of inactive cystine in 58% yield, but optically active cystine was made by the oxazoline salt rearrangement in 42% yield. Both yields are based on sulfur and do not take recovered sulfur into account.



Hydrogen sulfide will add to methyl α-benzamidoacrylate (V) to yield the corresponding cysteine derivative (IV), but this reaction is of no value in isotopic work because excess hydrogen sulfide was required for a high yield. A similar synthesis utilizing α-acetamidoacrylic acid and excess thioacetic acid

has recently been published (3). The addition of hydrogen sulfide to the oxazoline ester (I) also gave the cysteine derivative (IV), but the yield was small and it is probable that the principal product was the thiobenzamide (VI) analogous to that obtained by Goldberg and Kelly (4) from the reaction of hydrogen sulfide with 2-phenyloxazoline.

The replacement reaction. Sodium hydrosulfide in methanol reacted with methyl α-benzamido-β-chloropropionate[1] to give dibenzoyllanthionine dimethyl ester as the main product, whereas with magnesium hydrosulfide the cysteine derivative (IV) predominated. This observation led to the use of magnesium hydrosulfide-pyridine in which the formation of the lanthionine derivative was further suppressed. The cysteine derivative was not isolated but was oxidized to a disulfide which proved to be the molecular compound formed from equal amounts of the DL and *meso* forms of inactive N,N′-dibenzoylcystine dimethyl ester. As this compound resulted from the optically active as well as inactive starting material, formulation of the chlorine replacement must include displacement of the hydrogen on the asymmetric carbon. Possible routes to the racemic cysteine derivative are through an enol salt such as VII, or the acrylic ester V, which might subsequently add hydrogen sulfide. Formation of an enol salt is unlikely, in view of the fact that N-benzoyl-L-cysteine methyl ester did not racemize when dissolved in magnesium methoxide solution, nor was any racemization such as that postulated by Elliott (6)[1] observed on alkaline hydrolysis of the oxazoline ester (I). The formation of the acrylate ester V from the chloride III and its bromine analog took place in pyridine solution, and because of the rapidity with which the latter reacted it was used to observe the course of the reaction in the presence of hydrogen sulfide. After an hour in cold pyridine solution, 24% of the bromine had become ionic, but none of the cysteine derivative could be isolated. Its formation on longer standing clearly involved addition to the double bond rather than a direct replacement. In the presence of magnesium ion the mechanism was not as obvious and it is speculative whether replacement took place at the time expulsion of hydrogen and chloride ions became imminent, or whether magnesium catalyzed a subsequent addition to the double bond.

Wood and Gutmann have recently described the resolution of labeled S-benzyl-DL-cysteine by the method of isotopic dilution (7). Following this general procedure, if L-cysteine were added to the N-benzoyl-DL-cysteine methyl ester and the mixture oxidized and hydrolyzed, the resulting L-cystine could easily be freed from the small amount of optically inactive cystine (predominately *meso*) by recrystallization of the hydrochloride salt (12) (If L-cystine were added to labeled DL-cystine that part of the labeled L-form bound as *meso*-cystine would, of course, not be recovered). But if a sample of high activity is desired or if the specific activity of the sulfur is low the following preparation is preferable.

Oxazoline salt rearrangement. The rearrangement of the hydrochloride of an oxazoline was first reported by Wislicenus and Körber (8), but apparently has

[1] In the previous paper (10b) two references were omitted. One concerns a preparation of methyl α-benzamido-β-chloro-DL-propionate by Painter (5) and the other is a pertinent oxazoline paper by Elliott (6).

not been studied with respect to organic acids. Although preliminary results indicated general applicability of this scheme, the present report deals with one example only.

By means of the brucine salt, benzoyl-L-serine was conveniently separated from its isomer and converted to 2-phenyl-4-carboxy-L-oxazoline. This acid was added to a pyridine solution of thiobenzoic acid prepared *in situ*, the mixture heated on the steam-bath for two minutes, and the crude N,S-dibenzoyl-L-cysteine isolated. Hydrolysis of the S-benzo group took place easily in sodium hydroxide or sodium methoxide, and the N-benzo group was subsequently removed by acid hydrolysis. Removal of both groups by acid gave somewhat lower yields and took more time.

The hydrogen chloride present in an equivalent amount in the reaction mixture might be expected to compete with the thiobenzoic acid, and it had been observed that heating pyridine hydrochloride with the oxazoline ester in alcohol readily gave III. However, the reactivity of the thio-acid was so much greater that the presence of hydrogen chloride did not noticeably decrease the yield.

EXPERIMENTAL

Preparation of D- *and* L-*benzoylserine.* An equivalent amount of brucine was added to N-benzoyl-DL-serine and the mixture dissolved in a solvent mixture of one part of alcohol and ten parts of acetone. Crystals formed and were filtered after one hour. This fraction was predominantly the brucine-salt of the L-form. Further purification was effected in the same solvent by solution in a little alcohol, and then adding ten times the volume of acetone. Rapidity of crystal formation was taken as an index of purity, but the chief criterion of purity was the absence of the D-form in the material (usually oily) left after removal of the acetone-alcohol mother liquor on the steam-bath under reduced pressure. The brucine salt of N-benzoyl-D-serine was found to be only slightly soluble in cold water, although the presence of the L-salt appeared to increase this solubility and to extend the time necessary for its separation from aqueous solution. To test for the presence of the D-salt, a small portion was dissolved in an equal volume of cold water. If no crystals formed after an hour in the ice-bath the sample was considered to be the L-salt and was recrystallized from alcohol-acetone. Due to the great solubility of the L-salt in water, purification of the D-salt by recrystallization from hot water was easily accomplished.

The brucine salts were dissolved in chloroform and the acid extracted into 2 *N* sodium hydroxide. Addition of hydrochloric acid gave the respective enantiomorphs. In a typical preparation, 39.3 g. of the L-salt was dissolved in 50 ml. of chloroform, extracted with 31 ml. of 2 *N* sodium hydroxide, and both solvents subsequently washed with a fresh portion of the other; then the alkaline solution was acidified and the product precipitated crystalline. The total recoverable *N-benzoyl-*L*-serine* was 11.8 g., m.p. 145–147°. Purified from water it separated in needle clusters and melted at 147–149° (gas). Its dimorphous nature was indicated by the fact that it melted completely when placed in the bath at 130°, resolidified and remelted at 147–148.5°, $[\alpha]_D^{22}$ +43.6° (*c*, 1 in 95% ethanol).

Anal. Calc'd for $C_{10}H_{11}NO_4$: C, 57.41; H, 5.30.
Found: C, 57.59; H, 5.29.

For N-benzoyl-D-serine, $[\alpha]_D^{22}$ −41.8° (*c*, 1 in 95% ethanol).

A commercial sample of L-serine was benzoylated in sodium carbonate solution with benzoyl chloride and although the product was predominately N-benzoyl-DL-serine, the N-benzoyl-L-serine obtained in this manner was used to identify the products of the separation described above. This result corresponds with similar racemizations using acetic anhydride (9).

*N-Benzoyl-*L*-serine methyl ester.* The conversion of the acid to the methyl ester using ethereal diazomethane did not always proceed smoothly, as some unidentified ether-in-

soluble oil was formed, but it is believed the trouble lay in allowing the reaction to take place at the surface of the undissolved acid. N-Benzoyl-L-serine, 6.0 g., was suspended in dry ether and the ethereal diazomethane solution added carefully, to keep the reaction in the solution phase, above and out of contact with the solid. The solution was stirred between additions of diazomethane in order to dissolve more of the acid. The product separated crystalline and no oily residue was apparent. It was filtered and more was obtained from the mother liquor. After recrystallization from benzene it weighed 5.1 g. (80%), m.p. 83–86°. The analytical sample had m.p. 84–86°, $[\alpha]_D^{26}$ +17.7° (*c*, 1 in 95% ethanol).

Anal. Calc'd for $C_{11}H_{13}NO_4$: C, 59.19; H, 5.87.
Found: C, 59.33; H, 5.87.

N-Benzyl-D-serine methyl ester was prepared as above, m.p. 84–86°.

Anal. Found: C, 59.15; H, 5.89. $[\alpha]_D^{23}$ −12.1° (*c*, 1 in 95% ethanol).

2-Phenyl-4-carboxymethyl-L-oxazoline. The preparation of the racemate has been described (10) but the optically active oxazoline salt was considerably less stable toward rearrangement to the β-chloropropionic acid derivative than the racemate. Its tendency to crystallize was less and this might have been a factor contributing to its instability. For example the DL-oxazoline salt could be kept for thirty minutes at room temperature without appreciable rearrangement, but under these conditions the D-salt (as an oil) completely rearranged to methyl α-benzoylamino-β-chloro-D-propionate. N-Benzoyl-L-serine methyl ester, 3.9 g., was covered with dry ether and 3 ml. of thionyl chloride slowly added while stirring by hand and keeping the temperature at approximately 5°. A heavy gum formed first; this became much lighter-bodied on continued manipulation and began to crystallize in about 20 minutes (the oil did not always crystallize). After approximately two hours, excess ether and thionyl chloride were removed under reduced pressure while keeping cold. Chilled dry pyridine (20 ml.) was slowly added with stirring and chilling. The dark red solution was then poured into a cold solution of 18 g. of sodium carbonate in 200 ml. of water. The product was taken into ether, then recovered, and distilled as a pale yellow oil, b.p. 133–137° at 2 mm. Distilled again at 131–133° (2 mm.), it weighed 2.88 g. (80%) $[\alpha]_D^{23}$ +118° (*c*, 1 in 95% ethanol).

Anal. Calc'd for $C_{11}H_{11}NO_3$: C, 64.38; H, 5.40.
Found: C, 64.18; H, 5.54.

This ester decomposed somewhat on standing several weeks. Hydrolysis in slightly more than the equivalent amount of 2 *N* sodium hydroxide gave a crystalline sodium salt which was recovered by concentrating the aqueous solution under reduced pressure and adding acetone, in which the salt is insoluble. The rotation was unchanged after solution in warm water and reprecipitation with acetone. Probably hydrated, the salt sintered at 85°, resolidified, and was unmelted at 250°. On the basis of four molecules of water of hydration indicated by titration, the yield was 75–80%.

2-Phenyl-4-carboxy-D-oxazoline sodium salt, similarly made, showed $[\alpha]_D^{25}$ −66° (*c*, 1 in 95% ethanol).

2-Phenyl-4-carboxy-L-oxazoline formed crystalline as an ice-cold suspension of the sodium salt was slowly and with vigorous stirring neutralized with an equivalent amount of 3 *N* hydrochloric acid. Care was necessary because of the ease with which the free acid hydrolyzed, and it was important that the acid separated during the titration. The suspension was seeded if necessary. The sodium salt (1.0 g.) required 1.2 ml. of 3.1 *N* hydrochloric acid to bring the *p*H of the suspension to 3.9 (Accutint 60). Filtered and washed with cold water and dried in a desiccator under reduced pressure, the product weighed 0.62 g., m.p. 125–126°. Yield, 92.5% based on an estimated salt hydration of four molecules of water. Recrystallization from hot, dry benzene lowered the melting point, probably because of unavoidable hydrolysis. $[\alpha]_D^{20}$ +225° (*c*, 1 in dry pyridine).

Anal. Calc'd for $C_{10}H_9NO_3$: C, 62.82; H, 4.74.
Found: C, 62.57; H, 4.94.

A pyridine solution showed no significant change in optical rotation on standing 23 hours at 20°.

*Methyl α-benzoylamino-β-chloro-*L*-propionate* was prepared by the method used for the L-oxazoline (see above) with the exception that the temperature was not lowered and the suspension was refluxed for an hour to assure rearrangement. Yield, before purification from alcohol, about 85%; m.p. 114–115.5°, $[\alpha]_D^{23}$ −14° (*c*, 1 in 95% ethanol). Comparable values for the D-isomer have been reported (11).

Anal. Calc'd for $C_{11}H_{12}ClNO_3$: C, 54.67; H, 5.01.
Found: C, 55.01; H, 5.23.

In one experiment the rearrangement of the oily oxazoline salt was complete in 30 minutes at room temperature.

*Methyl α-benzoylamino-β-bromo-*DL*-propionate.* 2-Phenyl-4-carboxymethyl-DL-oxazoline, 2.05 g., was dissolved in dry ether and the hydrobromide salt made by passing dry hydrogen bromide through the solution. The oil which separated soon crystallized. The ether was distilled and the salt held for five minutes on the steam-bath. The crude product was washed with water; 2.7 g. (94%), m.p. 115–118°. It was purified by dissolving in hot benzene and adding petroleum ether, m.p. 115–117°.

Anal. Calc'd for $C_{11}H_{12}BrNO_3$: Br, 27.93. Found: Br, 27.99.

*N,N′-Dibenzoyl-*DL*-cystine.* DL- and *meso*-cystine were prepared by the method of Loring and du Vigneaud (12). The reaction of benzoyl chloride with DL-cystine (from 5.0 g. of the hydrochloride dissolved in a sodium carbonate solution and chilled in an ice-bath) proceeded slowly over several hours. Acidification gave a solid which was purified by recrystallization from glacial acetic acid; 4.4 g., m.p. 164–167°. The analytical sample had m.p. 165–166.5°. An unidentified inactive form melting at 168° has been reported (13).

Anal. Calc'd for $C_{20}H_{20}N_2O_6S_2$: C, 53.55; H, 4.50.
Found: C, 53.46; H, 4.65.

Owing to the fact that this compound was also the principal product obtained from the benzoylation of *meso*-cystine, it was necessary to resolve it in order to prove its structure. Accordingly, N,N′-dibenzoyl-L-cystine was prepared and purified by recrystallization from glacial acetic acid; m.p. 190–192°, $[\alpha]_D^{20}$ −202° (*c*, 1 in 95% ethanol). The melting point 195.5–196.5° and $[\alpha]_D^{20}$ −222° have been reported (14). It was dissolved in alcohol together with an equivalent amount of quinine and the crystalline salt caused to precipitate by the addition of water. The salt had m.p. 161–163°. This same salt was separated from a solution of the quinine salt of N,N′-dibenzoyl-DL-cystine. A mixture melting point of the salts was not lowered, and on decomposition with hydrochloric acid the salt yielded N,N′-dibenzoyl-L-cystine, m.p. 192–194°, $[\alpha]_D^{20}$ −203° (*c*, 1 in 95% ethanol).

N,N′-Dibenzoyl-meso-cystine. The benzoylation of *meso*-cystine from 5.0 g. of dihydrochloride in the manner described for DL-cystine yielded a product which on purification from glacial acetic acid proved to be the above-described DL-form; yield 41%. The recrystallization mother liquor yielded a solid which was recrystallized from alcohol to give 0.6 g. (8%) melting at 186–188°. Further purification raised the melting point to 190–191°. It showed no optical activity and a mixture melting point with N,N′-dibenzoyl-L-cystine was lower.

Anal. Calc'd for $C_{20}H_{20}N_2O_6S_2$: C, 53.55; H, 4.50.
Found: C, 53.83; H, 4.66.

Its isolation along with the DL-form as one of the oxidation products of N-benzoyl-DL-cysteine further established its identity.

*N-Benzoyl-*DL*-cysteine.* N,N′-dibenzoyl-DL-cystine (0.5 g.) was stirred with zinc in a mixture of equal parts of 6 *N* HCl and dioxane (8 ml.). Most of the solid dissolved in an hour. After 2.5 hours the solvent was taken to a small volume under reduced pressure. The product crystallized, and was recovered. Hot benzene extraction of the product followed by benzene recrystalliation gave 0.14 g., m.p. 136–137°.

Anal. Calc'd for $C_{10}H_{11}NO_3S$: C, 53.32; H, 4.92.
Found: C, 53.80; H, 5.05.

*N,N′-Dibenzoyl-*DL*-cystine dimethyl ester.* The acid (0.2 g.) in ethereal suspension was reacted with etheral diazomethane. During the reaction the crystalline product replaced the acid in suspension. The ester was purified from alcohol, m.p. 168–169°, wt. 0.177 g. (83%).

Anal. Calc'd for $C_{22}H_{24}N_2O_6S_2$: C, 55.44; H, 5.08.
Found: C, 55.72; H, 5.23.

N,N'-Dibenzoyl-meso-cystine dimethyl ester. The ester was prepared as above with diazomethane; m.p. 169.5–171.5°.

Anal. Calc'd for $C_{22}H_{24}N_2O_6S_2$: C, 55.44; H, 5.08.
Found: C, 55.21; H, 4.98.

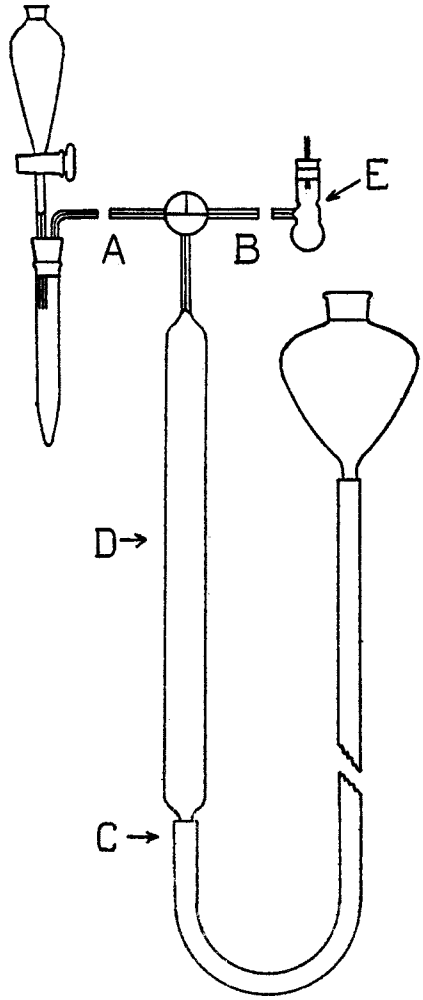


FIGURE 1. HYDROGEN SULFIDE REACTION APPARATUS

Apparatus for handling hydrogen sulfide. The apparatus used for all reactions in which hydrogen sulfide was a reactant appears in Figure 1. Stannous sulfide was used as the source of hydrogen sulfide and its properties make it well suited for this purpose. Sulfide in an alkaline solution was easily recovered by first adding stannous chloride solution, then acidifying with acetic acid and centrifuging. Stannous sulfide appeared to be slightly soluble in alkaline solution (lead acetate test), but was not decomposed by acetic acid. The air in the cylinder was displaced by mercury and the leveling bulb lowered below 76 cm. so that an empty space appeared at the top of the cylinder. Then the 15-ml. centrifuge tube containing stannous sulfide and connected at A was evacuated by a water-pump at

B, the stopcock turned to connect it with the cylinder, and the pump shut off. About 3 ml. of 85% phosphoric acid was added through the separatory funnel and the suspension heated with a flame to generate hydrogen sulfide. The leveling bulb was raised to increase the pressure, and hence the temperature to which the phosphoric acid could be heated. The sulfide dissolved to give a yellowish solution which became colorless after brief boiling. After all gas was displaced from the centrifuge tube by hot acid the cylinder was cut off with the stopcock. The reaction flask was attached at B, evacuated by a water-pump at A, and hydrogen sulfide admitted by turning the stopcock.

The cylinder was supported by a clamp at C. The rubber hose provided enough play so that this point was also the pivot for shaking. A cone-drive motor held a short piece of bent rod which was attached to the stopcock through a small spring. The apparatus was shaken at low motor speed and the degree of agitation controlled by a loosely fitting clamp at D.

A constriction in the reaction flask at E supported a circle of filter paper on which the sample of methyl α-benzoylamino-β-chloropropionate rested during absorption of hydrogen sulfide by magnesium methoxide. The tube through the rubber stopper (closed at the upper end) was used to push the sample into the flask, and at the end of the reaction to pass nitrogen through the solution to flush unreacted hydrogen sulfide into a sodium hydroxide absorption tube at A.

*Molecular compound of N,N'-dibenzoyl-*DL*-cystine dimethyl ester and N,N'-dibenzoyl-meso-cystine dimethyl ester. A.* This substance was obtained in 95% yield when 0.5 g. of each of the components were dissolved together in alcohol; m.p. 153–155°, unchanged by recrystallization.

Anal. Calc'd for $C_{22}H_{24}N_2O_6S_2$: C, 55.44; H, 5.08.
Found: C, 55.54; H, 5.05.

B. Methyl alcohol was removed from 2.1 ml. (2 × theory) of 2.0 *N* magnesium methoxide solution under reduced pressure, the crystalline solid transferred to the reaction flask, and 1.0 ml. of dry pyridine added. The filter paper disk was pressed into the neck of the flask, 0.50 g. of methyl α-benzoylamino-β-chloro-L-propionate placed on the paper, and the flask stoppered. It was attached to the hydrogen sulfide cylinder which contained 65 ml. of hydrogen sulfide generated from 0.390 g. of stannous sulfide (1.25 × theory). The reaction flask was carefully evacuated and the hydrogen sulfide *slowly* admitted (a sudden rush of gas might blow the solid into the nitrogen inlet tube). The flask was gently shaken with absorption of most of the hydrogen sulfide and formation of a yellow solution. After ten minutes it was put in an ice-bath and the pressure dropped in five minutes to a minimum of −27 cm. of mercury, measured by the leveling bulb which was lowered to keep mercury from being drawn into the flask. The solid was then pushed into the pyridine solution with the nitrogen inlet tube (solid which stuck to the sides was freed by tapping). In seven minutes the solid had dissolved to give a yellow-green solution which was shaken for one hour in the ice-bath, and then with a sodium hydroxide absorption tube in place the end of the inlet tube was opened and 0.5 ml. of 6 *N* hydrochloric acid was forced into the flask followed by a slow stream of nitrogen for thirty minutes. The colorless solution was then titrated with 14 ml. of 0.1 *N* iodine solution and the crystalline product recovered and purified from alcohol, wt. 0.363 g., m.p. 152–154.5°. Mixture melting point determinations showed this substance to be identical with that obtained from a similar preparation using inactive starting material and with the molecular compound prepared from N,N'-dibenzoyl-DL-cystine dimethyl ester and its *meso*-isomer.

All remaining organic material was taken into and recovered from chloroform. Five drops of water and 0.2 g. of potassium hydroxide was added and the mixture held on the steam-bath briefly until a solution resulted; then it was heated gradually to 410–420° and held at this temperature for five minutes during which time carbonization took place. The material was taken up in water and added to the sodium hydroxide solution previously used to trap unreacted hydrogen sulfide. Stannous sulfide was precipitated with stannous chloride solution followed by acetic acid. The sulfide was assayed by conversion to hydrogen sulfide which was oxidized by 0.1 *N* iodine solution.

S used, mole	0.00259	Product, mole	0.00152
S recovered, mole	0.00071	Yield on halide basis, %	73.5
S reacted, mole	0.00188	Yield on S basis, %	58.7
Halide used, mole	0.00207	Yield on recovered S basis, %	81

C. From methyl α-benzamidoacrylate. Methyl α-benzoylamino-β-bromo-DL-propionate, 0.15 g., was put in 0.5 ml. of cold pyridine and the suspension held in an ice-bath with occasional shaking for one hour; the solid dissolved. Dilute nitric acid was added in excess and 0.11 g. (72.4%) of starting material was recovered. Silver bromide, 0.024 g. (24%) was recovered from the mother liquor. Under the same conditions and in the presence of an equivalent amount of hydrogen sulfide dissolved in the pyridine, no N,N′-dibenzoyl-aminocystine dimethyl ester was isolated after removal of the hydrogen sulfide and titration with iodine solution (required only 2% of theory). In a similar experiment in which the cold pyridine solution was left in contact with excess hydrogen sulfide for twenty hours the yield of the molecular compound of the N,N′-dibenzoyl-DL- and *meso*-cystine dimethyl esters was 67%. At room temperature the yield was 60% after twenty-three hours with excess hydrogen sulfide. With an equivalent amount of hydrogen sulfide and a reaction time of seventy-two hours at room temperature, (the reaction was ended when the pressure over the reaction mixture stopped dropping) the yield of the isolated product was only 8%.

Although methyl α-benzamidoacrylate was not characterized due to the ease with which it polymerized, its formation was proved in the following way. Methyl α-benzamido-β-bromo-DL-propionate, 0.5 g., was dissolved in 1 ml. of pyridine and the separated pyridine hydrobromide filtered at the end of an hour. From this was obtained silver bromide representing 74% of the original bromine. The filtrate was taken to an oil under reduced pressure and the oil dissolved in 2 *N* sodium hydroxide. Acidification gave α-benzamidoacrylic acid; yield 72%, m.p. 152–155° (gas, turn orange). A mixture melting point with another sample (10b) proved its identity.

The same transformation took place with the chlorine analog but much more slowly. Ionic chlorine amounted to 59% after 24 hours at room temperature.

D. From 2-phenyl-4-carboxymethyl-DL-oxazoline. A solution of 0.5 g. of the oxazoline in 1 ml. of dry pyridine reacted with hydrogen sulfide containing some oxygen. The only crystalline material recovered weighed 0.033 g., m.p. 151–153°. Its identity as the molecular compound was established by a mixture melting point. The remainder of the material was not identified.

N,N′-Dibenzoyl-L-cystine dimethyl ester was prepared by the action of diazomethane on N,N′-dibenzoyl-L-cystine. It was purified from alcohol, m.p. 176–178°. This compound was also obtained by the action of hydrogen sulfide on 2-phenyl-4-carboxymethyl-L-oxazoline in the manner described for the optically inactive form and in the same poor yield. A mixture melting point of the two specimens was not depressed. A previously reported (14) melting point is 176–177°.

Anal. Calc'd for $C_{22}H_{24}N_2O_6S_2$: C, 55.45; H, 5.08.
Found: C, 55.78; H, 5.32.

Hydrolysis of DL-meso-dibenzoylcystine dimethyl ester. Three-tenths g. of the molecular compound in one ml. of 48% HBr became oily and evolved gas when the suspension was heated on the steam-bath. The oil shortly dissolved and the pale yellow solution was held on the steam-bath for four hours. During the hydrolysis benzoic acid separated. A little water and excess pyridine were added and the cystine allowed to crystallize over several hours. The yield varied between 0.130 and 0.139 g. (86–92%).

β,β′-Thiobis-(N-benzoylalanine dimethyl ester) or dibenzoyllanthionine dimethyl ester. When methyl α-benzamido-β-chloro-DL-propionate, 0.50 g., was added to an equivalent amount of sodium hydrosulfide in absolute methanol, the only product isolated weighed 0.14 g. and was purified from alcohol, wt. 0.11 g., m.p. 153–154°. A mixture melting point with the DL-*meso*-N,N′-dibenzoylcystine dimethyl ester molecular compound was strongly depressed.

Anal. Calc'd for $C_{22}H_{24}N_2O_6S$: S, 7.21. Found: S, 7.30.

In a comparable experiment using magnesium hydrosulfide in absolute methanol, only 0.04 g. of the sulfide was isolated; 52% of the product was the cystine derivative.

N,S-Dibenzoyl-L-cysteine. Stannous sulfide, 0.301 g., was converted to 50 ml. of hydrogen sulfide and allowed to react with 0.281 g. of benzoyl chloride dissolved in 1 ml. of dry pyridine. The reaction was exothermic and at the end a white salt (probably pyridine hydrochloride) was present in the yellow solution of thiobenzoic acid. A vacuum of 59 cm. of mercury had developed by the end of the reaction which was over in about 15 minutes. Air was admitted, the flask was detached, and 0.40 g. of 2-phenyl-4-carboxy-L-oxazoline was added to the solution. All solid dissolved on shaking and gentle warming, and the solution was then held for two minutes in the steam-bath. Excess 3 *N* HCl was added to the solution and crystallization of the product induced with a drop of benzene. After drying, the product was triturated with petroleum ether which removed a little oil. The crude material weighed 0.52 g. (79% based on SnS); m.p. 171–178°. Other runs gave yields of 78–82%. The compound was recrystallized by dissolving in hot ethyl acetate and concentrating the solution. The analytical sample melted at 179–182° with shrinking from 173°; $[\alpha]_D^{21}$ −76° (*c*, 1 in 95% ethanol).

Anal. Calc'd for $C_{17}H_{15}NO_4S$: C, 61.99; H, 4.59.
Found: C, 61.77; H, 4.61.

This compound was hydrolyzed with sodium hydroxide, converted to the methyl ester with diazomethane, and oxidized with iodine to give *N,N'-dibenzoyl-L-cystine dimethyl ester* in 60% yield. A mixture melting point with an authentic sample confirmed its identity.

N-Benzoyl-S-p-chlorobenzoyl-DL-cysteine was similarly made in over 80% yield. It was purified from glacial acetic acid, m.p. 203–204°.

Anal. Calc'd for $C_{17}H_{14}ClNO_4S$: C, 56.12; H, 3.88.
Found: C, 56.19; H, 4.11.

N,S-Dibenzoyl-DL-cysteine methyl ester was similarly made from 2-phenyl-4-carboxymethyl-DL-oxazoline. The crude product was obtained in 82% yield, m.p. 112–117°. It was purified by dissolving in alcohol and adding petroleum ether; m.p. 119–120° (resolidified to melt at 135–136°).

Anal. Calc'd for $C_{18}H_{17}NO_4S$: C, 62.96; H, 4.99.
Found: C, 62.67; H, 5.03.

N-Benzoyl-S-p-nitrobenzoyl-DL-cysteine was made by heating 2-phenyl-4-carboxy-DL-oxazoline and *p*-nitrothiobenzoic acid together in dry dioxane. The crude product was obtained in 80% yield and was recrystallized from glacial acetic acid, m.p. 178.5–180.5°.

Anal. Calc'd for $C_{17}H_{14}N_2O_6S$: C, 54.54; H, 3.77.
Found: C, 54.47; H, 4.03.

Hydrolysis of N,S-dibenzoyl-L-cysteine. A number of attempts to hydrolyze this compound with 48% HBr gave crude cystine in not over 48% yield (based on SnS). Both sodium hydroxide and sodium methoxide rapidly removed the S-benzoyl group, and after oxidation to the disulfide the N-benzoyl group was removed by heating in 48% HBr for 4–7 hours at 100°. Whereas the yield from the methoxide hydrolysis was higher (50% based on SnS), the optical activity of the cystine was lower, $[\alpha]_D^{21}$ −172° (*c*, 0.6 in 1% HCl). Since a sample of L-cystine proved relatively stable under these same conditions of heating in acid, partial racemization in sodium methoxide is indicated.

N,S-Dibenzoyl-L-cysteine, 0.27 g., was dissolved in 1.7 ml. of 2 *N* NaOH and after a few minutes the solution was acidified and titrated with 0.2 *N* KI_3 solution. The product mixed with benzoic acid came out as a solid which was removed, water-washed, and then heated on the steam-bath with 2 ml. of 48% HBr. The solid dissolved in approximately an hour and benzoic acid separated as the hydrolysis proceeded. After 4 hours the suspension was cooled, water and excess pyridine added and the cystine allowed to form overnight. The cystine was collected, dissolved in a little diluted HCl and the solution filtered. Reprecipitation with pyridine afforded the amino acid. After an hour it was filtered and washed with water and alcohol, wt., 0.051 g. (42.5% based on SnS); $[\alpha]_D^{22}$ −212° (*c*, 0.5

in 1% HCl). A sample of commercial cystine (Merck) showed $[\alpha]_D^{22}$ −230° (*c*, 0.5 in 1% HCl).

Anal. Calc'd for $C_6H_{12}N_2O_4S_2$: C, 29.99; H, 5.03.
Found: C, 29.78; H, 5.02.

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SUMMARY

Two syntheses of cystine are presented. One is a modification of an old method and the other depends on the rearrangement of an oxazoline salt. Both are designed for the use of isotopic sulfur.

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SOME MERCAPTOLES OF 1,2-ETHANEDITHIOL[1]

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Two dithiolanes from 1,2-ethanedithiol and simple ketones, acetone and benzophenone, are recorded (1). It seemed worth while to enlarge this group. Dithiolanes described herein have been prepared from several aliphatic ketones, from acyl benzenes—acetophenone to caprylophenone, from cyclopentanone,

TABLE I

PROPERTIES AND ANALYSES OF 1,3-DITHIOLANES WITH 2,2-SUBSTITUENTS

NO.	KETONE	B.P.		n_D^{25}	d_4^{25}	ANALYSES					
						C		H		S	
		°C.	MM.			Calc'd	Found	Calc'd	Found	Calc'd	Found
1	Methyl ethyl	55	3	1.5350	1.0680	48.60	48.83	8.16	8.33	43.24	43.45
2	Methyl isopropyl	61	3	1.5302	1.0511	51.80	51.87	8.69	8.86	39.51	39.71
3	Dipropyl	86	2	1.5200	1.0158	56.79	57.01	9.53	9.69	33.68	33.52
4	Ethyl butyl	102	5	1.5191	1.0126	56.79	57.01	9.53	9.69	33.68	33.52
5	Diisopropyl[a]	94	4	—	—	56.79	56.80	9.53	9.67	33.68	33.62
6	Methyl hexyl	120	6	1.5110	0.9926	58.77	58.87	9.86	10.13	31.37	31.72
7	Diisobutyl	115	6	1.5115	0.9892	60.49	60.43	10.16	10.43	29.36	29.64
8	Acetophenone	131	3	1.6162	1.1819	61.18	61.57	6.16	6.41	32.66	32.83
9	Propiophenone	135	3	1.6050	1.1542	62.80	63.12	6.71	6.93	30.49	30.62
10	Butyrophenone	145	4	1.5915	1.1287	64.24	64.44	7.19	7.48	28.57	28.32
11	Valerophenone	154	4	1.5830	1.1035	65.49	65.75	7.61	7.86	26.90	26.82
12	Caprylophenone	169	4	1.5755	1.0838	66.61	66.98	7.99	8.30	25.40	25.39
13	Cyclopentanone	89	5	1.5679	1.1464	52.45	53.14	7.55	7.67	40.00	39.89
14	Cyclohexanone	107	5	1.5650	1.1288	55.12	55.44	8.10	8.34	36.79	37.20
15	4-Methylcyclohexanone	126	13	1.5478	1.0907	57.40	57.97	8.57	8.77	34.05	33.89
16	Camphor	131	4	1.5606	1.0839	63.10	63.75	8.83	9.06	28.07	28.39
17	Fluorenone[b]	—	—	—	—	70.26	70.50	4.72	4.83	25.01	25.05
18	2-Acetylthiophene	123	1.4	1.6300	1.2756	—	—	—	—	47.52	47.64
19	2-Benzoylthiophene[c]	—	—	—	—	—	—	—	—	36.36	36.14

[a] M.p. 40°. [b] M.p. 125°. [c] M.p. 53.5°.

cyclohexanone, 4-methylcyclohexanone, camphor, and fluorenone. Those from the last five are *spiro* compounds. In addition there are two from thiophene derivatives, 2-acetylthiophene and 2-benzoylthiophene.[2] Properties and analyses are given in Table I.

[1] The compounds were prepared in Personal Laboratory at Johns Hopkins University. Determinations of properties and analyses were done at Du Pont Experimental Station, Wilmington, Delaware.

[2] Determination of properties and analyses by H. O. Hartough and S. L. Meisel of Socony-Vacuum Laboratories.

EXPERIMENTAL

All of the dithiolanes were prepared in practically the same way, saturating a mixture of the ketone and 1,2-ethanedithiol with hydrogen chloride. The two solid ketones were brought into solution by the addition of benzene. With the two active ketones, cyclopentanone and cyclohexanone, aqueous hydrochloric acid was used instead of the gas. In some cases the reactants were in stoichiometric proportions and in others the ketone was in slight excess while in one, No. 9, 84% excess of the dithiol was put in by mistake. Variations in the proportions appear to make no difference in the products. The aliphatic ketones reacted at once, with evolution of heat; so did cyclopentanone and cyclohexanone and its 4-methyl derivative, while the acyl benzenes reacted appreciably slower. To facilitate the collection of the separated water, calcium chloride was added to some and zinc chloride to others. The zinc salt is better. After a reaction mixture had stood overnight the organic layer was decanted and resaturated with hydrogen chloride. Ether was added, the ether solution separated, washed with water and dilute alkali, and dried over potassium carbonate. After removal of the ether the residue was distilled through an 8-inch Vigreux column. There were no appreciable distillation residues. The dithiolane from diisopropyl ketone was further purified by recrystallization from methanol. Those from fluorenone and benzoylthiophene were not distilled but were recrystallized from ethanol.

SUMMARY

The preparation and properties of 19 new 2,2-substituted-1,3-dithiolanes, 7 from aliphatic, 5 from aralkyl, 5 from cyclic, and 2 from thiophene ketones, are described.

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[CONTRIBUTION FROM CHELSEA POLYTECHNIC, AND MINING AND TECHNICAL COLLEGE, WIGAN]

THE NATURE OF THE CATALYST IN THE PERKIN CONDENSATION

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The conclusion that the catalyst in the Perkin condensation may be a sodium compound other than the salt of a fatty acid has been re-examined in the light of fresh evidence.

The difference of opinion which existed amongst workers at the close of the last century as to the respective rôles of the acid anhydride and the sodium salt of the fatty acid (1, 2) has been resolved in recent years, and it is now held that condensation occurs between the acid anhydride and the aldehyde, the salt acting as a basic catalyst. A considerable amount of evidence has been offered in support of this view. Kalnin (3) showed that the sodium salts of fatty acids were not specific as catalysts in this condensation, and that the reaction would also proceed in the presence of the stronger tertiary organic bases, and of carbonates, phosphates, sulfites, and sulfides of sodium and potassium. In consequence of this evidence Kalnin (3) proposed a mechanism for the reaction involving the addition of the aldehyde to the enolized anhydride, followed by enolization of the condensation product, and subsequent elimination of a molecule of fatty acid to give the unsaturated product.

Therefore it is to be expected that other basic catalysts will serve to bring about the change, and further evidence has been provided by the work of Kuhn and Ishikawa (4) and Bakunin and Pecerillo (5), who also confirmed that organic tertiary bases were effective in catalyzing the reaction, although differing somewhat with the views of Kalnin as to the mechanism involved. An intensive study of the mechanism was later made by Breslow and Hauser (6) who showed that by heating the sodium salt and the anhydride of unlike fatty acids an equilibrium was established (confirming indications by earlier workers), so that in the presence of benzaldehyde a mixture of two cinnamic acids was obtained, the relative proportions of which varied with changing temperature. In the light of these facts the catalytic function of the sodium salt of the organic acid is rendered acceptable and a general basic mechanism for aldolization processes is extended to this reaction (7, 8); further proof was furnished by the isolation of the intermediate aldol product in the condensation of benzaldehyde with ethyl isobutyrate in the presence of sodium triphenylmethyl.

We have successfully repeated Kalnin's experiments using a tertiary organic base and have added sodium borate, sodium formate, and disodium tartrate to the list of effective condensing agents. In the case of sodium and potassium carbonates and sodium sulfite, however, we have demonstrated that carbon dioxide or sulfur dioxide is evolved in the course of the condensation, and that in each case sodium or potassium acetate must really be the catalyst. Although sodium

formate appears to be a catalyst it rapidly loses carbon monoxide during reaction and sodium acetate is produced in quantity.

Independent experiments have been conducted in the absence of benzaldehyde. The greatest care was taken to remove all traces of acetic acid from the acetic anhydride and to exclude the ingress of moisture to the anhydrous reagents, because, as water is formed in the Perkin condensation, it was important to see if reaction between the two components could be initiated in its absence. We are satisfied, therefore, that with sodium and potassium carbonates the carbon dioxide arises in the manner indicated by the following equation:—

$$Na_2CO_3 + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + CO_2$$

In the case of sodium carbonate, quantitative yields of carbon dioxide and sodium acetate were obtained, but with potassium carbonate, although the correct amount of carbon dioxide was evolved, the solid product was shown to be a double compound of potassium acetate and acetic anhydride the proportions of which appeared to vary appreciably. Separate experiments with potassium acetate and acetic anhydride alone at room temperature and at 100° led to the double compound of variable composition.

With the use of sodium sulfite and sodium formate the chief interaction with acetic anhydride in each case is set out in the equations:

$$Na_2SO_3 + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + SO_2$$
$$2\ HCOONa + (CH_3CO)_2O \rightarrow 2\ CH_3COONa + 2\ CO + H_2O$$

In cases where the resultant acid anhydride is not gaseous, *i.e.* with sodium borate and disodium tartrate, an equilibrium is doubtless established between acetic anhydride and the salt added as condensing agent [*cf.* (6)] and, on this basis, the condensation which occurs in the presence of all the salts heretofore described, may be attributed to the intervention of sodium (or potassium) acetate. The production of this salt is also implied if sodium alkoxide and sodium triphenylmethyl are employed as condensing agents, but we and Muller (9) have used the latter compound under customary experimental conditions without conclusive results Nevertheless it must be borne in mind that Hauser, *et al.* (6, 7) have employed sodium triphenylmethyl to bring about a Perkin type of reaction involving the ester of a fatty acid as the second component in place of the anhydride; it is also noteworthy that the conditions were much milder than in the orthodox reaction using sodium acetate as catalyst.

The experiments described in the present paper have helped to place in their proper perspective the pieces of evidence that have accrued in favor of the application of the theory of general basic catalysis to the Perkin reaction. Without in any way doubting the validity of this viewpoint, it must be recognized that the supporting evidence is confined to the observed catalytic effects of certain tertiary organic bases, and presumably to the limited successful use of sodium triphenylmethyl. It cannot now be doubted that sodium (or potassium) acetate is formed when the alkali metal salts of weak inorganic and organic acids are used to promote the Perkin reaction. This in no way implies that any specific

catalytic influence is to be ascribed to sodium (or potassium) acetate; it means simply that the production of this salt in such cases is unavoidable and that the experiments in question do not themselves provide valid support for the application of the general basic mechanism to the Perkin reaction.

According to this mechanism, acetic anhydride is not a necessary second component, and so other sources of the acetyl group might be used to advantage. It is significant, therefore, that we have succeeded in utilizing diacetanilide and acetamide as alternatives in this connection, namely, in preparing specimens of cinnamic acid from benzaldehyde in the presence of anhydrous sodium acetate.

EXPERIMENTAL

Perkin reaction under anhydrous conditions. The Perkin condensation between benzaldehyde and acetic anhydride under the influence of various catalytic agents was conducted with scrupulously dried materials.

Benzaldehyde (0.091 mole), acetic anhydride (0.15 mole), and the anhydrous catalyst (0.06 mole) were heated together under reflux for eight hours at 180°, the product was then cooled and added to water (150 ml.). After removing benzaldehyde by steam-distillation, the residue was boiled with charcoal, filtered, acidified, and cooled. The deposited acid was recrystallized from water, and the yields of purified cinnamic acid produced by the various condensing agents are set out below. It is noteworthy that with the borate a homogeneous melt was produced but contrary to anticipation a superior yield of acid was not obtained.

CONDENSING AGENT	YIELD, %
Sodium acetate (fused)	54
Sodium formate	48
Disodium tartrate	17
Sodium borate (fused)	19
Sodium sulfite	12
Sodium carbonate	32
Potassium carbonate	21
Pyridine	1.4

In the progress of the condensations, evolution of carbon dioxide was observed where carbonates were the condensing agents, and of sulfur dioxide where sodium sulfite was employed. During the experiment in which sodium formate was used, copious evolution of carbon monoxide occurred in the first hour of heating; in the absence of benzaldehyde this also happens, and sodium acetate (confirmed by qualitative and quantitative analysis) was obtained in good yield as an end product. From the experiment employing disodium tartrate no evolution of gas was noted.

PURIFICATION OF REAGENTS

Acetic anhydride. Acetic anhydride (500 g.) was allowed to stand over phosphorus pentoxide (50 g.) for three hours, decanted and allowed to stand over ignited potassium carbonate for a further three hours. The supernatant liquid was then distilled, the fraction b.p. 136–138° being collected. After standing over phosphorus pentoxide for a further twelve hours the anhydride was shaken with ignited potassium carbonate, when no detectable reaction occurred. The product was finally distilled through a five-section Young and Thomas' fractionating column, and the distillate b.p. 136.0–138.0° refractionated, the final cut being collected in a weighing-burette, b.p. 137.8–138.0°/759.

Sodium carbonate and potassium carbonate. The carbonates of Analar quality were heated for one hour at 270° and stored *in vacuo* over phosphorus pentoxide for fourteen days.

Sodium sulfite. Hydrated sodium sulfite of Analar quality was dried *in vacuo* over phosphorus pentoxide for fourteen days. The loss in weight was theoretical and the satisfactory purity of the sulfite was established by volumetric analysis.

Sodium formate. The salt, freshly prepared from aqueous formic acid and sodium hydroxide, was dried at 90° under reduced pressure for two hours, and then stored over phosphorus pentoxide for one day (the purity was established by a sodium estimation).

Sodium tartrate. This salt was prepared in the same manner as for sodium formate, and gave a satisfactory sodium analysis.

Benzaldehyde. Benzaldehyde (250 g.) was shaken with dilute sodium carbonate solution, dried over calcium chloride, and distilled under reduced pressure. Further drying and refractionation gave pure benzaldehyde (b.p. 177.5–178.0°/767) collected in a weight-burette.

Apparatus for studying the reaction of acetic anhydride with anhydrous condensing agents. The reaction vessel consisted essentially of a flask (100 ml.) with a side-neck closed by a ground-glass stopper. Into the main neck was fitted a spiral water-cooled condenser closed at the end by a two-way stopcock, one exit connected to a calcium chloride tube and the other to a Mohr absorption apparatus containing aqueous potassium hydroxide (30%) fitted with a drying tube. A short inlet-tube closed by a stopcock passed through the main neck of the flask, so as to be just above the surface of the reactants, for flushing out the apparatus with carbon dioxide-free air. After thorough drying, the apparatus was quickly assembled and a current of dry, carbon dioxide-free air was passed through the apparatus. The Mohr absorption apparatus was then connected, and showed no change in weight over several hours.

Acetic anhydride (5 g. approx.) was next introduced into the flask from the weight-burette *via* the side-arm against a counter current of dry air and the side neck closed. The apparatus was connected by the two-way stopcock to the Mohr absorption apparatus, the flask was then immersed in an oil-bath at 150°, and a slow stream of dry air passed through the apparatus. Several experiments were conducted using different speeds of flow for the gas and it was found that the most satisfactory rate was 500 ml. per hour.

Volume of gas passed through the apparatus (ml).	*Wt. of acetic anhydride carried over (mg).*
500	27.0
1000	49.2
1750	82.2
2250	99.8

Mean weight of acetic anhydride carried over per 500 ml. of gas at 150° = 23.3 mg.

The corrections for experiments relating to other temperatures (110° and 145°) were also determined in this way.

Reaction of condensing agents with acetic anhydride. The dried reagents were introduced into the apparatus as previously described, a large excess of acetic anhydride being employed. The flask was placed into an oil-bath and raised to the required temperature, and when this point was reached a stream of dry air (500 ml./hr.) from the aspirator was passed through the apparatus. The carbon dioxide absorption vessel was weighed at intervals, and heating was continued until the absorption apparatus showed no further increase in weight. When the reaction was complete the contents of the flask were diluted with dry ether (50 ml.), filtered, the solid residue washed with ether, dried, weighed, and analysed both qualitatively and quantitatively.

Details of the experiments are given below.

Sodium carbonate. Sodium carbonate, 0.9666 g.; acetic anhydride, 5.8200 g.; temperature of reaction, 150°. There was no apparent reaction between the carbonate and anhydride until a temperature of 90° was reached; reaction was quite rapid at 150°.

VOL. OF GAS PASSED THROUGH APPARATUS, ML.	INCREASE IN WT. OF ABSORPTION BULBS, MG.	CORRECTED WT., MG.	CO_2 EVOLVED, %
500	427.8	392.8	97.9
1000	450.0	391.7	97.6
1500	473.2	391.6	97.6
2000	498.4	393.5	98.0
2500	523.8	395.6	98.5

Weight of solid from reaction, 1.5027 g. (100.4 %, based on sodium acetate). Qualitative tests showed the residue to be sodium acetate and this was confirmed as follows:—
200.4 mg. of the residue on ignition gave sodium carbonate (128.6 mg.; 99.5%) which on treatment with sulphuric acid gave sodium sulfate (182.6 mg.; 99.7%) and barium sulfate (675.5 mg.; 96.6%).

Sodium sulfite. Sodium sulfite, 1.2416 g.; acetic anhydride, 5.9585 g.; temperature of reaction, 145°. Reaction commences at 90–95°, and proceeds only slowly at 145°.

Vol. of gas passed through apparatus, ml.: 500, 1000, 1500, 2000, (3000), 4270, 6000.
SO_2 evolved, %: 44, 61, 78, 82, (90), 89, 89.

Weight of solid from reaction, 1.6885 g. (98.0% based on sodium acetate). The residue was shown to be sodium acetate by qualitative tests and by satisfactory gravimetric determinations as in the experiments with sodium carbonate.

Potassium carbonate. Potassium carbonate, 1.5352 g.; acetic anhydride, 3.6230 g.; temperature of reaction 110°. The reaction commences at 100° and above this temperature becomes vigorous. At 150° excessively large quantities of acetic anhydride are swept over, and so it was necessary to conduct the experiment at a much lower temperature.

Vol. of gas passed through apparatus, ml.: 500, 1000, 1500, 2000, 2500, 3000.
CO_2 evolved, %: 46, 70, 81, 92, 96, 100.

Weight of residue in flask, 2.6215 g. Theoretical weight of potassium acetate, 2.180 g. Qualitative tests indicated that the brown crystalline residue in the flask was a complex compound of potassium acetate and acetic anhydride. The ratio of the two molecules in the complex did not appear to be constant as quantitative analyses of specimens derived from four separate preparations did not give good agreement. It is noteworthy that a product of the same character is obtained by shaking a mixture of the two components themselves for two days at room temperature or for eight hours at 100°. The solid obtained is washed with ether and dried under reduced pressure. Analysis yielded results similar to those for the products obtained in the earlier experiments with potassium carbonate.

The proportion (by weight) of potassium acetate in the specimens examined, (which varied from 49% to 89%) was estimated by (a) calculation from the weights of potassium carbonate used and of solid residue formed, (b) gravimetric analysis of the residue (for potassium), and (c) electrometric titration of the residue (for acetic anhydride).

Perkin reaction using diacetanilide. Diacetanilide (14.0 g.; 0.08 mole), benzaldehyde (6.0 g.; 0.06 mole), and sodium acetate (3.2 g.; 0.04 mole) were heated under reflux for eight hours at 180° in an atmosphere of nitrogen. After cooling the mixture was steam-distilled to remove the excess benzaldehyde, the residue was made alkaline by the addition of sodium carbonate, any solid was removed, and the alkaline solution was extracted with ether. After acidification of the aqueous layer, cinnamic acid was precipitated (after purification, 1.5 g. *i.e.* 18% yield).

Perkin reaction using acetamide. Acetamide (12 g.; 0.21 mole), benzaldehyde (10 g.; 0.1 mole), and sodium acetate (5 g.; 0.06 mole) were heated as in the last experiment. After diluting with water and steam-distilling, the product was basified and extracted with chloroform. The aqueous layer was acidified and, on standing, an impure solid deposited; this upon purification (including sublimation) yielded cinnamic acid (0.12 g.).

SUMMARY

Many of the experiments providing support for the application of a general theory of basic catalysis to the Perkin condensation utilize alkali metal salts of weak acids as condensing agents. It has now been established that in these experiments acetic anhydride gives rise to sodium (or potassium) acetate, and the validity of the general mechanism can no longer rest on this kind of evidence. It is not doubted, however, that the Perkin condensation does proceed under the catalytic influence of certain organic tertiary bases.

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THE CONSTITUTION OF (+)-*trans*-CARYOPHYLLENIC ACID

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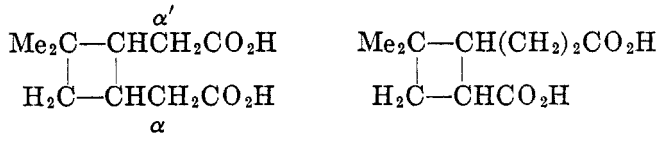
Oxidation of caryophyllene and various of its derivatives gives a mixture of (+)-*trans*-norcaryophyllenic acid and its homolog (+)-*trans*-caryophyllenic acid (1, 2, 3; compare 4, 5). The formula (I) for (+)-*trans*-norcaryophyllenic acid was deduced from degradational evidence by Ruzicka and Zimmermann (2) and by Ramage and Simonsen (6) and has been confirmed by Rydon's synthesis (7) of the (±)-*trans*- and (±)-*cis*-norcaryophyllenic acids and their resolution into optically active forms. Two formulas, (IIa) and (IIb), are possible for (+)-*trans*-caryophyllenic acid and it is generally considered that published evidence does not enable a distinction to be drawn between the two. It would appear, however, that this is not the case. Ruzicka, Bardhan, and Wind (8) showed that (+)-*trans*-caryophyllenic acid gave a tetramethylglycol (IIIa) or (IIIb) with the Grignard reagent, which on oxidation by chromic acid afforded $\alpha:\alpha:\alpha':\alpha'$:-tetramethylglutaric acid (IV). The latter is not an expected oxidation product and its formation can best be explained by rearrangement of (IIIa) in the manner indicated. Since analogous rearrangements of (IIIb) *cannot* be devised to explain the reaction, the formula (IIa) is most probably correct for (+)-*trans*-caryophyllenic acid.

When caryophyllene is treated with maleic anhydride it gives an "adduct" which is undoubtedly formed by allylic substitution (2, 9). Vigorous oxidation of this "adduct" furnishes a mixture of homologous acids, among which have been identified (+)-*trans*-norcaryophyllenic acid (I), (+)-*trans*-caryophyllenic acid, (IIa) and (+)-*trans*-homocaryophyllenic acid (3). The latter acid must be represented by either (Va) or (Vb). Although a partial synthesis of (+)-*trans*-homocaryophyllenic acid was attempted by Ramage and Simonsen (10), their results were complicated by the possibility of racemization and no final conclusion as to its structure was reached. Now it is unlikely that oxida-



(Va) (Vb)

tive attack on an acid of structure (Va) would proceed exclusively at the α rather than the α' position. This is true no matter whether the attack be radical or ionic in character. It would be anticipated, therefore, that oxidation of an acid of structure (Va) would give both (IIa) and (IIb), whereas degradation of the side chain of (Vb) could only give (+)-*trans*-caryophyllenic acid (IIa).

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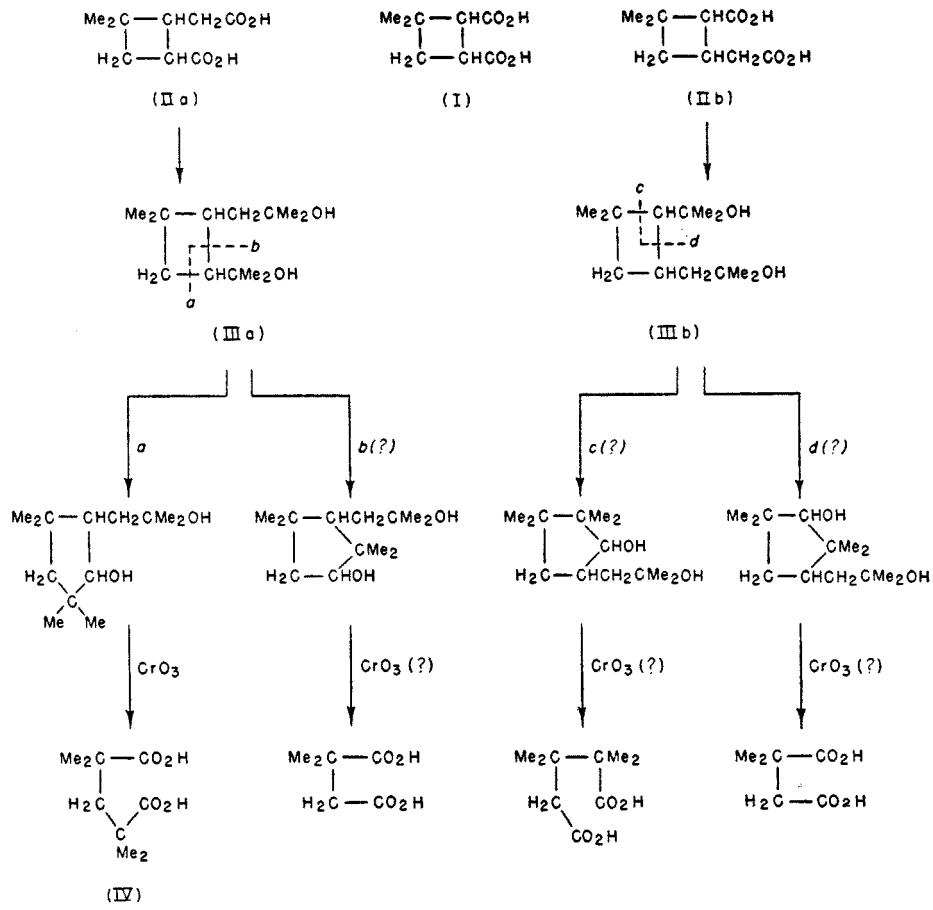
Since no indication has been found of the existence of (IIb) among the oxidation products of caryophyllene it seems probable that (+)-*trans*-homocaryophyllenic acid must be represented by (Vb) rather than (Va).

I am much indebted to Sir John Simonsen, F.R.S., for a valuable discussion on this and related ropics.



SUMMARY

Evidence bearing on the constitution of (+)-*trans*-caryophyllenic acid is critically discussed.

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THE PREPARATION AND DEGRADATION OF SOME PROPIONYLATED NITRILES OF ALDONIC ACIDS

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The degradation of the acetylated or benzoylated nitriles of aldonic acids, the only acylated types known to date, by application of the Wohl reaction, was considered to give in all cases the diacetamide or dibenzamide derivatives of the lower aldose sugar, until Hockett and Chandler (1), treating hexaacetyl-D-gluco-D-*gulo*-heptonic acid nitrile with 29% aqueous ammonia, obtained as the only degradation product N-acetyl-D-glucofuranosylamine.

The formation of the "diamide" derivatives was always expected and it is not surprising that, when Brigl and co-workers (2) in 1931 by the degradation of hexabenzoyl-D-manno-D-*gala*-heptonic acid nitrile, isolated D-mannose dibenzamide and a small amount of D-mannose benzamide, they announced without further proof that this substance was a secondary reaction product, formed from the original D-mannose dibenzamide, — a possibility that requires experimental confirmation. Hexaacety-D-manno-D-*gala*-heptonic acid nitrile gave instead only D-mannose diacetamide.

Although N-acetyl-D-glucofuranosyl amine has been obtained by Niemann and Hays (3) by the direct action of ammonia on pentaacetyl-D-glucose, a circumstance that shows how complicated is the interpretation of its formation in the Wohl reaction, it is evident that in the case of the two acetylated heptonic nitriles so far employed, whatever the details of the mechanism that favors the production of the monoacetamide compound, the change in the configuration of the aldose has determined an important difference in the type of the reaction product obtained.

Isbell and Frush (4) have proposed an interpretation of the mechanism of the Wohl reaction based on the formation of intermediate cyclic orthoesters of acetic acids, an interpretation that has received experimental support from the work of Hockett, Deulofeu, and Defarreri (5) who employed labelled ammonia (N^{15}) to ascertain the origin of the acetamide that combines with the newly formed aldose molecule. The Isbell and Frush interpretation allows for the formation of diacetamide or monoacetamide compounds.

To determine the influence of the acylating radical on the reaction, we have begun in our laboratory the preparation of nitriles of aldonic acids acylated with different radicals. Some benzoylated nitriles have been prepared (6) and, although by treatment with ammonia the dibenzamide derivatives of the lower sugars were always obtained, it was found that when a primary alcoholic hydroxyl is benzoylated the benzoyl group is retained through the degradation and appears in the dibenzamide compounds.

In this paper we present data on the preparation and degradation of some propionylated nitriles of aldonic acids. Propionic acid derivatives were selected

because of the availability of propionic anhydride and the hope that if they could not be crystallized easily, distillation could be applied as a method of purification (7).

It is well known that when aldose oximes are treated at low temperatures with a mixture of pyridine-acetic anhydride the type of product obtained varies with the nature of the sugar (8). In some cases acetylated cyclic or open-chain oximes are obtained, while in others the acetylated nitriles are the main or only product of the reaction. When open-chain acetylated oximes are produced, they can be transformed into nitriles by simple heating.

By employing a mixture of pyridine-propionic anhydride this reaction has been applied to the preparation of the propionylated nitriles.

From L-rhamnose oxime a crystalline *aldo*-pentapropionyl-L-rhamnose oxime was obtained in high yield, showing that the free oxime reacts almost quantitatively in the open-chain form under the conditions applied for propionylation. By heating, propionic acid was lost, and the oxime transformed into tetrapropionyl-L-rhamnonic acid nitrile.

The other oximes studied gave, even when treated with the reagent at low temperatures, syrups that did not crystallize. It was then decided to treat them with the mixture of pyridine-propionic anhydride at 100°. The impure nitriles obtained were in all cases purified by molecular-distillation at 0.001 mm. Previous heating transformed all the open-chain propionylated oximes that could be present in the reacting syrup into nitriles.

Pentapropionyl-D-gluconic acid nitrile, pentapropionyl-D-galactonic acid nitrile, and tetrapropionyl-L-rhamnonic acid nitrile were obtained as crystalline solids. The pentapropionyl-D-mannonic acid nitrile always remained a syrup.

Pentapropionyl-D-gluconic acid nitrile and pentapropionyl-D-galactonic acid nitrile when submitted to a classical Wohl degradation gave what can be considered the normal degradation products: D-arabinose dipropionamide and D-lyxose dipropionamide. Degradation of the pentapropionyl-D-gluconic acid nitrile by the Zemplén method gave D-arabinose. This nitrile when treated with hydrobromic acid in acetic acid solution yielded pentaacetyl-D-gluconic acid amide.

As shown in Table I certain regularities emerge when the rotatory power of the propionyl aldonic acid nitriles and their degradation products are compared with the corresponding acetylated compounds. Those regularities are not of a general character.

In the case of the first three nitriles noted in Table I, there is a constant difference between the rotatory powers of the acetyl and propionyl derivatives. This constancy disappears in the case of L-rhamnonic acid nitrile. With the first two nitriles the molecular rotatory power is almost the same, larger differences being encountered with the last two.

The molecular rotatory powers are practically identical in the case of the diacetamide and dipropionamide derivatives of D-arabinose and D-lyxose. It is remarkable that this identity of value of the molecular rotatory power is retained when the D-arabinose diacetamide and dipropionamide are acetylated, and the solvent for the determination is changed from water to chloroform.

NOTE ON THE MOLECULAR-DISTILLATION OF ACYLATED ALDONIC NITRILES

Molecular-distillation has been employed by Hurd and co-workers (7) for the separation and purification of propionyl derivatives of the sugars. We have found it very useful for the purification of propionylated aldonic nitriles as described in the experimental part. A still of the Washburn type (9) was employed for the distillation of solid nitriles and a horizontal-flask molecular still similar to that described by Morton (10) for the syrups.

TABLE I

ROTATORY AND MOLECULAR ROTATORY POWER OF ACETYLATED AND PROPIONYLATED ALDONIC ACID NITRILES AND THEIR DEGRADATION PRODUCTS

SUBSTANCE	$[\alpha]_D^\circ$	Δ°	$[M]_D^\circ/100$	Δ°
Pentaacetyl-D-gluconic acid nitrile	+47.8		+177.3	
Pentapropionyl-D-gluconic acid nitrile	+40.1	+7.7	+183.2	−5.9
Pentaacetyl-D-galactonic acid nitrile	+43.2		+160.3	
Pentapropionyl-D-galactonic acid nitrile	+36.7	+6.5	+167.7	−7.4
Pentaacetyl-D-mannonic acid nitrile	−1.8		−6.7	
Pentapropionyl-D-mannonic acid nitrile	+5.7	−7.5	−25.5	−33.0
Tetraacetyl-L-rhamnonic acid nitrile	−4.0		−14.8	
Tetrapropionyl-L-rhamnonic acid nitrile	−6.0	+2.0	−27.4	−12.6
D-Arabinose diacetamide	−9 5		−23.7	
D-Arabinose dipropionamide	−9.8	+0.3	−27.2	+3.5
Tetraacetyl-D-arabinose diacetamide	+72.5		+303.0	
Tetraacetyl-D-arabinose dipropionamide	−67.7	+4.8	+301.9	+1.1
D-Lyxose diacetamide	−9.2		−23.0	
D-Lyxose dipropionamide	−8.5	+0.7	−23.4	+0.4

When pure acetylated nitriles of aldonic acids were submitted to molecular-distillation they sublimed without passing into the liquid state, and at temperatures lower than the melting point a solid began to collect in the condenser.

The following acetylated nitriles were sublimed at 0.001 mm; the temperature in parentheses is the temperature of the outside bath: D-arabonic, m.p. 119° (85–100°): L-rhamnonic, m.p. 65° (50–55°); D-xylonic, m.p. 81° (70°); D-gluconic, m.p. 83° (70°); D-galactonic, m.p. 137° (110°); D-mannonic, m.p. 93° (70–85°).

Benzoylated nitriles (6) required higher temperatures for distillation, and decomposition took place. As an example pentabenzoyl-D-gluconic acid nitrile, m.p. 117°, could be distilled only above 200° (0.001 mm) and the collected solid melted at 65° and had a yellow tinge. After two recrystallizations from methanol the melting point of the pure nitrile was again obtained.

Separation of a mixture of an acetylated and a benzoylated nitrile can be

realized by heating at the temperature of sublimation of the acetylated nitrile. By heating at 110–120° (0.001 mm) a 1:1 mixture of pentaacetyl-D-galactonic acid nitrile and pentabenzoyl-D-galactonic acid nitrile, the acetylated nitrile was collected in the sublimate and purified by a second sublimation (m.p. 137°); the benzoylated nitrile remained in the residue (m.p. 144°).

EXPERIMENTAL

Pentapropionyl-D-gluconic acid nitriles. D-Glucose oxime (20 g.) was dissolved in 100 ml. of pyridine, 100 ml. of propionic anhydride was added, and the mixture was heated to 100° for one hour. It was then poured into iced-water, and a heavy oil precipitated. This oil was washed well with water, dissolved in ether, and the ether washed with sodium bicarbonate, then with water, dried, and evaporated. The residue was a syrup that was distilled at 0.001 mm. and 140–150° bath temperature; 14.1 g. of a solid, m.p. 58–60°, was collected (yield 60%). Recrystallized from ethanol, 9.7 g. of small prisms, m.p. 67–69°, was obtained. By further recrystallization the melting point 68–70° was attained. Insoluble in water and petroleum ether, very soluble in ether, chloroform, less in methanol and ethanol; $[\alpha]_D^{20}$ +40.1° in chloroform (*c*, 1.7).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6,78; −CN, 5.68; Propionyl, 62.36.
Found: C, 55.62; H, 6.92; −CN, 5.63; Propionyl, 62.23.

The propionyl groups were determined according to Gerzenstein (11).

D-*Arabinose dipropionamide.* Pentapropionyl-D-gluconic acid nitrile (5 g.) was dissolved in 25 ml. of ethanol and 35 ml. of ammonia water (28–29%) containing silver oxide (from 2.5 g. of silver nitrate) was added. After 48 hours the precipitated silver cyanide was filtered and the filtrate evaporated in a vacuum. The residue was a syrup that solidified on addition of a small amount of water. It was then dissolved in 250 ml. of water, the silver eliminated with hydrogen sulfide, and the filtered solution decolorized with Norit and evaporated to dryness. The residue crystallized on the addition of a small amount of ethanol and 1 g. of D-arabinose dipropionamide (yield 33%), m.p. 168–170°, was collected. Recrystallized from ethanol, fine needles, m.p. 177–178°, were obtained. The compound has a low solubility in methanol and ethanol and is insoluble in ether and chloroform. It is soluble in water but less so than the corresponding diacetamide compounds. $[\alpha]_D^{22}$ −9.8° in water (*c*, 0.76).

Anal. Calc'd for $C_{11}H_{22}N_2O_6$: C, 47.48; H, 7.91; N, 10.07.
Found: C, 47.18; H, 8.09; N, 9.95.

D-Arabinose dipropionamide was also obtained, but with a lower yield, by treating 5 g. of the nitrile with 50 ml. of conc'd ammonia, and heating to dryness in a boiling-water bath (12). The reaction seems less rapid than with acetylated nitriles; 0.76 g. (yield 25%) of crude D-arabinose dipropionamide was obtained. After recrystallization the melting point 175–177° was attained.

Tetraacetyl-D-arabinose dipropionamide. D-Arabinose dipropionamide (0.58 g.) was treated with 7 ml. of pyridine and 7 ml. of acetic anhydride was added; the mixture was heated to solution and left overnight at room temperature. The solution was then evaporated at 30° and the residue crystallized first from chloroform-petroleum ether and then from ethanol to give long prisms, m.p. 171–172°; soluble in chloroform, less soluble in ether and in water, insoluble in petroleum ether. $[\alpha]_D^{22}$ +67.7° in chloroform (*c*, 0.72).

Anal. Calc'd for $C_{19}H_{30}N_2O_2$: C, 51.11; H, 6.72; N, 6.27.
Found: C, 51.42; H, 6.95; N, 6.07.

Degradation of pentapropionyl-D-gluconic acid nitrile according to Zemplén. Pentapropionyl-D-gluconic acid nitrile (5 g.) was dissolved in 7 ml. of chloroform and cooled to −5°. A solution of 0.84 g. of sodium in 10 ml. of absolute methanol was added, and by shaking, a jelled mass was produced. After five minutes, 14 ml. of water and 2.5 ml. of acetic acid were added, and the aqueous solution was separated from the chloroform and evaporated in a vacuum at 70–80°. Absolute ethanol (20 ml.) was added; the residue almost

dissolved and it was evaporated again. The new residue was brought to 26 ml. with water. From 13 ml. of the solution, 0.97 g. of D-arabinose diphenylhydrazone, m.p. 204°, was obtained in the usual way, corresponding to a total yield of 0.88 g. of D-arabinose (54%).

Pentapropionyl-D-gluconic amide. The nitrile (2 g.) was dissolved in 10 ml. of glacial acetic acid saturated with hydrobromic acid. After five hours the solution was poured into iced-water, no precipitate being formed. The solution was then extracted with chloroform, the chloroform washed with sodium carbonate solution and water, dried, and evaporated. The resulting syrup crystallized on standing for some days in a desiccator. Recrystallized from ether-petroleum ether, long needles, m.p. 67–69°, were obtained. Mixed with the original nitrile (m.p. 68–70°), the m.p. 56–69°, was obtained. $[\alpha]_D^{20}+20.7°$ in chloroform (*c*, 0.85).

Anal. Calc'd for $C_{21}H_{33}NO_{11}$: C, 53.05; H, 6.94.
Found: C, 53.32; H, 7.12.

Pentapropionyl-D-galactonic nitrile. D-Galactose oxime (6 g.) was dissolved in 30 ml. of pyridine and 30 ml. of propionic anhydride was added. The solution was heated at 100° for one hour and poured into iced-water. A syrup precipitated that was washed well with water, dissolved in ether, the ether washed with sodium bicarbonate solution and water, dried, and evaporated. The resulting syrup was evaporated at 0.001 mm. (bath temperature 110°). An oil distilled that crystallized easily; 9.5 g. (yield 65%) of a substance, m.p. 48–50°, was collected and was purified by recrystallization from *n*-butanol. Large prisms, m.p. 60–61°, were obtained. Insoluble in water, soluble in chloroform, ether, benzene, toluene, methanol, and ethanol. $[\alpha]_D^{22}+36.7°$ in chloroform (*c*, 0.83).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6.78; N, 3.06; −CN, 5.68.
Found: C, 55.70; H, 7.01; N, 3.33; −CN, 5.62.

D-Lyxose dipropionamide. Pentapropionyl-D-galactonic acid nitrile (5 g.) was treated with ammonia-silver oxide in the same way as has been described for the pentapropionyl-D-gluconic acid nitrile. The D-lyxose dipropionamide crystallized easily. Yield, 0.91 g. (30%); m.p. 173–176°. Recrystallized from ethanol, it formed very long needles, m.p. 180–182°; $[\alpha]_D^{24}-8.5°$ in water (*c*, 1.0).

Anal. Calc'd for $C_{11}H_{22}N_2O_2$: C, 47.48; H, 7.91; N, 10.07.
Found: C, 47.69; H, 7.82; N, 10.28.

Pentapropionyl-D-mannonic acid nitrile. D-Mannose oxime (5 g.) was finely divided and suspended in 25 ml. of pyridine and 25 ml. of propionic anhydride was added. The suspension was heated at 100°; the oxime dissolved and heating was continued for one hour. The solution was then poured into iced-water. The insoluble syrup was washed with water, dissolved in ether, and the ether washed with sodium bicarbonate solution and water, dried, and evaporated. The residue was distilled at 0.001 mm. (bath temperature 100°). Yield, 5 g. (43%) of an oil which could not be induced to crystallize even by repeated distillation and separation into several fractions. Insoluble in water, very soluble in ether, chloroform, methanol, ethanol, benzene, and toluene. For analysis one of the middle fractions was employed. $[\alpha]_D^{24}+5.6°$ in chloroform (*c*, 0.13).

Anal. Calc'd for $C_{21}H_{31}NO_{10}$: C, 55.14; H, 6.78; N, 3.63; −CN, 5.68.
Found: C, 55.57; H, 6.60; N, 3.35; −CN, 5.74.

Pentapropionyl-D-rhamnose oxime. L-Rhamnose oxime (3 g.) was dissolved in 15 ml. of pyridine and 15 ml. of propionic anhydride was added slowly, keeping the temperature at 40–50°. After solution of the oxime the solution was left at room temperature 24 hours and then poured into iced-water. The oil that separated crystallized very easily on agitation. The solid was filtered, washed well with water, dried, and recrystallized from the minimum amount of petroleum ether. Yield 7.5 g. (97%) of fine needles, m.p. 47–49°. By further recrystallization from petroleum ether the m.p. 50–52° was attained. Insoluble in water, very soluble in ether, chloroform, benzene, toluene, ethanol, and methanol. $[\alpha]_D^{22}+4.0°$ in chloroform (*c*, 2.12).

Anal. Calc'd for $C_{21}H_{23}NO_{10}$: C, 54.90; H, 7.18; Propionyl, 62.09.
Found: C, 55.15; H, 7.07; Propionyl, 61.75.

Tetrapropionyl-L-rhamnonic nitrile. Pentapropionyl-L-rhamnose oxime (2 g.) was placed in a molecular-still and heated with a bath above the melting point. Propionic acid was evolved. The temperature was then slowly raised to 100° and an ordinary vacuum applied, until liberation of the acid had ceased. The remaining oil was distilled at a bath temperature of 100°, and 0.001 mm. Yield, 1.44 g. (87%) of an oil that on long standing at 5° crystallized. The crystals, m.p. 26–28°, were suspended in petroleum ether and filtered, but could not be recrystallized owing to their high solubility in all solvents employed. By adding petroleum ether to the solutions or by diluting with water, oils were always obtained from the crystals. The original crystals were then employed for analysis. $[\alpha]_D^{24}$ −6.0° in chloroform (*c*, 2.31).

Anal. Calc'd for $C_{18}H_{27}NO_8$: C, 56.10; H, 7.01; −CN, 6.75; Propionyl, 59.22.
Found: C, 55.85; H, 7.11; −CN, 6.87; Propionyl, 59.40.

SUMMARY

1. By the action of pyridine-propionic anhydride on some oximes of monosaccharides a series of propionylated nitriles of aldonic acids have been prepared.

2. The oximes employed reacted with preference in an aldo form, as shown by the high yields of nitriles obtained. L-Rhamnose oxime reacted only in the aldo form.

3. Degradation of the nitriles with ammonia-silver oxide gave the usual dipropionamide derivative of the lower sugar.

4. Molecular distillation was found to be a good method for the purification of the propionylated nitriles of aldonic acids. Acetylated nitriles can be sublimed without decomposition, but the benzoylated nitriles, while distillable, are partially decomposed.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, IMPERIAL COLLEGE]

THE STEREOCHEMISTRY OF SANTONIN, β-SANTONIN, AND ARTEMISIN

D. H. R. BARTON[1]

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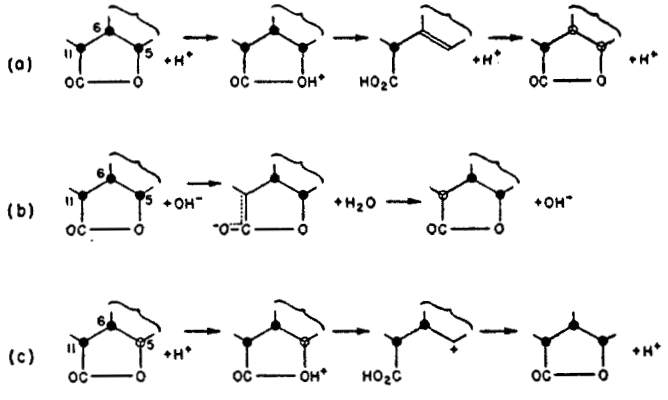
Huang-Minlon (1) has recently discussed the stereochemistry of the desmotroposantonins (I; R = H). The arguments advanced in his paper seem, for the most part, very plausible and are accepted in the present article. Huang-Minlon showed that treatment of an α-desmotroposantonin (2) with acidic reagents led to inversion at the asymmetric centers 5 and 6, whilst fusion of a β-desmotroposantonin with potassium hydroxide caused inversion at C_{11}. The isomerisation caused by acid was formulated in accordance with mechanism (a), whilst inversion by alkali was suggested to proceed as in (b). It is the purpose of the present article to show that, for appropriate compounds, there must be a third mechanism, (c), for acid-induced stereochemical rearrangement at C_5.



I II III

As Huang-Minlon pointed out it seems to be satisfactorily established that the desmotroposantonins must have the lactone ring fused in the more stable *cis*-position at C_5 and C_6. This must also be the case in *iso*hyposantonin (II). In contrast, the isomeric hyposantonin must be *trans*-fused at these positions as indeed was first recognised many years ago (3). The existence of mechanism (c) can only be detected in compounds where the fusion of the lactone ring is *trans*.

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Huang-Minlon, by a consideration of the molecular rotations of the desmotroposantonins and of the related santonous and desmotroposantonous acids, proposed tentatively, according to the Principle of Optical Superposition, signs for the contributions of the various asymmetric centers. In actual fact the additivity of the molecular rotations is not very satisfactory and it would seem preferable to discuss the stereochemistry on the following basis. Let the configurations at C_5, C_6, and C_{11} in (−)-α-desmotroposantonin be denoted by X, Y, and Z and let the alternative configurations at these centers be X′, Y′, and Z′ respectively. On this nomenclature the conclusions on relative configuration reached by Huang-Minlon can be conveniently summarised as in Table I.

When santonin (IV; R = H) is treated with acidic reagents under mild conditions it is isomerized, with loss of the asymmetric center at C_9, to (−)-α-desmotroposantonin. Under more drastic conditions (+)-β-desmotroposantonin is the product of this reaction. Although this might be taken to imply that the configurations at C_5, C_6, and C_{11} are the same in both santonin and (−)-α-desmo-

TABLE I

SUMMARY OF RELATIVE CONFIGURATIONS; AFTER HUANG-MINLON

SUBSTANCE	Configurations relative to (−)-α-desmotroposantonin[a]		
	C_5	C_6	C_{11}
(−)-α-Desmotroposantonin	X	Y	Z
(+)-β-Desmotroposantonin	X′	Y′	Z
(+)-α-Santonous acid	—	Y	Z
(−)-β-Santonous acid	—	Y′	Z

[a] The lactone ring is *cis*-fused in both types of desmotroposantonin.

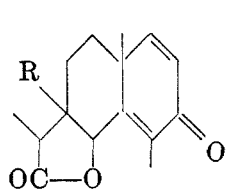
troposantonin, as Huang-Minlon has already mentioned, this is not so. Santonin β-oxime, its acetate, and the phenylhydrazone can all be transformed under very mild reducing conditions to hyposantonin (4). Santonin must, therefore, have the lactone ring fusion *trans* and be either $C_5(X'):C_6(Y):C_{11}(Z)$ or $C_5(X):C_6(Y'):C_{11}(Z)$. The fact that the transformation of santonin (*trans*-fused) to the acid-stable configuration of (+)-β-desmotroposantonin (*cis*-fused) proceeds *via* (−)-α-desmotroposantonin (also *cis*-fused) proves that santonin must be $C_5(X'):C_6(Y)$; $C_{11}(Z)$ and that there must be a mechanism (c) for the inversion of C_5 without altering C_6.[2] Santonin is strongly levorotatory ($[\alpha]_D$ −172° in chloroform). Since the asymmetric centers at C_5, C_6, and C_{11} make relatively small contributions to the molecular rotation (1) the strong levorotation must be due to the asymmetry induced by the center at C_9 in the closely neighboring and very unsaturated dienone system. For convenience the configuration at C_9 in santonin may be denoted as W (alternative configuration would be W′).

That these views with regard to the stereochemistry of santonin are correct is

[2] The alternative is that there is a mechanism for inverting C_6 without affecting C_5. This would mean that santonin was $C_5(X):C_6(Y'):C_{11}(Z)$. Such a mechanism is inherently improbable and, indeed, is excluded by the evidence discussed later.

shown by several other pieces of published evidence. First, both hyposantonin and *iso*hyposantonin are reduced, under conditions not likely to lead to inversion at C_6, to hyposantonous acid (5) (III; R = H), which, from its rotation ($[\alpha]_D$ +76° in alcohol) must correspond to (+)-α-santonous acid ($[\alpha]_D$ +75° in alcohol) and have $C_6(Y):C_{11}(Z)$. Hyposantonin and *iso*hyposantonin differ therefore only in configuration at C_5 being $C_5(X'):C_6(Y):C_{11}(Z)$ and $C_5(X):C_6(Y):C_{11}(Z)$ respectively.

Second, we may invoke the chemistry of artemisin (IV; R = OH). Treatment of artemisin under fairly drastic acid conditions causes dehydration with formation of artemisic acid (6) (V; R = OH) which has $[\alpha]_D$ +70.4° (in alcohol) and is clearly analogous to santinic acid $[\alpha]_D$ +64.4° in alcohol) (V; R = H) obtained by dehydration and mild oxidation of hyposantonin. The configuration of artemisin at C_{11} must therefore be (Z). Now when santonin is electrolytically reduced in aqueous acetic acid solution it gives a dilactone, santonone (7) (VI; R = H) presumably formed *via* the corresponding pinacol (VII). Santonone, which has $[\alpha]_D$ +130° in benzene, is readily isomerised to *iso*santonone, $[\alpha]_D$ −265° in acetic acid, and the two compounds are related to each other in the



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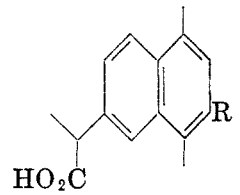

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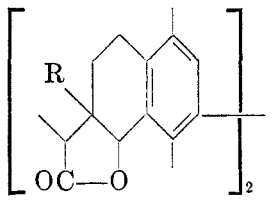

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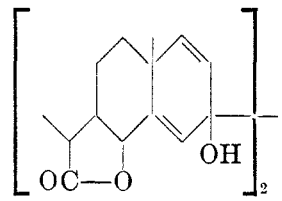

VII

same way, as hyposantonin ($[\alpha]_D$ +33° in benzene) and *iso*hyposantonin ($[\alpha]_D$ −70° in benzene). On similar reduction using zinc dust in aqueous acetic acid Bertolo and Ranfaldi (8) obtained artemisone (VI; R = OH) ($[\alpha]_D$ +159° in acetic acid) from artemisin. Like santonone, artemisone was readily isomerised to *iso*artemisone ($[\alpha]_D$ −153° in acetic acid.) It must be concluded, therefore, that the lactone ring in artemisin is *trans*-fused as in santonin, and that artemisone and *iso*artemisone are isomeric about C_5 and C_5'. Treatment of artemisin under mild acid conditions, such as cause the isomerisation of santonin to (−)-α-desmotroposantonin (see above), leads to the formation of desmotropoartemisin (I; R = OH) ($[\alpha]_D$ −84° in alcohol) having the lactone ring *cis*-fused. The formation of this compound provides a further proof of the existence of isomerisation mechanism (c) formulated above. Assuming that the substitution of a hydroxyl group for a hydrogen atom does not alter the sign of the molecular

rotation contribution of an asymmetric centre possessing a particular spatial configuration, then reference to the isomeric desmotroposantonins shows that desmotropoartemisin must be analogous to (−)-α-desmotroposantonin and must therefore be formulated as $C_5(X):C_6(Y):C_{11}(Z)$. Since the conversion of artemisin to desmotropoartemisin cannot involve a change at C_6, artemisin must be $C_5(X'):C_6(Y):C_{11}(Z)$ and, by reason of its strong levorotation (compare above), $C_9(W)$.

Knowing the configurations for santonin it is possible to deduce the stereochemical nature of β-santonin (9). On treatment with acidic reagents the latter affords (−)-β-desmotroposantonin (1) and therefore it must be $C_{11}(Z')$. The change in molecular rotation from β-santonin ($[M]_D$ −337° in chloroform) to (−)-β-desmotroposantonin ($[M]_D$ −261° in alcohol) is +76 units. This is almost exactly the same as the change in molecular rotation (+79 units) on going from santonin ($[M]_D$ −423° in chloroform) to (−)-α-desmotroposantonin ($[M]_D$ −344° in alcohol), and implies a similarity in stereochemistry at C_5, C_6, and C_9. β-Santonin must, therefore, be $C_5(X'):C_6(Y):C_{11}(Z'):C_9(W)$.

TABLE II

SUMMARY OF RELATIVE CONFIGURATIONS; PRESENT PAPER

SUBSTANCE	LACTONE RING FUSION	Configurations relative to (−)-α-desmotroposantonin			
		C_5	C_6	C_{11}	C_9
Santonin	*trans*	X′	Y	Z	W
Hyposantonin	*trans*	X′	Y	Z	—
*iso*Hyposantonin	*cis*	X	Y	Z	—
Desmotropoartemisin	*cis*	X	Y	Z	—
Artemisin	*trans*	X′	Y	Z	W
β-Santonin	*trans*	X′	Y	Z′	W

The conclusions on stereochemical relationships reached here are summarised in Table II.

The mechanism (c), established above by stereochemical arguments, constitutes an interesting example analogous to alkyl-oxygen fission (10).

Acknowledgement. The author is indebted to Sir John Simonsen, F.R.S., for his interest.

SUMMARY

The discussion of Huang-Minlon (1) on the stereochemistry of santonin derivatives is extended. Relative configurations are assigned *inter alia*, to santonin, desmotropoartemisin, artemisin, and β-santonin.

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[CONTRIBUTION FROM THE POLYCHEMICALS DEPARTMENT—CHEMICALS OF E. I. DU PONT DE NEMOURS AND COMPANY, INC.]

ETHYLENEUREA. I. SYNTHESIS FROM UREA AND ETHYLENEDIAMINE

CARL E. SCHWEITZER

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Starting in December, 1941, at the request of the National Defense Research Committee, methods were developed for the synthesis of ethyleneurea, 2-imidazolidone.[1] Results of this investigation indicated several possibilities for commercial scale production, and removal of security restrictions has made it possible to describe these developments in a series of papers of which this is the first.

When this investigation of an ethyleneurea synthesis was begun, there were several preparative methods in the literature (1-5), but each of these was subject to certain limitations, judged by the requirements of a commercial process. However, other theoretically possible routes were apparent and of these, four were developed which were based upon the reactions of:

(A) Ethylenediamine with carbon dioxide
(B) Ethylenediamine with urea
(C) Ethylene glycol with urea or with ammonia and carbon dioxide
(D) Ethanolamine with urea

Starting with ethylenediamine and carbon dioxide as indicated in (A) above, excellent yields (*ca.* 98%) of ethyleneurea were obtained at elevated temperatures and pressures. However, this reaction, studied independently at about the same time by others (6), has already been described. Results were comparable with those obtained in this laboratory.

The reaction of ethylenediamine with urea, which is the subject of this paper, likewise proved to be a highly satisfactory method for synthesizing ethyleneurea. It may be carried out in one step at atmospheric pressure with yields of 98% or better. Because operation by this route is relatively simple, it is of interest both commercially and as an especially attractive laboratory procedure. After this work had been completed, it was found that the ethylenediamine-urea reaction had been tried, but the yield of ethyleneurea was less than 10% (7). Here the important role of water as a moderator for the reaction was not recognized. This probably accounts for the marked difference.

Using ethylene glycol and urea (or carbon dioxide and ammonia in place of urea) or ethanolamine and urea (C or D) it was possible to obtain ethyleneurea in good yields and the results of these phases of the study will be presented in papers to follow.[2]

[1] OSRD contract No. OEMsr-373.

[2] The following patents have been granted which pertain to certain aspects of the ethyleneurea problem: Dittmar and Loder, U. S. Patent 2,416,046; Larson and Loder, U. S. Patent 2,416,057; Loder, U. S. Patent 2,245,627; Larson, Loder, and Dittmar, U. S. Patent 2,436,311; Loder, U. S. Patent 2,474,004.

ETHYLENEDIAMINE-UREA REACTION

Urea undergoes reaction with a variety of amines to produce alkyl-substituted ureas (8), and with diamines to yield polyalkylureas (9). It has now been found that urea and ethylenediamine will react to give ethyleneurea in high yields provided water is present as a moderator.

$$NH_2CH_2CH_2NH_2 + NH_2CONH_2 \rightarrow \underline{NHCH_2CH_2NHCO} + 2\,NH_3$$

Thus, an equimolar mixture of urea and aqueous ethylenediamine (68% diamine, 32% water by weight) was permitted to reflux while water was removed slowly and ammonia, liberated by the reaction, was allowed to escape. The mixture changed from a liquid to a thick pasty mass and finally again to a clear melt of substantially pure ethyleneurea in nearly quantitative yield. With no sacrifice in yield it was possible to maintain a reasonably fluid charge if a 5–20% molar excess of the diamine-water azeotrope was used. This excess diamine was separated by vacuum-distillation from the final product.

If water is not removed as the reaction proceeds, the relatively low reflux temperature retards the desired reaction but permits a partial hydrolysis of urea. This reduces the yield of ethyleneurea. Under these conditions the chief product appears to be crude 2-aminoethylurea which upon further heating is converted partly to ethylenediamine and partly to a white unidentified high-melting solid.

If water is omitted from an equimolar charge of ethylenediamine and urea, the anhydrous materials react slowly to liberate ammonia until a temperature of about 140° is attained. At this point an extremely vigorous reaction occurs which produces a white solid melting near 270°. In one case the reaction was violent enough to eject the thermometer and part of the solid from the flask.

Attempts to accelerate the reaction by replacing water with higher-boiling liquids such as *n*-butyl alcohol, dimethylformamide or methoxymethoxyethanol resulted in high-melting, unidentified products rather than ethyleneurea. If, however, the desired higher temperature is attained by operating under pressure, the reaction is accelerated and satisfactory yields of ethyleneurea may be obtained in an aqueous system. At 245–275° the reaction is complete within an hour.

At ordinary temperatures ethyleneurea is a white, neutral solid which is odorless when pure. It melts at 133.7° (corr.); [lit., 131° (1, 6)] and may be distilled at 163°/3 mm.; 187°/10 mm.; 192°/16 mm. The last value is in good agreement with the one published boiling point (6). Crystallized from a water solution, it is obtained as the hemihydrate which at room temperature effloresces slowly to the anhydrous form.

There are two crystalline modifications with a transition temperature of about 80°. Optical constants, obtained under the petrographic microscope by the method of Bryant (10), are as follows:

ETHYLENEUREA (anhydrous)

Biaxial (+). Refractive indices (25 ± 3°; 5461 Å): $\alpha = 1.537$, $\beta = 1.563$, $\gamma = 1.694$; all ±0.003. Optic Axial Angles: $2H_a = 57°$ (4358 Å); 59° (5461 Å); 60°

(6908 Å); all ±1°. Second anhydrous modification (unstable at room temperature) is uniaxial (+).

ETHYLENEUREA HEMIHYDRATE

Uniaxial (+). Refractive indices (25 ± 3°; 5461 Å): *omega* = 1.521 ±0.003, *epsilon* > 1.56.

Solubilities in several solvents at different temperatures are given in Table I.

EXPERIMENTAL

Synthesis of ethyleneurea at one atmosphere. A mixture composed of 732 g. of the ethylenediamine-water azeotrope [498 g. (8.3 moles) of ethylenediamine and 234 g. (13 moles) of water] plus 498 g. (8.3 moles) of urea, was charged into a two-liter, three-necked, round-bottom flask. The flask was fitted with a sturdy stirrer, a thermometer, and a 20 mm. × 60 cm. Vigreux column carrying a condenser which could be set for various reflux ratios.

TABLE I

SOLUBILITIES OF ETHYLENEUREA

SOLVENT	TEMP., °C.	SOLUBILITY[a]
Water	8	41
	35	60
	56	75
Methanol	64	79
Ethanol	25	*ca.* 23
n-Butanol	25	<10
Chloroform	61	20
Acetone	0	<0.2
	25	2
	56	3-4

[a] Expressed as grams of anhydrous ethyleneurea per 100 grams of solution.

Contents of the flask were stirred and heated to vigorous reflux. During a four-hour period, liberated ammonia was allowed to escape and water was slowly removed from the top of the column so that the temperature of the reaction mixture rose from 110° to 240–250°. At the end of approximately three hours, when the temperature had reached 160–180°, the mixture became quite pasty and rather difficult to stir, but during the final hour it changed to a clear, pale amber liquid. This, upon cooling, solidified to give 710 g. of ethyleneurea, m.p. 127–131° (yield, 99+%). One recrystallization from chloroform brought the melting point to 130–131° and by repeated recrystallizations from chloroform and from dioxane the melting point was raised to 133.7° (corr.).

Synthesis of ethyleneurea under pressure. A charge comprising 87.9 g. of the water-ethylenediamine azeotrope [containing 60 g. (1.0 mole) of diamine] plus 60 g. (1.0 mole) of urea, was heated at 250° in an agitated, silver-lined, steel bomb of 325-cc. capacity at a pressure of 160 atmospheres for one hour. The resulting product was distilled at reduced pressure to remove volatiles, including water and 10% of the charged ethylenediamine. Ethyleneurea, 66.6 g., remaining as the residue melted at 119–125° and represented a yield of 85% based upon the diamine and 77% based upon urea. When recrystallized from chloroform it had m.p. 129–131°.

SUMMARY

A practical laboratory procedure is reported for the synthesis of ethyleneurea in nearly theoretical yield from urea and ethylenediamine in the presence of water

as a moderator. Variables affecting yields are discussed and certain physical properties of ethyleneurea are recorded.

WILMINGTON 98, DELAWARE

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[CONTRIBUTION FROM THE POLYCHEMICALS DEPARTMENT—CHEMICALS OF E. I. DU PONT DE NEMOURS AND COMPANY, INC.]

ETHYLENEUREA. II. SYNTHESES FROM ETHYLENE GLYCOL OR ETHANOLAMINE AND UREA (OR CARBON DIOXIDE AND AMMONIA)

CARL E. SCHWEITZER

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Of the several routes to ethyleneurea, explored in 1941 at the request of the National Defense Research Committee[1] and summarized briefly in the initial report of this work,[2] those based on ethylene glycol and urea (or carbon dioxide and ammonia) or ethanolamine and urea are the subject of this paper.

Urea can react with glycols to produce carbamate esters without formation of a C—N bond. Thus at 100–200°, urea and 1,3-butylene glycol yield the corresponding mono- and di-carbamates (1). Similarly, urea and ethanolamine produce 2-hydroxyethylurea without amination of the carbon skeleton (2).

During this investigation, however, conditions were found under which urea, or carbon dioxide and ammonia, could be made to aminate either ethylene glycol or ethanolamine to produce satisfactory yields of ethyleneurea. This work represents an extension of urea chemistry and is reported here in detail. Patents have been granted which pertain to certain aspects of the problem.[3] Of the reactants cited above, urea and ethylene glycol were selected for most thorough study because these raw materials were readily available at low cost and could be made to react at atmospheric pressure.

ETHYLENE GLYCOL AND UREA AT ONE ATMOSPHERE

The synthesis of ethyleneurea from urea and ethylene glycol was achieved most satisfactorily in two steps. In the first step, ethylene glycol and a several molar excess of urea were heated gradually from 150 to 240° during a period of several hours. Ammonia and carbon dioxide were evolved and the product was a liquid which set to a brittle resinous solid when cool. Pyrolysis of this resin at 240–270° under reduced pressure resulted in the formation of some ethyleneurea (yield, based upon ethylene glycol, 25%), but a substantial portion decomposed to a carbonaceous product. If, as the second step, the resinous intermediate was hydrolyzed at about 250°, the yield of ethyleneurea was more than doubled (55%).

Course of the reaction. In Table I, data are presented from two typical experiments which show the relative rates of formation of ammonia and carbon dioxide. These data serve to indicate a possible course of the urea-ethylene glycol reaction. Clearly, the synthesis of ethyleneurea did not proceed through simple elimination of two moles of water from an equimolar mixture of reactants for there

[1] OSRD Contract No. OEmsr-373.

[2] Ethyleneurea I. (Preceding paper).

[3] Dittmar and Loder, U. S. Patent 2,416,046; Larson and Loder, U. S. Patent 2,416,057; Loder, U. S. Patent 2,425,627; Larson, Loder, and Dittmar, U. S. Patent 2,436,311; Loder, U. S. Patent 2,474,004.

was no evidence that water *per se* was obtained from the reaction. Indeed, it did not appear to be even a primary product since, if it had been and if it had reacted with urea, then the quantity of carbon dioxide relative to ammonia would have been much higher in the early stages of the reaction. From the very large quantity of ammonia evolved it appeared that the primary product was a carbamate. This carbamic acid ester of ethylene glycol subsequently lost carbon dioxide with formation of the desired C—N bond as indicated by the following equations:

$$HOCH_2CH_2OH + 2\ NH_2CONH_2 \rightarrow NH_2COOCH_2CH_2OCONH_2 + 2\ NH_3$$
$$NH_2COOCH_2CH_2OCONH_2 \rightarrow NH_2CH_2CH_2NH_2 + 2\ CO_2$$

TABLE I

RATES OF FORMATION OF AMMONIA AND CARBON DIOXIDE

MOLE RATIO: UREA/GLYCOL	TOTAL TIME, HOURS	TEMP., °C.	VARIATION WITH TIME OF COMPOSITION IN MOLES			MOLES CO_2/ GLYCOL CHARGED	MOLES NH_3/ GLYCOL CHARGED	MOLES NH_3/ UREA CHARGED
			Urea	Glycol	Biuret			
3.5	0	156	21.0	6.0	0.0	0.0	0.0	0.0
	1.0	162	14.5	2.75	1.71	.14	0.96	.28
	2.0	169	10.2	1.51	2.04	.36	1.74	.50
	3.0	171	8.45	0.79	2.06	.67	2.38	.68
	4.0	176	6.1	.43	2.10	.94	2.86	.82
	5.0	181	4.65	.20	1.94	1.13	3.36	.96
	6.0	222	0.96	.03	1.85	1.53	4.20	1.20
	7.0	275	.13	.02	0.91	1.87	4.84	1.38
	8.0	260	.13	.01	.0	1.84	4.86	1.39
4.15	0	160				0.0	0.0	0.0
	1.0	170				.16	1.41	.34
	2.0	172				.53	2.34	.56
	3.0	175				.88	3.41	.82
	4.0	181				1.13	3.72	.89
	5.0	200				1.53	4.35	1.04
	6.0	240				1.81	5.28	1.27
	7.0	240				1.98	5.40	1.30

Once ethylenediamine had been formed, it could react with urea to produce the resinous ethyleneurea intermediate.

The data of Table I were obtained in typical experiments in which the evolved gases were analyzed continuously. This was accomplished by passing them through standard sulfuric acid to remove ammonia and then through soda-lime or through standard sodium hydroxide to absorb carbon dioxide. Aliquots of the liquid charge were removed periodically and subjected to analyses for *urea* by a method using urease (3), *biuret* by a colorimetric method based upon the purple copper complex formed in alkaline solution (4), and *free ethylene glycol* by either the periodate method (5) or by titration with Karl Fischer reagent of the water released on esterification (6).

During early stages of the reaction biuret accumulated. This, of course, arose

from rapid reaction of urea with itself, but it accounted for a relatively small portion of the ammonia liberated early in the reaction. As the reaction progressed this biuret was consumed.

Ratio of urea to glycol. Variations in the mole ratio of urea to glycol, as might be expected, have a pronounced effect upon the yield of ethyleneurea and upon the character of the resinous intermediate. As shown in Table II, the intermediate changes from a clear, viscous liquid to a porous, opaque solid as the quantity of urea is increased. Yields of ethyleneurea, based upon ethylene glycol, increase

TABLE II

EFFECTS PRODUCED BY CHANGES IN THE RATIO OF UREA TO GLYCOL

RATIO MOLES UREA: MOLE GLYCOL	YIELD OF ETHYLENEUREA, %		APPEARANCE OF INTERMEDIATE
	Based on glycol	Based on urea	
1.0	2	2	Clear viscous syrup
2.0	23	11.5	Tacky, clear resin
3.0	38	12.7	Clear, brittle glass
3.5	39	11.1	Clear, somewhat porous glass
4.0	55	12.5	Opaque, porous, white solid
5.0	57	11.4	Opaque, porous, white solid

TABLE III

EFFECT OF TIME AND TEMPERATURE ON YIELD

UREA/GLYCOL MOLE RATIO	OVER-ALL TIME AND TEMPERATURE RANGE	YIELD OF ETHYLENEUREA BASED UPON GLYCOL, %
3.0	"Standard"*	38
3.0	4.5 hrs.; 150–240°	26
3.0	9.5 hrs.; 175–215°	15
3.5	"Standard"	39
3.5	4.5 hrs.; 150–240°	10
5.0	"Standard"	57
5.0	3.5 hrs.; 160–240°	56

* "Standard" schedule: Six hours at 160–180°, three hours at 180–240°, one hour at 240°.

with increase in urea, the sharpest rise occurring as the mole ratio changes from 3.5 to 4. The yield, based upon urea, remains about the same if the mole ratio is two or greater.

Time and temperature. Changes in these variables have a pronounced effect upon the yield of ethyleneurea which may be derived from ethylene glycol and urea (after hydrolysis of resinous intermediates) and typical data are presented in Table III. Most satisfactory results—chemically, judged by yields, and physically, judged by freedom from mechanical difficulties such as excessive foaming—were obtained with charges which were heated at 160° to 240° for about ten hours. The temperature was raised from 160° to 180° during six hours, 180° to 240° during three hours and then maintained at 240° for one hour; this was the

"standard" schedule. If the same temperature range was observed but if the over-all time was reduced to three or four hours, yields were lower than those obtained with "standard" schedules and often there was troublesome foaming. A final temperature near 240° was essential to effect complete evolution of carbon dioxide and to obtain maximum yields.

Attempted catalysis. A number of experiments were carried out to test the possible catalytic activity of substances such as potassium carbonate, cupric carbonate, ammonium chloride, ammonium sulfate, potassium silicate, boron phosphate, and silica gel, but in no case was there any indication that the reaction could be catalyzed.

Water treatment of the intermediate. In order to recover the maximum quantity of ethyleneurea, it was necessary to treat the resinous polymeric intermediate with water. If the resin was reasonably fluid at 234–270° it was possible to recover ethyleneurea in high yield simply by passing superheated steam through it at these temperatures.

Resins obtained as products from mixtures in which the ratio of urea to glycol was greater than 3.5 to 1 could not be steam-distilled readily because their viscosities were too high. However, it was found that any of the intermediate resins could be cleaved if they were heated with approximately an equal weight of water to about 270° under autogenous pressures for twenty minutes to one hour. If water treatment was carried out at 300° or higher, ethyleneurea itself was hydrolyzed quite extensively and ethylenediamine was obtained.

ETHYLENE GLYCOL AND UREA UNDER PRESSURE

Investigation of the synthesis of ethyleneurea from glycol and urea under pressure demonstrated that higher temperatures and therefore shorter reaction times could be employed than at one atmosphere. Also, less urea was required for a given yield of product, based upon glycol. Thus in three hours at 275° and about 400 atmospheres pressure, the yield of ethyleneurea was 47%; reducing the reaction time resulted in lower yields. An increase in temperature permitted a reduction in reaction time, but at 360°, for example, substantial amounts of ethanolamine and ethylenediamine formed at the expense of ethyleneurea. Increasing the ratio of urea to glycol above four did not improve the ethyleneurea yield.

ETHYLENE GLYCOL, AMMONIA, AND CARBON DIOXIDE[4]

The direct synthesis of ethyleneurea from ethylene glycol, ammonia, and carbon dioxide under pressure was investigated until it became evident that rather high pressures probably would be required. Best results (58% yield) were obtained from a charge consisting of 1 mole of glycol, 8 moles of ammonia, 4 moles of carbon dioxide, and $1\frac{1}{3}$ moles of water, which was heated for 30 minutes at 250°

[4] Similarly, ethyleneurea was obtained when ethanolamine was used in place of ethylene glycol. However, only a limited number of experiments were carried out so that optimum conditions probably were not found. Maximum yield was about 20% from a charge composed of one mole of carbon dioxide, one mole of ethanolamine, and five moles of ammonia which was processed at 250° for 70 minutes under a pressure of 330 atmospheres.

under a pressure of 900 atmospheres. If water was eliminated from a similar charge the yield declined to 52%. Decreasing the pressure to 400 atmospheres resulted in a yield of only 30%.

ETHANOLAMINE AND UREA AT ONE ATMOSPHERE

Major attention was devoted to syntheses of ethyleneurea based upon ethylenediamine or ethylene glycol, but reactions of ethanolamine were explored briefly. In general, there seemed to be no advantage over using ethylene glycol, considering availability of raw materials and their costs. Best results were obtained when a mixture of three moles of urea and one mole of ethanolamine was heated for about nine hours at 110° to 245° and the resinous intermediate hydrolyzed under pressure. The yield of ethyleneurea was 55%, based upon ethanolamine, and compared favorably to that obtained from four moles of urea and one mole of ethylene glycol.

ETHANOLAMINE AND UREA UNDER PRESSURE

The reaction under pressure of ethanolamine and urea, preferably in excess ammonia, was investigated only briefly. It was found to proceed rapidly to produce yields of approximately 38%, based upon the alkanolamine, at 300° and about 900 atmospheres pressure.

EXPERIMENTAL

Ethylene glycol and urea at atmospheric pressure. A typical preparation of the intermediate resin was carried out as follows: A mixture composed of 360 g. (6.0 moles) of urea and 93 g. (1.5 moles) of ethylene glycol was placed in a three-neck, two-liter, round-bottom Pyrex flask fitted with a ten-bulb reflux condenser, a thermometer, and an oil-sealed stirrer. The stirrer was started and the temperature of the mixture was raised slowly from 160 to 180° during 3 hrs., 180–240° during 3 hrs., and finally was maintained at 240° for 1 hr. Ammonia and carbon dioxide liberated by the reaction were allowed to escape through the reflux condenser which was heated by steam to prevent formation of dangerous plugs of ammonium carbonate. The product, a faintly cloudy, colorless white liquid, was poured into a large evaporating dish while still hot. Upon cooling it set to a porous, opaque white solid which weighed 172 g.

Ethyleneurea was obtained from this resinous intermediate by (a) direct thermal decomposition or (b) water treatment. (a) *Thermal decomposition.* The product prepared above (172 g.) was placed in a 500-cc. round-bottom Pyrex flask fitted with an air-condenser of 20-mm. glass tubing bent at a 60° angle, in the manner of a glass retort. The air condenser was connected to a water-cooled receiver attached to a vacuum pump. After the system had been evacuated to about 1 mm. the polymer was heated to 240–270°. Ethyleneurea distilled from the polymer as it decomposed. Pyrolysis was continued until a rise in pressure ndicated the formation of permanent gases. A total of 32.1 g. of ethyleneurea melting at 125–132° was obtained; yield, based on ethylene glycol, 25%.

(b) *Water treatment.* A mixture of 150 g. of the intermediate resin, prepared as described above, and 100 g. of water was charged into a silver-lined bomb of about 300-cc. capacity and heated at 250° under an autogenous pressure of 585 atm. for 2 hrs. The bomb was allowed to cool and the liquid product was discharged. This was distilled at reduced pressure through a 20 mm. × 60 cm. Vigreux column. Water and a small quantity of ammonia were removed at about 100 mm. pressure. The pressure was reduced and 76.5 g. of ethyleneurea distilling at 160–170°/2–3 mm. was obtained. The crude product, which melted at 118–125°, was recrystallized from chloroform giving 60 g. of ethyleneurea, m.p. 128–131°. Yield, based upon glycol, 55%.

Ethylene glycol and urea under pressure. Two charges, each composed of 60 g. (1 mole) of urea and 62 g. (1 mole) of ethylene glycol, were processed in similar silver-lined bombs of 325-cc. capacity at 275° and a pressure estimated to have been 400 atm. for 3 hrs. The bombs were allowed to cool to room temperature and discharged. The combined products were distilled under reduced pressure and 35% of the ethylene glycol was recovered. Ethyleneurea, b.p. 150–170°/1–2 mm., was obtained which, after crystallization from chloroform, amounted to 51 g. for a net yield of 47%, based on ethylene glycol.

Ethylene glycol, ammonia, and carbon dioxide. Two charges, each composed of 46.6 g. (0.75 mole) of ethylene glycol, 102 g. (6.0 moles) of ammonia, 132 g. (3.0 moles) of carbon dioxide, and 18 g. (1.0 mole) of water were processed in silver-lined bombs at 250° for 30 min. under a pressure of 900 atm. The products were combined and distilled at reduced pressure to give crude ethyleneurea which was purified by crystallization from dioxane. The final product weighed 74.8 g. Yield, based upon glycol, 58%.

Ethanolamine and urea at atmospheric pressure. Equipment described above for the reaction of ethylene glycol and urea at atmospheric pressure was used in this experiment. A mixture of 720 g. (12 moles) of urea and 244 g. (4 moles) of ethanolamine was heated with stirring according to the following schedule: 1 hr., 110–150°; 1 hr. 150–160°; 1.5 hrs. 160–195°; 1.25 hrs., 195°; 2 hrs., 195–224°; and 2 hrs., 224–240°. Ammonia and carbon dioxide were permitted to escape through the steam-heated reflux condenser and were passed through a scrubber containing 200–400 cc. of water. The scrubber was made from a 1-liter, 3-neck, round-bottom Pyrex flask fitted with a stirrer and a gas inlet tube which dipped just below the surface of the water. Ethanolamine (35 g.) which escaped with the gases was collected in the scrubber and recovered by distillation. The product remaining in the reaction flask weighed 465 g. When cool it was a very viscous clear, amber liquid.

This liquid (370 g.) was hydrolyzed by heating it with an equal weight of water to 250° for 2 hrs. in an agitated 800-cc. silver-lined bomb under an autogenous pressure of 925 atm. The resulting product was distilled. Ethylenediamine in 10% yield, based upon ethanolamine, was obtained in the first fraction. The pressure was reduced and 155 g. of ethyleneurea, m.p. 126–129°, distilling at 170–180°/4 mm. was obtained; crude yield, 55%, based upon ethanolamine.

Ethanolamine and urea under pressure. A mixture consisting of 60 g. (1.0 mole) of urea, 61 g. (1.0 mole) of ethanolamine, and 85 g. (5.0 moles) of ammonia was processed in a silver-lined bomb at 300° under a pressure of 930 atm. for 10 min. The product was distilled; 12.0 g. of ethanolamine was recovered together with 59 g. of crude ethyleneurea. One recrystallization from chloroform gave 35 g., m.p. *ca.* 123°. Assuming this product to be 75% pure, the net yield, based upon ethanolamine, was 38%.

SUMMARY

Procedures are reported for the synthesis of ethyleneurea from ethylene glycol or ethanolamine either with urea or with ammonia and carbon dioxide. Pressure and other variables affecting the reactions are discussed and a mechanism is suggested by which amination of the carbon skeleton takes place.

WILMINGTON 98, DELAWARE

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, REED COLLEGE]

THE VON RICHTER REACTION[1]

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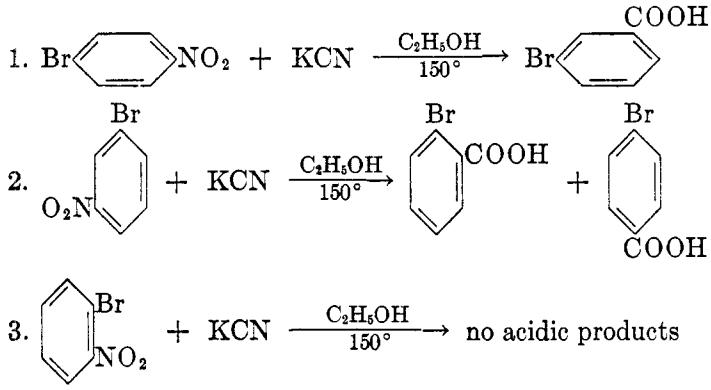
Victor von Richter in 1871–1875 reported (1, 2, 3) the reaction of *p*-nitrobromobenzene with alcoholic potassium cyanide to give *m*-bromobenzoic acid, together with some equally odd reactions of other nitrohalobenzenes with the same reagent. This paper presents experimental confirmation of some of these reports, improvements in the experimental procedure, and investigations of the behavior of additional aromatic nitro compounds with alcoholic potassium cyanide. We believe that we are dealing with a general reaction of aromatic nitro compounds, and present our ideas on its mechanism.

It is remarkable that in the three-quarters of a century elapsed since von Richter's[4] papers, only Holleman (4) has done further work on the same sort of reaction. In Table I Holleman's results are displayed along with von Richter's.



We repeated von Richter's experiments on the three nitrobromobenzenes, and our findings are in substantial agreement with his reports. We found *para*-nitrobromobenzene to give *meta*-bromobenzoic acid, *meta*-nitrobromobenzene to give a mixture of *ortho*- and *para*-bromobenzoic acids (he reported only the *ortho* isomer; a trace of *p*-bromobenzoic acid he ascribed to a minor "Umsetzung"), and *ortho*-nitrobromobenzene to give no acidic products. Our yields were about 20%.

[1] Presented in part at the 114th National Meeting of the American Chemical Society, Portland, Oregon, September 14, 1948. We thank the Research Corporation for financial support through a Frederick Gardner Cottrell grant-in-aid, and Dr. D. S. Tarbell for criticism of the manuscript.

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[4] von Richter encountered this reaction in the course of work on the problem of orientation in disubstituted benzenes, and made arguments about orientation relationships on the basis of it! In his 1875 paper, he recognized the contributions of Körner and others to this problem and provided an interpretation of his reactions that is satisfactory today.

We also discovered that certain other aromatic nitro compounds react in the same way with alcoholic potassium cyanide. Nitrobenzene produced benzoic acid (21%). The nitroanisoles behaved much like the nitrobromobenzenes except that yields were much lower; from *p*-nitroanisole there resulted 3% of *m*-anisic acid, while *p*-anisic acid (1%) was the product from *m*-nitroanisole. *o*-Nitroanisole yielded no acidic products. Incomplete experiments appear to indicate the same sort of behavior in the nitrobiphenyl series.

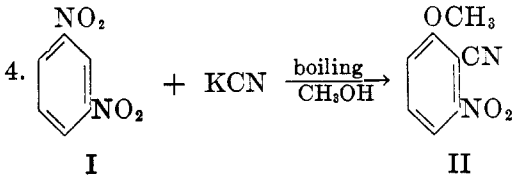
TABLE I

PREVIOUS WORK ON THE VON RICHTER REACTION

STARTING MATERIAL	TEMP., °C.	PRODUCTS	REFERENCE
p-Nitrobromobenzene	180	*m*-Bromobenzoic acid	(1)
m-Nitrobromobenzene	200	*o*-Bromobenzoic acid (40%) + *p*-bromobenzoic acid (trace)	(1, 5)
o-Nitrobromobenzene	200	No acidic products	(1)
p-Nitrochlorobenzene	200	*m*-Chlorobenzoic acid	(1)
m-Nitrochlorobenzene	250–270[a]	*o*-Chlorobenzoic acid	(1)
o-Nitrochlorobenzene		No acidic products	(3)
m-Nitroiodobenzene	200	*p*-Iodobenzoic acid + *o*-iodobenzoic acid	(1)
2-Nitro-4-bromotoluene		*m*-Toluic acid	(3)
3-Nitro-4-bromotoluene		No reaction	(3)
2,5-Dibromonitrobenzene	120–140	2,5-Dibromobenzoic acid (20%)	(2, 3)
2,4-Dibromonitrobenzene	250	3,5-Dibromobenzoic acid	(3)
2,4,6-Tribromonitrobenzene	250	No acidic products	(3)
2,3,4,6-Tetrabromonitrobenzene		No acidic products	(3)
"*o*-Nitrobenzoic acid" (probably *m*-nitrobenzoic acid)		Terephthalic acid	(6)
o-Dinitrobenzene	170	No reaction (in alcohol)	(7)
m-Nitrobenzenesulfonic acid	190–200	*o*-Sulfobenzoic acid (15%) + *p*-sulfobenzoic acid (15%) + 2-amino-4-sulfobenzoic acid + other aminosulfobenzoic acids (see text)	(4)

[a] No reaction at 200°.

It thus appears that a wide variety of aromatic nitro compounds give, with alcoholic potassium cyanide, carboxylic acids in which the carboxyl group, however, occupies a position *ortho* to that previously occupied by the nitro group. We call this general behavior the von Richter Reaction in honor of its discoverer.



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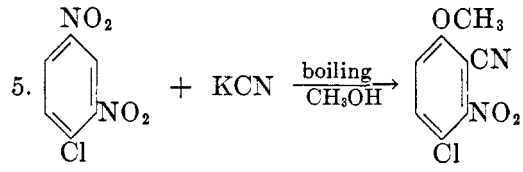

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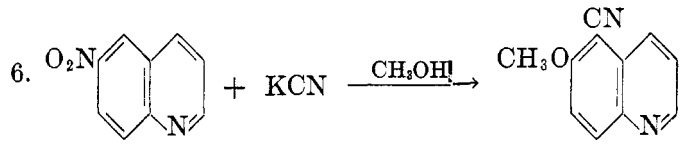


V VI

TABLE II

THE VON RICHTER REACTION WITH *p*-NITROBROMOBENZENE

SOLVENT AND TECHNIQUE	TEMP., °C.	SOLVENT, ML.	YIELD OF *m*-C_6H_4-BrCOOH, %	M.P., °C. CRUDE	RECOVERED NEUTRAL MATERIAL	
					YIELD, %	M.P., °C.
Abs. alc., sealed tube	175	25	7	142–145	87	95–110[a]
Abs. alc., sealed tube	195[b]	25	8	114–140	6	58[c]
Alc., 95%, sealed tube	140–150	25	16	152–153[d]	35	greasy
Alc., 48%, sealed tube	145–155	25	22	154.5–155.4[d]	35	118–122[e]
Glycol, 98%, 3 hrs. reflux		75	3	151–154	4	120–125
Glycol, 90%, 3 hrs. reflux		75	10	151–154[d]	21	125–127
Glycol, 75%, sealed tube	170[f]	50	1.7	150–153[d]	90	123–127
Glycol, 50%, 3 hrs. reflux		75	5	153–154	84	123–125
Cyclohexanol, 98%, 3 hrs. reflux		75	1.5	153–154	49	121–125
Glycol, 90%, 3 hrs. reflux[g]		150	16	150–153		

[a] When recrystallized, m.p. 122–124°; did not depress m.p. of *p*-nitrobromobenzene. [b] Eight hours. [c] Did not depress m.p. of *p*-nitrophenetole. [d] Did not depress m.p. of *m*-bromobenzoic acid. [e] Did not depress m.p. of *p*-nitrobromobenzene. [f] Three hours. [g] Used 8 g. of *p*-nitrobromobenzene and 30 g. of potassium cyanide.

It should be understood, however, that some aromatic nitro compounds react with alcoholic cyanide in another fashion. *m*-Dinitrobenzene (I) with potassium cyanide in boiling methanol gives 2-methoxy-6-nitrobenzonitrile (II) (7, 8); 2,4-dinitrochlorobenzene (III) yields 2-nitro-3-chloro-6-methoxybenzonitrile (IV) (9), and similarly 5-cyano-6-methoxyquinoline (VI) is produced from 6-nitroquinoline (V) (10). In these cases, the point of entrance of the cyano group is doubly activated: there are either two nitro groups or a nitro group and a hetero nitrogen atom located so as to activate it. We shall presently devote more attention to these doubly activated compounds.

Experimental considerations. von Richter's reports were lean on experimental detail. Moreover, his identification of products was not wholly satisfying, and

his method for isolating and purifying products was most laborious. Our desire to gain better information on yields and to check the identity of the reported products motivated our repetition of his work on the nitrobromobenzenes; incidentally, we have employed a more simple technique (steam-distillation) for isolating products in pure form.

The structures assigned to von Richter's products were based mainly on their analyses and melting points although in a few cases these halobenzoic acids were converted to hydroxybenzoic acid derivatives by alkali fusion, a reaction which itself might take an abnormal course. In the present work all products were identified by mixed melting points with authentic samples.

von Richter's reactions were run in "alcohol" solution in sealed tubes at 180–200° or higher, although Holleman used water as a solvent for the reaction of potassium *m*-nitrobenzenesulfonate. To check the effect on yield of variation in conditions such as time, temperature, and solvent composition, we ran a series of reactions mainly on *p*-nitrobromobenzene. In most of these the molar ratio of cyanide to nitro compound was 2:1. This study showed that although the reaction could be run in 100% or 95% ethanol, a better product was obtained in 50% ethanol-water. It also showed that yield (in lime-dried ethanol) was roughly independent of temperature in the range 155° to 195°, and was not improved by heating for longer than one hour. The latter observation and the recovery of much unreacted starting material suggest that hydrolysis (or alcoholysis) competes with the nitro compound for cyanide ion to the extent that hydrolytic destruction of cyanide is the yield-limiting factor; it is known that cyanide ion is rapidly hydrolyzed in water solution at elevated temperatures (11a).

We were early aware of limitations inherent in the use of ethanol solvent with its requirement of sealed tubes, and sought to find a high-boiling solvent in which the reaction could be run at reflux. Ethylene glycol suggested itself, but yields in 90% and 95% ethylene glycol (b.p. 142° and 152°, respectively) were only 10% as compared to yields of about 20% previously obtained in 50% ethanol. However, when a 12:1 ratio of cyanide to *p*-nitrobromobenzene was used, the yield in 90% glycol rose to 16%. Although this technique still is not very good so far as yields are concerned, it does represent a tolerable reflux procedure which allows the reaction to be run on a large scale. No unreacted starting material was recovered from runs according to this technique, suggesting that reduction of the nitro group by the alkaline alcoholic solvent or by the large excess of cyanide (12) was now limiting the yield. It is clear that a more satisfactory high-boiling solvent would be desirable.

Reaction mechanism. An acceptable mechanism for this reaction must be consistent with the following facts:

(a) "Normal" replacement of halogen from nitrohalobenzenes by sodium or potassium cyanide in aqueous or alcoholic solution has not been observed. [However, cuprous cyanide gives "normal" replacement of halo by cyano (13)].

(b) Recovered starting materials have been found free from contamination by isomers.

(c) Product structure has a specific relationship to starting material orientation. *para*-Substituted nitrobenzenes give *meta*-substituted benzoic acids free from isomeric contamination, and *meta*-substituted nitrobenzenes give *ortho*- and *para*-substituted benzoic acids with no traces of the *meta* isomer.

(d) There is no evidence that the entering carboxyl has ever taken the same ring position that the nitro group vacated.[5]

(e) Nitro compounds with an *ortho* substituent react less readily than those without substituents *ortho* to nitro. In most cases, *ortho*-substituted nitro compounds have failed to react under conditions which are sufficient for reaction by their *meta*- and *para*-isomers. (See Table I).

(f) Nitrite ion is eliminated in the reaction (3).

We assume that in this reaction a cyano group is introduced into the ring and later hydrolyzed to carboxyl. This assumption is in accord with general chemical experience, and is supported in particular by some observations of Rosenmund and Struck (13).

The above facts rule out three mechanistic possibilities which one is compelled to consider:

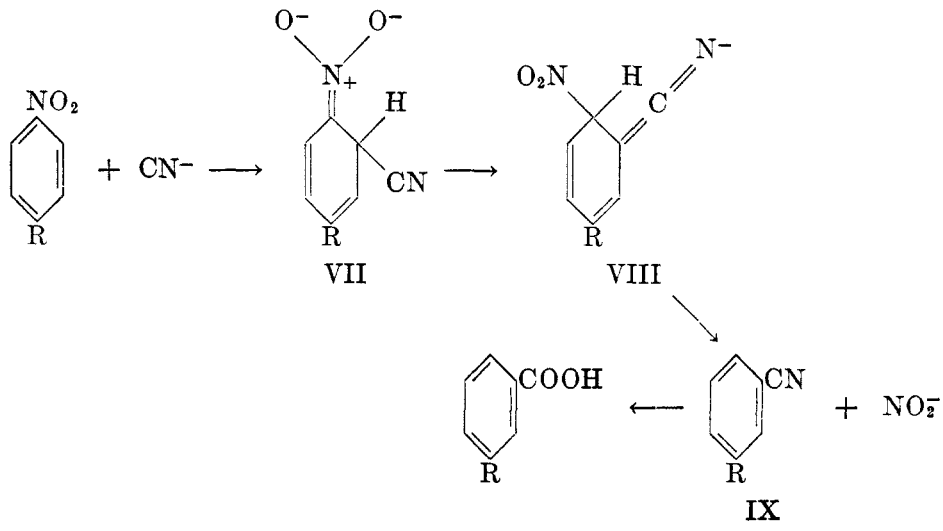
There cannot have been rearrangement of the starting material followed by "normal" replacement of nitro by cyano because of (b), (c), and (d). Furthermore, the formation of *ortho* substituted benzoic acids from *meta* substituted nitrobenzenes cannot have gone through *ortho* substituted nitrobenzenes, because the latter are unreactive (e).

There cannot have been "normal" replacement of nitro by cyano followed by rearrangement of the resulting nitrile or one of its hydrolysis products because of (c) and (d).

There cannot have been dissociation of the nitro compound to form a substituted phenyl radical or ion which, after rearrangement or because of its resonance state, later united with a cyano group to form the predecessors of the observed products because of (c). Such a process would lead to formation of the same sort of products from both *meta*- and *para*-substituted nitrobenzenes.

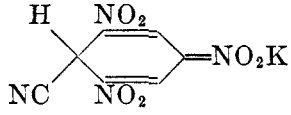
We believe the following is a reasonable mechanism for the von Richter reaction (illustrated for a *p*-substituted nitrobenzene): (A) There is attack by cyanide at an unoccupied position *ortho* to the nitro group; this produces the intermediate ion VII. (B) Ion VII releases in some way a hydride ion which displaces the nitro group; for the transition state in the displacement, VIII is an important resonance structure; resulting from the displacement are nitrite ion and nitrile IX. (C) Hydrolysis of the nitrile yields a *meta*-substituted benzoic acid.

[5] However, it has been reported by Blanksma (*Beilstein*, Erstes Ergänzungswerk, **X**, p. 53) and by Lobry de Bruyn (12) that the nitro group in position 6 of 2-methoxy-5,6-dinitrobenzonitrile is directly replaced by cyano in reaction with alcoholic potassium cyanide.



Crucial to this mechanism is our postulate that only attack of cyanide *ortho* to a nitro group can result in the von Richter reaction.[6] The evidence for this is good but not conclusive. That the structures of all observed products are consistent with this postulate is necessary and permissive evidence. One should observe, though, that a few products (such as *ortho*-bromobenzoic acid from *meta*-nitrobromobenzene) could also be regarded as the result of attack *para* to nitro. Exclusive *ortho* attack is strongly supported by the reactions of *m*-dinitrobenzene and 2,4-dinitrochlorobenzene with cyanide ion (equations 4 and 5), in which attack occurs exclusively *between* two nitro groups (*ortho* to both) in spite of the availability of, respectively, two or one positions which are *ortho* to one nitro and *para* to another. In addition, as we shall presently show, the postulate of exclusive *ortho* attack makes comprehensible the failure, in general, of *ortho*-substituted nitro compounds to react.

The structure of intermediate VII is analagous to that (X) assigned by Meisenheimer (14) to the stable *sym*-trinitrobenzene—potassium cyanide adduct (15). Regarding VIII, the transition state in the nitro group displacement, it should be noticed that its negative charge resides in the cyano group; in other words, the cyano group, following entry in the first stage of this process, activates replacement of nitro in the second stage.

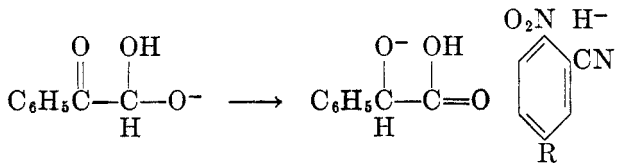


X

Energy considerations make it improbable that hydride ion is actually set free in the transformation of VII into VIII; more likely there is intramolecular mi-

[6] Lobry de Bruyn (12) also believed that the point of entry of the cyano group was *ortho* to nitro; his mechanism for the von Richter reaction is in other respects quite different from ours.

gration with the hydrogen atom always more or less bonded to one carbon atom or the other. A similar case occurs in the rearrangement of phenylglyoxal to mandelic acid, for which tracer studies (16, 17) indicate hydride ion migration from XI to XII to be the essential step. For this transformation, Doering, Taylor and Schoenewaldt (16) have sketched a mechanism which avoids the liberation of free hydride ion. In the same vein, one may visualize the transition state in the VII to VIII transformation to be a resonance hybrid of these two structures, with in addition some contribution from structure XIII in which hydride is free.



XI XII XIII

We may now point out that intramolecular hydride ion transfer along the lines we have postulated would not be possible if cyanide had attacked *para* to nitro. Intermolecular transfer of hydride is conceivable, but it would surely require greater energy of activation and have as well a lower probability factor.

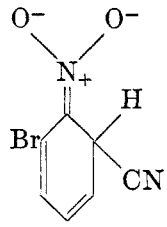
Reactions 4, 5, and 6 occur at lower temperatures than the von Richter reaction. Doubly-activated compounds like *m*-dinitrobenzene would be expected to form complexes with cyanide of type VII or X, with intermediate stability. At the temperatures employed for reactions 4, 5, and 6 there was likely not sufficient activation for hydride migration of the VII to VIII type. Instead, there was evidently oxidation of the complex (probably by nitro groups of other molecules) to a substituted *o*-nitrobenzonitrile which then suffered replacement of nitro by alkoxyl (from the alkaline alcoholic medium) to give the observed products.

The reactions of *m*-nitrobenzenesulfonic acid, in which there is weak activation by the ionized sulfo group, represent borderline behavior. The von Richter reaction (forming *o*- and *p*-sulfobenzoic acids) predominates, but aminosulfobenzoic acids are formed as by-products. Holleman (4) claimed to have isolated 2-amino-6-sulfobenzoic acid, 2-amino-4-sulfobenzoic acid, and 4-amino-2-sulfobenzoic acid in unspecified yields. Identification of aminosulfobenzoic acids is difficult because they decompose without melting when heated; in place of melting points, solubility and conductance values have been used by some workers as characteristics of identity. However, Holleman applied no such criteria; he heeded only analyses and the presence or absence of a blue fluorescence in assigning structures. Comparison with the careful identification of several aminosulfobenzoic acids by van Dorssen (18) has persuaded us that Holleman had evidence only for 2-amino-4-sulfobenzoic acid and probably one other isomer.

This point is of great interest to us, for if the other isomer were 4-amino-2-sulfobenzoic acid, attack of cyanide ion *para* to a nitro group would be shown to be possible, and this would necessitate fundamental alterations in the mechanism we postulate in this paper. It is clear that a re-examination of the action of

aqueous cyanide on *m*-nitrobenzenesulfonic acid with a careful search for 4-amino-2-sulfobenzoic acid as a possible product would be instructive.

The failure of most *ortho*-substituted nitro compounds to react with potassium cyanide probably can be ascribed to steric interference with resonance in the transition state. In the case of *o*-nitrobromobenzene, a large contribution by structure XIV would be essential to make the energy level of the transition state accessible under the reaction conditions used, but structure XIV is of high energy because of the strain on a coplanar nitro group between the two other groups *ortho*-situated (19).



XIV

One of the strangest features of the von Richter reaction is the failure of *o*- and *p*-nitrohalobenzenes to give simple replacement of halo by cyano, as one would expect by analogy with other reactions of these compounds. Examination of two recent reviews on the preparation of nitriles (11, 20) reveals, however, that there are only a few isolated examples (and these involve compounds of very unusual structure) in which an aromatic substituent has been replaced by a cyano group in reaction with an alkali cyanide at moderate temperatures; in general, such replacements are obtained only under fusion conditions or by the use of copper compounds. This indisposition of cyanide to replace aromatic substituents is in contrast to its propensity to enter an unsubstituted position on an aromatic nucleus; examples of the latter are the facile cyanation of quinoline compounds by aqueous cyanide (11b) and the action of aqueous-alcoholic potassium cyanide on 1-nitroso-2-naphthol to form 1-amino-4-cyano-2-naphthol (21).

The failure of other common nucleophilic reagents to react with nitro compounds as cyanide does is probably due in part to the circumstance that they would become, after entry *ortho* to nitro, groups such as amino, alkoxyl or mercapto which would not activate the replacement of nitro by hydride. One might expect, from these considerations, sulfinate ions to react with nitro compounds in the von Richter manner, for they would become, after entry, sulfonyl groups which have considerable activating power (22). A number of reactions of sulfinates with nitro compounds have been studied; they appear, however, to go in a "normal" fashion.

EXPERIMENTAL

Melting points are uncorrected.

Materials. Eastman Kodak Co. preparations of the three nitrobromobenzenes and of *m*-nitroanisole were employed. Messrs. Henry Richanbach, David Williams, and Franklin Draper, Jr. graciously prepared for us *p*-nitroanisole, *o*-nitroanisole, and *m*-anisic acid, respectively. Fresh Mallinckrodt Purified granular potassium cyanide was used.

Standard procedure. Nitro compound, potassium cyanide, and solvent were sealed in a stout Pyrex tube which was heated in a furnace. In other cases, the mixture was refluxed in an open apparatus. When cool, the sealed tubes were opened; there was usually a mild pop signifying the release of gas pressure. The reaction mixture was washed into a flask with water and the mixture made strongly basic with sodium or potassium hydroxide. In early runs, the mixture was then refluxed for two hours (to hydrolyze nitriles); this treatment was later discontinued because it did not improve the yield of acids and caused deterioration of unreacted starting material. Steam-distillation of this basic mixture served to remove the organic solvent (ethanol or ethylene glycol) and unreacted starting material; when glycol was the solvent, two liters of distillate were collected *per* 75 ml. of solvent. Starting material was collected by filtration of this distillate.

The residue from the first steam-distillation was acidified and steam was run through again until 500 ml. of distillate had been collected for each gram of starting material used. This distillate, in which one could occasionally see a few crystals of the acid product, was made slightly alkaline with sodium carbonate, boiled down to about 200 ml., and acidified. The precipitated acid product was collected.

Runs with p-nitrobromobenzene. On this compound we tested various modifications of the experimental procedure. Representative runs are summarized in Table II. Except where otherwise noted, 4.0 g. of *p*-nitrobromobenzene and 2.6 g. of potassium cyanide were used with one hour of heating. Absolute ethanol was prepared by the lime method.

Behavior of m-nitrobromobenzene. A mixture of 4 g. of *m*-nitrobromobenzene, 2.6 g. of potassium cyanide, and 25 ml. of 95% ethanol was heated in a sealed tube one hour at 155°. No starting material was recovered when the reaction mixture was treated in the standard way, although 0.92 g. (23%) of crude acid product, m.p. 139–170°, appeared. (There was also 1.09 g. of tar.) The losses in fractional crystallization of this crude acid from water were large, but we estimate that roughly equivalent amounts of *ortho-* and *para*-bromobenzoic acid were present. At any rate, 0.30 g. of the more soluble *ortho* isomer, m.p. 141–142° (mixed m.p. with authentic *o*-bromobenzoic acid, 145–149°) and 0.10 g. of the *para* isomer, m.p. 249° (mixed m.p. with authentic *p*-bromobenzoic acid, 248–252°) were eventually isolated (*ortho, meta,* and *para*-Bromobenzoic acids melt at 150°, 155°, and 253° respectively, and melting points of isomer mixtures are strongly depressed).

Behavior of o-nitrobromobenzene. Tubes containing 4 g. of *o*-nitrobromobenzene, 2.6 g. of potassium cyanide, and 25 ml. of lime-dried ethanol were heated at 175° for one hour and for seven hours. Neither yielded, when treated in the standard way, either acidic product or unreacted starting material.

Behavior of nitrobenzene. Nitrobenzene (2.5 g.) and 15 g. of potassium cyanide were allowed to react in refluxing 90% ethylene glycol for three hours. By the standard method of purification, 0.54 g. (21%) of acid of m.p. 111–114° was obtained (no recovery of starting material). Recrystallized, this melted at 120–121° and did not depress the m.p. of authentic benzoic acid.

Behavior of p-nitroanisole. A mixture of 4 g. of *p*-nitroanisole, 3.4 g. of potassium cyanide, and 24 ml. of 48% ethanol in a sealed tube was heated an hour at 170–180°. By treatment of the reaction mixture in the standard way, 0.34 g. (8.5%) of starting material, m.p. 40–47° (recrystallized, it melted at 48–51° and did not depress the m.p. of authentic *p*-nitroanisole), and 0.12 g. (3%) of acid product, m.p. 95–102°, were isolated. Recrystallized, the acid melted at 101.5–102.5°. With authentic *m*-anisic acid of m.p. 104–105°, it gave mixed m.p. 104–105°.

Behavior of m-nitroanisole. A sealed tube containing 4 g. of *m*-nitroanisole, 3.4 g. of potassium cyanide, and 25 ml. of 95% ethanol was heated 85 minutes at 175–190°. By the standard purification procedure, 0.05 g. (1%) of acid, m.p. about 170° were obtained. After recrystallization from dilute ethanol, its m.p. was 180–182°. With authentic *p*-anisic acid of the same m.p., the mixed m.p. was not depressed. Recovered starting material, m.p 30–35°, weighed 0.81 g. (20%).

Behavior of o-nitroanisole. A sealed tube containing 4 g. of *o*-nitroanisole, 3.4 g. of potassium cyanide, and 25 ml. of 48% ethanol was heated an hour at 175–185°. The standard

isolation procedure yielded 1.0 g. of a neutral oil, presumably unreacted *o*-nitroanisole, but no acid product.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE
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A NEW METHOD FOR THE PREPARATION OF ORGANIC IODIDES

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During the synthesis of various macrocyclic ketones it became necessary to develop an efficient method for converting large quantities of complex ethers into their corresponding iodides. This method was then applied for the preparation of iodides from olefins and alcohols.

The more efficient procedures for cleaving ethers into halides involve the use of either gaseous or aqueous hydrogen iodide (1, 2, 3, 4) and hydrogen bromide (5, 6), acetyl iodide (7), acetyl chloride (8), and various halogenated derivatives such as phosphorus oxychloride (9), aluminum chloride (10), and phosphorus pentabromide and chloride (5). A similar conversion of ethers into esters of inorganic acids has been effected with phosphoric anhydride (11) and sulfuric acid (12). Gaseous or aqueous hydrogen iodide has been the reagent most frequently used; however, it has the disadvantages that large excesses of an expensive reagent are required, extensive reduction of the reaction product often occurs, and reaction is slow in heterogeneous medium.

In an effort to obviate these disadvantages the reactions of various ethers with excess orthophosphoric acid and potassium iodide were studied. Phosphoric acid and potassium iodide are of value in that they serve as a convenient, readily available source of hydrogen iodide, and advantage is taken of the acid-catalyzed solvolytic cleavage of ethers by strong acids (13). Cleavage of simple aliphatic ethers by these reagents is illustrated by the following equation:

$$R—O—R + 2\ KI + 2\ H_3PO_4 \rightarrow 2\ RI + 2\ KH_2PO_4 + H_2O$$

In initial experiments (Table I) with dibutyl ether, potassium iodide, and excess 50% phosphoric acid at 110° it was found that no reaction occurred. When the concentration of the phosphoric acid was increased to 85% by weight and finally to an optimum concentration of 95%, cleavage of the ether proceeded rapidly, with minimum reduction and dehydration, to give 1-iodobutane in 75.1% and 81.0% yields respectively. Since anhydrous phosphoric acid and tetraphosphoric acid were found to have marked dehydrating action and hydrogen iodide is relatively insoluble in these solvents, a general routine procedure using excess 95% orthophosphoric acid was adopted. Sodium iodide could be substituted for potassium iodide without appreciably altering the reaction efficiency.

Upon extension of the method to various aliphatic and alicyclic ethers (Table II), it was found that the procedure was generally applicable and had many advantages over previous methods. Cleavage of the mixed aryl-alkyl ether, β-naphthyl ethyl ether, into β-naphthol and iodoethane occurred readily, but the reagent had no effect on diphenyl ether. No attempt was made to obtain maximum yields in this series; however, the reaction was accelerated and made almost quantitative by increasing the mole ratio of potassium iodide to ether.

Because of the general efficiency obtained with the potassium iodide-orthophosphoric acid reagent, the method (Table III) was extended to various alcohols and olefins as indicated:

$$ROH + KI + H_3PO_4 \rightarrow RI + KH_2PO_4 + H_2O$$
$$RCH=CH_2 + KI + H_3PO_4 \rightarrow RCHICH_3 + KH_2PO_4$$

TABLE I

EFFECT OF PHOSPHORIC ACID CONCENTRATION[a] ON THE CLEAVAGE OF DIBUTYL ETHER

ACID CONC., %	TIME, HRS.	CONVERSION[b] TO 1-IODOBUTANE, %	YIELD[b] OF 1-BUTANOL, %	YIELD[b] OF 1-IODOBUTANE, %
50	3	0	0	0
85	3[c]	56.0	5.7	56.0
85	3	57.2	17.1	72.4
85	6	61.6	7.6	75.1
95	4	73.0	9.6	77.7
T.P.A.[d]	5	47.5	3.9	52.8[e]

[a] All experiments were conducted with dibutyl ether, potassium iodide, and phosphoric acid in a mole ratio of 1:3:3.9 at 135°; with tetraphosphoric acid a mole ratio of 1:3:1.3 was used. [b] Conversions are based on dibutyl ether added to the reaction; yields are based on ether consumed. [c] Sodium iodide was used instead of potassium iodide. [d] The tetraphosphoric acid was 82–84% phosphoric anhydride. [e] An 8.3% yield of 1-butene was obtained.

TABLE II

CLEAVAGE OF ETHERS WITH POTASSIUM IODIDE AND 95% PHOSPHORIC ACID[a]

COMPOUND	TIME, HRS.	CONVERSION TO IODIDE, %	YIELD OF IODIDE, %
Dibutyl ether	5	77.7[b]	81.0
Diisopropyl ether	3	68.7	89.8
Tetrahydrofuran	5	96.0	96.0
Diphenyl ether	6	0	0
β-Naphthyl ethyl ether	3	60.5	77.7[c]

[a] Experiments were conducted with an ether, potassium iodide, and 95% phosphoric acid mole ratio of 1:4:5.9 at the reflux temperature of the reaction mixture. With dibutyl and diisopropyl ethers, mole ratios of 1:3.5:5.3 and 1:6:8.7 were used. [b] A 7.3% yield of 1-butanol was obtained. [c] A yield of β-naphthol of 89.9% was obtained.

Previous studies have shown that alcohols are converted into iodides by aqueous hydrogen iodide (14) and phosphorus and iodine (15) and that addition of hydrogen iodide to alkenes may be effected either in aqueous medium or in glacial acetic acid or by the action of sodium iodide either in aqueous hydrochloric acid or in glacial acetic acid (16, 17).

A study (Table IV) of the effect of the phosphoric acid concentration on the reaction of alcohols and olefins gave further evidence that these reactions are acid-catalyzed (18, 19), and maximum efficiency was obtained with 95% phosphoric acid. Excellent yields of iodides (88.0–95.3%) were obtained from various

TABLE III

CONVERSION OF ALCOHOLS AND OLEFINS INTO IODIDES WITH POTASSIUM IODIDE AND 95% PHOSPHORIC ACID

COMPOUND[a]	TIME, HRS.	YIELD OF IODIDE, %
Cyclohexanol	6	79.5[b]
1-Propanol	6	90.5
2-Methyl-1-propanol	5	88.0
2-Methyl-2-propanol	5	89.8
1,6-Hexanediol	3	95.3
Phenol	5	0
Cyclohexene	3	90.5
Cyclohexene	6	90.7[c]
1-Hexene	5	93.3
2,3-Dimethyl-2-butene	4	91.4

[a] All experiments conducted with alcohols had an alcohol, potassium iodide, and phosphoric acid mole ratio of 1:2:2.96; that with 1,6-hexanediol, 1:4:6; those with olefins, 1:3–3.2:4.1–4.3. [b] 85% Phosphoric acid was used. A 16.6% yield of cyclohexene, identified as the dibromide, was obtained. [c] A mole ratio of cyclohexene, potassium iodide, and phosphoric acid of 1:1.5:2.1 was used.

TABLE IV

EFFECT OF PHOSPHORIC ACID CONCENTRATION ON THE CONVERSION OF ALCOHOLS AND OLEFINS INTO IODIDES

COMPOUND[a]	ACID CONC., %	TIME, HRS.	CONVERSION, %	YIELD OF IODIDE, %
2-Methyl-2-propanol	85	5	30.0[b]	30.0
	95[c]	5	89.8	89.8
2-Methyl-1-propanol	85	5	45.0	79.0[d]
	95	5	64.2	88.0
1-Propanol	85	6	44.8	74.8
	95	6	75.3	90.3
	95	5	75.5	90.5
Cyclohexene	50[e]	5	14.3	48.7
	85	6	52.4	87.8
	95	6	90.5	90.5

[a] All experiments using phosphoric acid were conducted with an alcohol or olefin, potassium iodide, and phosphoric acid mole ratio of 1:2:2.1; those conducted with 95% phosphoric acid had a mole ratio of 1:2:2.9–3.0. [b] An 18.5% yield of 2-methylpropene was obtained. [c] This experiment was conducted at 40°; all other experiments were conducted at the reflux temperature of the reaction mixture. [d] The only products isolated were the iodide and either unreacted alcohol or olefin. [e] A mole ratio of cyclohexene, potassium iodide, and phosphoric acid of 1:1.5:2.0 was used.

primary, secondary, and tertiary alcohols and olefins; however, phenols were not converted into iodides. No organic phosphates were found as products of these reactions.

EXPERIMENTAL

Since the procedures for the reactions of potassium iodide and orthophosphoric acid with various ethers, alcohols, and olefins are essentially the same, a detailed procedure is described for only a single member of each class of compounds. Characterization of all compounds was based on their densities, refractive indices, and boiling and melting points. Volatile olefins produced during the reaction were converted into dibromides and identified in the preceding manner. The composition of binary azeotropes was determined by the methods of Lorentz and Lorenz (20).

Phosphoric acid of the desired concentration was prepared by adding the calculated quantity of 85% phosphoric acid to either water or phosphoric anhydride with stirring and cooling. The quantity of potassium iodide varied from 1.5–3.0 times the theoretical. The mixture was cooled before adding the potassium iodide to prevent evolution of hydrogen iodide and oxidation to iodine. The reaction proceeded more rapidly with large excesses of potassium iodide. Separation of the reaction products was accomplished either with a precision rectifying-column or a modified Claisen distilling-flask at various pressures.

Dibutyl ether, potassium iodide, and 95% phosphoric acid. Orthophosphoric acid (85%; 346 g.; 202 ml; 3.0 moles) was added, with stirring, to 79 g. of phosphoric anhydride (= 95% phosphoric acid) in a dry 1-l. three-necked flask equipped with a sealed stirrer, a reflux condenser, and a thermometer. After the mixture had cooled to room temperature, 445 g. (2.68 moles) of potassium iodide and 100 g. (0.77 moles) of dibutyl ether (b.p. 139.5–140.5°) were added. The mixture was stirred and heated at reflux temperature for five hours during which time a dense oil separated from the acid layer. The stirred mixture was cooled to room temperature, and 150 ml. of water and 250 ml. of diethyl ether were added. The ether layer was separated, decolorized with sodium thiosulfate solution, washed with a cold saturated sodium chloride solution, and dried over sodium sulfate. The ether was evaporated, and the mixture was rectified at atmospheric pressure in a four-foot rectifying-column packed with glass-helices. Three fractions were obtained: (a) an azeotrope (19 g.; b.p. 110°) consisting of 11 g. of 1-iodobutane and 8 g. of 1-butanol, (b) 1-iodobutane (200 g.; b.p. 129.5–130.5°; n_D^{20} 1.504; d_4^{20} 1.630), and (c) dibutyl ether (4 g.; b.p. 140°; n_D^{20} 1.402; d_4^{20} 0.770). Yield of 1-iodobutane; 77.7%.

2,3-Dimethyl-2-butene, potassium iodide, and 95% phosphoric acid. Anhydrous potassium iodide (250 g.; 1.5 moles) and 2,3-dimethyl-2-butene (42 g.; 0.5 moles; b.p. 72.6–72.8°; n_D^{20} 1.4141) were added to 95% orthophosphoric acid (216 g.; 2.1 moles) in a 1-l. flask equipped with a reflux condenser, a sealed stirrer, and a thermometer. The mixture was stirred and refluxed for four hours during which time a dense oil separated. The reaction mixture was cooled and extracted with 150 ml. of water and 250 ml. of diethyl ether. The ether layer was separated, decolorized with sodium thiosulfate, extracted with a saturated sodium chloride solution, and dried over sodium sulfate. The ether was evaporated on a water-bath, and the residue distilled from a modified Claisen flask at atmospheric pressure to yield, after a small fore-run, 96 g. (91.4%) of 2,3-dimethyl-2-iodobutane, n_D^{20} 1.495; d_4^{20} 1.448.

1,6-Hexanediol, potassium iodide, and 95% phosphoric acid. Recrystallized 1,6-hexanediol, (60 g.; 0.5 moles), m.p. 40–41°, was added to a stirred mixture of potassium iodide (332 g.; 2 moles) and 95% orthophosphoric acid (296 g.; 3.02 moles) at room temperature in a 1-l. three-necked flask equipped with a reflux condenser, a stirrer, and a thermometer. The reaction mixture was heated for three hours at 100–120° during which time two phases separated and finally the organic product settled through the acid layer. After the reaction mixture had cooled, it was extracted with 150 ml. of water and 250 ml. of diethyl ether. The ether layer was separated, decolorized with sodium thiosulfate solution, extracted with a saturated sodium chloride solution, and dried over sodium sulfate. The ether was evaporated on a steam-bath and the residue was distilled from a modified Claisen flask under reduced pressure. The fraction boiling at 112.5–113.5° at 3 mm. was collected. Yield of 1,6-diiodohexane (n_D^{20} 1.585; d_4^{20} 2.03; m.p. 8.5–9.0°), 161 g. (95.3%).

SUMMARY

A general method for the conversion of ethers, alcohols, and olefins into iodides by reaction with potassium iodide or sodium iodide and phosphoric acid has been described. Both the rates of reaction and the yields of iodide obtained from ethers, alcohols, and olefins are markedly influenced by the concentration of the orthophosphoric acid used.

COLUMBUS 10, OHIO

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF HYNSON, WESTCOTT, AND DUNNING, INC.]

THE OXIDATION OF IODINATED PHTHALIC AND BENZOIC ACIDS

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In the course of an investigation concerning the mobility of iodine atoms in tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydrides, it was discovered that the action of concentrated nitric acid on a suspension of these derivatives in concentrated sulfuric acid produced, not the expected replacement of one or more of the substituents by a nitro group, but an oxidation of the iodine atoms. The resulting compounds were extremely explosive and quantitative analysis showed that, with all the former constituents present, four active oxygen atoms had been added to each molecule of the starting material. The anhydrides were not affected by digestion with concentrated nitric acid, while boiling merely caused a slow destructive oxidation. It was subsequently noted that the same tetraoxy derivatives were obtained, although less conveniently, by treating the anhydrides with a solution of potassium dichromate in dilute sulfuric acid. Furthermore, tetraiodophthalic acid and dimethyl tetraiodophthalate yielded the same oxidation product as the anhydride when subjected to the nitric-sulfuric acid treatment.

It seemed of interest to ascertain where the active oxygen atoms in the oxidation products are located. Their distribution might be such as to affect all four iodine atoms, thus producing a tetraiodoso derivative, or, by involving only two iodine atoms, to yield a diiodoxy derivative. In other words, the new compounds may contain either four—IO groups or two iodine atoms and two—IO_2 groups.

In the investigation presented here, an attempt has been made to solve this problem one way or the other, and it may be stated in advance that our evidence appears to be most favorably interpreted, although by no means conclusively, by assuming the formation of 4,5-diiodo-3,6-diiodoxy derivatives. In order to reach this conclusion it was necessary to extend the work to include a comparative study of the similar oxidation of a number of lower halogenated phthalic and benzoic acids. Although the authors realize that a number of questions remain unanswered, the work is being published in its present form as other activities require their attention for the time being.

In favor of the view that the oxygen atoms are not evenly distributed over the four iodine atoms is the finding that 4,5-diiodophthalic acid (I) and 4-iodophthalic acid are not subject to oxidation under the experimental conditions. From this it may be inferred that in the tetraiodo derivatives the iodine atoms in positions 3 and 6 were oxidized to iodoxy groups while those in positions 4 and 5 had remained unaltered. Our observation that 3,6-dichloro-4,5-diiodophthalic anhydride (1) also failed to take up oxygen, lent added support to this concept.

Apparently contradictory to these conclusions were our observations that 3,6-diiodophthalic acid (II), instead of taking up four active oxygen atoms, added two when subjected to the same oxidation method, 3-iodophthalic acid one in-

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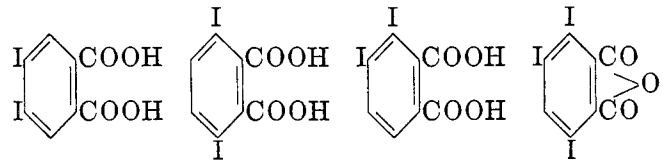
stead of two, while 3,4-diiodophthalic acid (III) alone took up two active oxygen atoms as expected. 4-Iodophthalic acid proved to be unsuitable for this investigation, since it was nitrated to a considerable extent and thereby confused the issue.



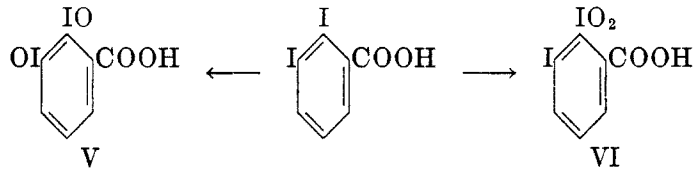
I II III IV

Triiodophthalic anhydride was also included in the investigation. Of the two possible isomers only the 3,4,6-triiodo derivative (IV) is known (1). It proved to be difficult to obtain a sufficient quantity of pure material for experimental purposes. The oxidation of our samples [m.p. 217–225° (cor.)] invariably yielded two substances, the active oxygen contents of which corresponded to triiodophthalic acids which had taken up two and three oxygen atoms per molecule. We therefore concluded that our sample of anhydride consisted of a mixture of 3,4,6- and the unknown 3,4,5-triiodophthalic anhydride, present in the ratio of about 3:1. These anhydrides were actually isolated by reducing the oxidation products and crystallizing the acids so obtained from acetic anhydride. The main fraction [m.p. 217–224° (cor.)] took up three oxygen atoms and corresponded to the 3,4,6-triiodo anhydride, although Pratt and Perkins (1) give a higher melting point. The second fraction, (m.p. 227–229°) obtained from the more soluble oxidation product, took up two oxygen atoms and represented the 3,4,5-triiodo isomer.

The investigation was then extended to a number of iodobenzoic acids. Previously, Meyer and Wachter (2) treated the three isomeric monoiodobenzoic acids with boiling concentrated nitric acid and found that only the iodine atom situated *ortho* in the carboxyl group could thus be oxidized to form an iodoso group, while the iodine in the *meta* and *para* isomers remained unchanged. The same results were noted with our nitric-sulfuric acid oxidation, and in addition it was found that 2,3-diiodobenzoic acid, like III, took up two active oxygen atoms. The oxidation of 3-chloro-2-iodo-, 3-bromo-2-iodo-, and 2-bromo-3-iodobenzoic acids, prepared for the purpose, yielded resinous products with liberation of iodine in some cases, and were therefore unsuitable for this study.

The general procedure for determining the active oxygen content of the oxidation products consisted of reducing a sample in aqueous sodium iodide slightly acidified with acetic acid and titrating the liberated iodine with sodium thiosulfate using starch as indicator. It is worthy of note that, when titrating the tetraoxy derivative of tetraiodophthalic anhydride without the presence of acetic acid, only an average of 2.5% active oxygen (corresponding approximately to the titration of one active oxygen atom) was found against a theoretical value of 8.72%. A similar observation was made by Willgerodt (3), and it may be stated that the phenomenon is characteristic of iodoso as well as iodoxy derivatives.

The experimental results obtained by us with the iodinated phthalic and benzoic acids were in good agreement but still left the phenomenon subject to dual interpretation. For example, oxidized 2,3-diiodobenzoic acid could be either a diiodoso derivative (V) or a 3-iodo-2-iodoxy derivative (VI).

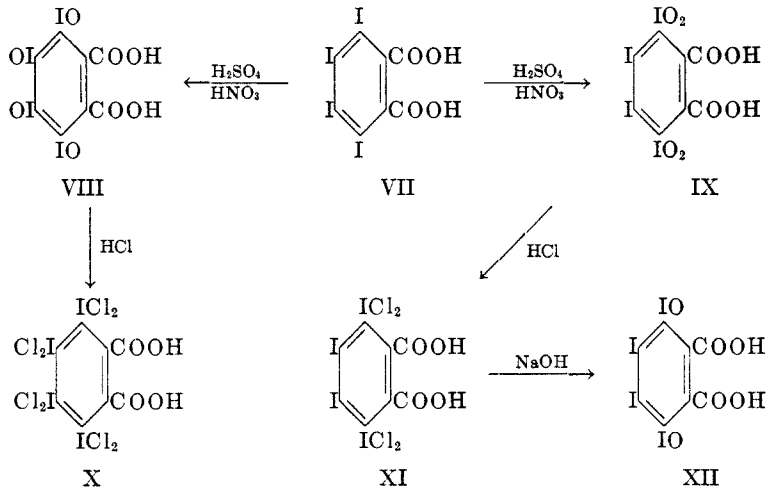


It was expected that the problem could definitely be solved with the aid of two known reactions. According to Willgerodt (3,4), hydrochloric acid reacts with an iodoso derivative quantitatively according to equation (a), and with an iodoxy derivative, also quantitatively, according to equation (b),

$$R{-}IO + 2\,HCl \longrightarrow R{-}ICl_2 + H_2O \qquad (a)$$

$$R{-}IO_2 + 4\,HCl \longrightarrow R{-}ICl_2 + 2\,H_2O + Cl_2 \qquad (b)$$

Applied to the oxidation product of tetraiodophthalic anhydride or acid (VII), treatment with hydrochloric acid would produce an octachloro derivative (X) from the tetraiodoso derivative (VIII), and a tetrachloro derivative (XI) from the diiodoxy derivative (IX).



The spontaneous evolution of chlorine, when hydrochloric acid was added to an ice-cold aqueous suspension of the oxidation product, seemed to decide in favor of formula IX, especially since formation of this tetrachloro derivative (XI) was actually confirmed by analytical data. XI was obtained as a light tan substance, formed in a strongly exothermic reaction. It should be mentioned here that it is dangerous to add hydrochloric acid to the dry tetraoxy derivative. Compound XI is difficult to isolate owing to the fact that it loses chlorine readily to regen-

erate the bright yellow tetraiodophthalic acid. This decomposition takes place within a few hours on standing in the medium in which it was formed and frequently, without apparent reason, in a vacuum desiccator over calcium chloride.

An attempt was made to prepare the tetrachloro derivative (XI) more conveniently by pouring a cold solution of the tetraoxy compound in nitric-sulfuric acid into ice-cold glacial acetic acid saturated with hydrogen chloride. Although chlorine was evolved immediately no spontaneous precipitation occurred, but pure tetraiodophthalic acid crystallized in the course of 12 hours.

The determination of chlorine in compound XI was based on a titration with sodium thiosulfate of the iodine liberated from an acidified solution of potassium iodide according to equation (c).

$$\text{R-ICl}_2 + 2\ \text{KI} \rightarrow \text{RI} + 2\ \text{KCl} + 2\text{I} \qquad \text{(c)}$$

By this method the average per cent chlorine found was 19.24 compared with a theoretical value of 17.47. On the other hand, a direct determination as silver chloride indicated 16.82% chlorine.

It was anticipated that the decomposition of XI with dilute aqueous alkali would take place with formation of an iodoso derivative (4) [equation (d)],

$$\text{R-ICl}_2 + \text{NaOH} \rightarrow \text{RIO} + 2\ \text{NaCl} + \text{H}_2\text{O} \qquad \text{(d)}$$

and that the hypothetical diiodoso derivative (XII) thus formed could be titrated with potassium iodide and sodium thiosulfate. However, taking the conversion factor of 0.8646 into account for the intermediate change of compound XI into XII, the average active oxygen content in the latter was found to be only 2.03, compared with the calculated value of 4.57, probably indicating a more involved decomposition (5).

Masson, Race, and Pounder (6) reported that iodosobenzene may be distinguished from iodoxybenzene by the fact that the former can be titrated quantitatively with sodium thiosulfate by virtue of the iodine liberated from sodium iodide in a saturated borax solution, while iodoxybenzene does not liberate any iodine under these conditions. When applying this test to the tetraoxy derivative to which we have tentatively assigned formula IX, it was noted that iodine was actually freed but not to the full amount (6.9% active oxygen as compared with the theoretical value of 8.7%). We cannot offer a satisfactory explanation for this discrepancy unless it be assumed that the oxidation product really possesses formula VIII, and that, even at low temperatures, a partial conversion into the diiodoxy derivative IX had occurred by intramolecular rearrangement in a manner analogous to the change of simple iodoso compounds into a molar mixture of iodo and iodoxy derivatives under more vigorous conditions (3):

$$2\ \text{RIO} \rightarrow \text{RI} + \text{RIO}_2 \qquad \text{(e)}$$

However this hypothesis would necessitate the additional postulate that the four chlorine atoms in the—ICl_2 groups in positions 4 and 5 (X) are so loosely bound that they are expelled spontaneously under the experimental conditions. Although this view cannot be entirely ignored owing to lack of evidence to the

contrary, it may be pointed out that the difference in behavior of iodoso- and iodoxybenzene in borax solution may not be a general characteristic of the group, and may not hold for acidic derivatives as unstable as the one under discussion; the importance of *p*H will be dealt with in a later paragraph.

In this connection it may be mentioned that the titrations in saturated aqueous borax were carried out with samples of the freshly prepared tetraoxy derivative. Unfortunately, no old preparations were at this time available to ascertain whether under the same conditions the titration result would indicate a shift according to the equation (e).

The spontaneous evolution of chlorine by the action of hydrochloric acid, also on freshly prepared samples of tetraoxy derivative, even under carefully controlled conditions, may either indicate a spontaneous decomposition of compound X or be due to the oxidizing effect of compound IX. Though the reaction cannot decide definitely between the formulas VIII and IX, the authors lean somewhat toward the latter in view of the evidence presented.

It has thus been shown that in the oxidation of iodinated phthalic and benzoic acids with nitric-sulfuric acid an iodine atom between a carboxyl group and a free position is converted into an iodoso group, while iodine atoms *meta* to a carboxyl group and adjacent to two free positions are not susceptible to oxidation. If an iodine atom next to a carboxyl group has another iodine atom in the second adjacent position, our experimental evidence tends to indicate that the first iodine atom is subject to renewed activation and is oxidized to an iodoxy group. However, it should be stated that to date we have no definite proof against the opposite and perhaps less probable contention that the second iodine atom is also converted into an iodoso group. In either case these rules of oxidation completely reconcile the apparently contradictory observations referred to at the beginning of this paper. In view of the remaining element of uncertainty we prefer at present to designate the oxidation products of tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydride as tetraoxy derivatives rather than specify iodoxy or iodoso groups.

There still remains to be discussed the fate of the anhydride ring during the oxidation of tetraiodophthalic and tetraiodo-*o*-sulfobenzoic anhydrides. In the latter case a free sulfonic acid group was suggested by the fact that the compound was spontaneously soluble in dilute alkali, apparently without decomposition. However, oxidized tetraiodophthalic anhydride behaves differently. If highly concentrated alkali was added to the oxidation product, previously thoroughly moistened in order to prevent explosion, a rather insoluble sodium salt precipitated. It dissolved upon dilution with water to form a yellow solution, a phenomenon accompanied by destructive changes made noticeable by the distinct odor of iodoform. In concentrated alkali this sodium salt seemed to be stable. It was also formed if dilute alkali was added to an aqueous suspension of the tetraoxy derivative; the suspended particles first became granular, then gradually dissolved. Acidification with dilute sulfuric acid while cooling in ice failed to regenerate any of the starting material. At *p*H 9.5 the solution turned amber and, without liberating iodine, dark brown at *p*H 6.3. Only after the addition of a

large excess of acid was an amorphous chocolate-brown substance precipitated, containing about 76% iodine. It was soluble in aqueous sodium hydroxide, sodium bicarbonate and sodium acetate, also in alcohol and ether, but was not investigated further.

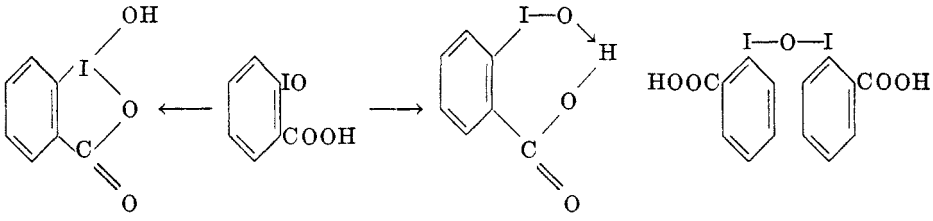
Although the active oxygen values of oxidized tetraiodophthalic anhydride agree better for the acid than for the anhydride structure, the assumption that in the oxidation process the anhydride ring is opened rests mainly on circumstantial evidence; the fact that the same product is obtained from tetraiodophthalic acid and its dimethyl ester, the gradual solution of the anhydride in the medium during oxidation, the spontaneous formation of an alkali salt and, above all, the ready solution in reducing agents such as potassium iodide with formation of tetraiodophthalic acid under conditions sufficiently mild to exclude the possibility of the hydration of a stable anhydride ring.

Tetraoxytetraiodo-phthalic and -*o*-sulfobenzoic acids are yellow, very explosive substances, and, being sensitive toward friction and percussion, as well as heat, should be handled with the greatest care. They are soluble in the nitric-sulfuric acid mixture in which they are formed, precipitate quantitatively if the solution is poured on ice and are harmless if thoroughly wet. A solution of the phthalic acid derivative in the concentrated acid mixture may be heated at 130° without decomposition, but at 160–170° it gives off iodine and is gradually destroyed. The compounds are not affected by light, water or alcohols, but in some dry samples a slow loss of oxygen was noted in the course of time, presumably under the catalytic influence of traces of impurities. For example, a sample of the tetraoxy derivative IX, analyzing for 8.69% active oxygen, had 8.31% left after about four months. On the other hand, other samples have completely preserved their active oxygen content after a year under propyl alcohol or carbon tetrachloride or in a desiccator.

Tetraoxytetraiodophthalic acid shows a strong tendency to form a colloidal suspension in water, but not in acetic or sulfuric acids. It is very sensitive toward reducing agents, regenerating tetraiodophthalic acid under the influence of dilute solutions of sulfur dioxide, sodium iodide, sodium thiosulfate or sodium bisulfite at room temperature. The compound possesses very weak acid properties as evidenced by its insolubility in aqueous sodium bicarbonate and ammonia. A sample suspended in 7% sodium bicarbonate had not dissolved completely after standing for eight months at room temperature. The undissolved portion still contained the full amount of active oxygen. That the dissolved fraction had undergone some destructive decomposition was indicated by the crystals of iodoform which had sublimed into the neck of the flask.

The explosive's insolubility in ammonia is difficult to explain. It is interesting to note that Hartmann and Meyer (7) reported *o*-iodoxybenzoic acid to be considerably stronger than *o*-iodosobenzoic acid and that only the latter regenerates the free acid if an ammoniacal solution is evaporated to dryness. This may indicate that iodoso compounds form a chelate structure whereas the corresponding iodoxy compounds cannot do so. In order to interpret the susceptibility to oxidation of *o*-iodo atoms in iodobenzoic acids, as compared with those in other posi-

tions, Meyer and Wachter (2) advanced the view, supported by Lütjens (8), that a five-membered ring may be formed between the iodoso and the adjacent carboxyl group (XIII). While this hypothesis cannot be upheld in the light of more recent knowledge, its more modern equivalent, chelation, seems unlikely as it would involve the formation of a seven-membered ring (XIV). Chelation seems even less probable in *o*-iodoxybenzoic acid, as steric hindrance would prevent the required coplanar configuration of the molecule and this condition would be aggravated by additional iodine atoms (9). The weak acid properties of the carboxyl groups in our tetraoxy compound are undoubtedly at least partially due to the cumulative effect of the massed ring substitution.



XIII XIV XV

To test the possibility that the varying extent of oxidation of the iodine atoms in the isomeric iodobenzoic acids is in some way associated with an adjacent free carboxyl group, dimethyl tetraiodophthalate was prepared and oxidized. Unfortunately, oxidation was accompanied by complete saponification of the ester to give tetraoxytetraiodophthalic acid.

The part which acid plays in the titration for active oxygen is not yet clear (10). The fact that *o*-iodosobenzoic acid gives up half of its active oxygen when no acid is present could be explained by complex formation between a mole of *o*-iodobenzoic acid as it is produced with a mole of iodoso compound to yield XV. If this explanation were correct, then neutral titration in the presence of excess *o*-iodobenzoic acid should result in practically no liberation of iodine. Instead of this, all the active oxygen was liberated, just as if acetic acid had been added, indicating that it may be merely a matter of *p*H and that iodobenzoic acid was strong enough to replace the acetic acid usually present. If this is the correct explanation it must also explain why only half the active oxygen is liberated from 2-iodosobenzoic acid while from the analogous iodosophthalic acid all the active oxygen is removed in the absence of acid. While *o*-iodosobenzoic acid is a very weak acid, the iodosophthalic acid has its second carboxyl group free, which may make the molecule acid enough to liberate the active oxygen from itself. When samples of our tetraoxy compound were titrated without addition of acetic acid, one oxygen was removed, and if the titration was then completed after addition of acetic acid the total iodine liberated from the combined titrations was always somewhat less than if the acid had been added at the beginning.

Our hope that a clue in the structure problem might come from these differences in active oxygen titration with and without acid disappeared when the following confusing facts were added to those already encountered. 2,3-Diiodobenzoic acid

can be looked upon as tetraiodophthalic acid which has been bisected by a horizontal line through its center; the oxidized compound would then be expected to act like half an oxidized tetraiodophthalic acid molecule. It was found that two active oxygens may be titrated with, and only one (*i.e.*, half of the total) without acid; on the other hand, in the case of tetraoxytetraiodophthalic acid, one (*i.e.*, a quarter of the total) instead of the two active oxygens predicted by this analogy can be titrated without acid. It is interesting to note that it was found that iodoxybenzoic acid titrated for two active oxygens in the presence of acid but only half an oxygen (*i.e.*, a quarter of the whole) in its absence. Just what the removal of half an oxygen could mean is difficult to imagine.

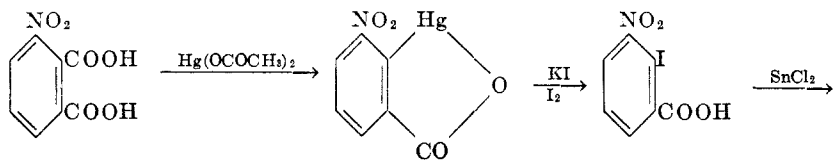
Finally, a few words should also be said about the preparation of the starting materials. Tetraiodophthalic anhydride was prepared according to the original method of Juvalta (11), by iodinating phthalic anhydride in fuming sulfuric acid of high sulfur trioxide content. The process has frequently been described in the literature. For example, Pratt and Shupp (12), using a 50% fuming acid reported an almost quantitative yield. Contrary to our experience, Perkins and Quimba (13) stated that a 60% oleum is essential for insuring a satisfactory reaction, but we also noted excellent results with acids of low sulfur trioxide content. For example, a 90% yield was obtained with a fuming acid containing only 7% sulfur trioxide. We further noted that the reaction also takes place, although somewhat less conveniently, with 100% sulfuric acid. Tetraiodo-*o*-sulfobenzoic anhydride was prepared by the same method (14).

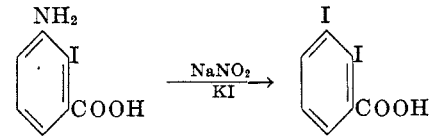
Attempts to prepare 4,5-dibromo-3,6-diiodophthalic anhydride by iodination of the corresponding 4,5-dibromo compound resulted in the formation of a tribromoiodophthalic anhydride instead. We were unable to isolate any 4,5-dichlorophthalic anhydride for iodination purposes, but 3,6-dichlorophthalic anhydride was successfully converted to 4,5-diiodo-3,6-dichlorophthalic anhydride.

3,4,6-Triiodo-, 3,4-, and 3,6-diiodo-phthalic acids were prepared according to Pratt and Perkins (1), and are by-products of the incomplete iodination of phthalic anhydride in fuming sulfuric acid. The compounds are difficult to obtain pure and the recrystallizations involve a considerable loss of material.

The 3- and 4-iodophthalic acids could not be synthesized by reported procedures (see Experimental), but were prepared from the corresponding dimethylnitrophthalates by catalytic reduction to amino esters, replacement of the amino group by iodine *via* the Sandmeyer reaction, and subsequent saponification of the esters.

The three monoiodobenzoic acids were prepared from the corresponding amino acids by known procedures, but 2,3-diiodobenzoic acid is a new compound, synthesized from 3-nitrophthalic acid following the scheme below.





Attempted catalytic hydrogenation of the intermediate 2-iodo-3-nitrobenzoic acid resulted in elimination of the halogen group due to its extreme lability (15). 3-Chloro-2-iodo-, 3-bromo-2-iodo-, and 2-bromo-3-iodo-benzoic acids, also unreported in the literature, were synthesized by analogous procedures.

Acknowledgement. Our thanks are due to Mr. Grant Spurrier for carrying out a portion of the analytical work.

EXPERIMENTAL

General method of oxidation. The finely powdered iodine derivative (8 g.) was suspended in 60 cc. of concentrated sulfuric acid and 16 cc. of concentrated nitric acid (*d.*, 1.4) was added dropwise with stirring but without cooling. The reaction started spontaneously and the liquid turned brown owing to the liberation of nitrogen dioxide and the formation of nitrosylsulfuric acid. The mixture was heated on the steam-bath until a clear yellow solution was obtained (about 30 to 40 minutes), and poured on cracked ice after cooling. The oxidation product, which precipitated almost quantitatively, was filtered, washed, and dried *in vacuo* over calcium chloride. Deviations from this general outline are mentioned under the compounds concerned.

Determination of active oxygen. In a glass-stoppered Erlenmeyer flask containing 0.2 to 0.3 g. of the oxidized material in 100 cc. of water were added in succession 5 g. of potassium iodide in 10 cc. of water and 2 cc. of glacial acetic acid. The suspended particles were broken up mechanically if necessary and the closed flask heated on a water-bath at 60–70° for about 30 minutes. After cooling, the liberated iodine was titrated with 0.1 *N* sodium thiosulfate, using starch as the indicator. Based on the equation: $RIO_2 + 4\ HI \rightarrow RH + 2\ H_2O + 4\ I$, the active oxygen content is given by the formula [O] = 8vf/100w, where v is the volume of thiosulfate in cc., f the factor of the same, and w the weight of the sample in grams.

Iodine determination. In a nickel or platinum crucible a small sample of the oxidation product was thoroughly moistened, some concentrated sodium bisulfite solution was added and, after complete reduction, an excess of 40% sodium hydroxide solution. It is dangerous to add the alkali to the dry compound. The mixture was carefully evaporated to dryness, heated for about 15 minutes at dull red heat, the melt dissolved in water, reduced with sulfur dioxide, and the iodine determined with silver nitrate in the usual manner.

Oxidation of tetraiodo-o-sulfobenzoic anhydride. The oxidation product obtained as described above exploded violently with heat, percussion or friction and should be handled with great care.

Anal. Calc'd for $C_7H_2I_4O_9S$: 4[O], 8.31. Found: [O], 7.73, 7.86, 7.95.

Oxidation of tetraiodophthalic anhydride. The resulting product seems to explode even more readily than the previous compound and should be handled accordingly. As it shows a tendency to form a colloidal suspension in dilute acid, the latter cannot be removed completely by washing. In earlier experiments this was accomplished with aqueous sodium bicarbonate but later more conveniently by washing with glacial acetic acid and drying *in vacuo* in the presence of sodium hydroxide.

The average active oxygen content in ten analyses of six different samples was found to be 8.66 with lower and upper limits of 8.32 and 8.75 respectively, while only in one case a value of 9.03 was obtained.

Anal. Calc'd for $C_8H_2I_4O_8$: 4[O], 8.72; I, 70.95. Found: I, 70.89.

The same compound was obtained from the oxidation of dimethyl tetraiodophthalate; [O], 8.37, 8.21. On reduction with aqueous potassium iodide the product gave the same titra-

tion curve as did tetraiodophthalic acid and on drying at 110° tetraiodophthalic anhydride was obtained.

Nine titrations of four different samples, carried out with omission of acetic acid gave an average [O], 2.46 (calc'd for 1 [O], 2.23), while slightly less than normal values were obtained if acetic acid was subsequently added (average [O], 8.2). On the other hand, the titration of a sample with [O], 9.03 in the presence of acetic acid, gave [O], 6.96, 6.86, if titrated in a saturated borax solution.

Reduction. Tetraoxytetraiodophthalic acid (10 g.) was suspended in 400 cc. of water, 100 cc. of glacial acetic acid was added, and, after cooling in ice, 30 g. of potassium iodide in 100 cc. of water was added dropwise with stirring. After standing for two days, 9.3 g. of dipotassium tetraiodophthalate had crystallized. It was dried at 110°.

Anal. Calc'd for $C_8I_4K_2O_4$: I, 68.0. Found: I, 67.6.

The free acid was obtained by dissolving the salt in water and precipitating with hydrochloric acid.

Anal. Calc'd for $C_8H_2I_4O_4$: I, 75.81; Calc'd for $C_8I_4O_3$: I, 77.9.
Found: I, 77.53, 78.04.

Evidently the acid had changed into the anhydride on drying. Analogous results were obtained if the reduction was carried out with sodium thiosulfate or sulfur dioxide.

Action of hydrochloric acid. A sample of dry tetraoxy derivative was thoroughly moistened, covered with some water and, while stirring and cooling, about 20 volumes of concentrated hydrochloric acid was gradually added. It is dangerous to add the acid to the dry compound. The yellow suspension assumed a light tan color and after about 15 minutes the product was filtered off and dried *in vacuo* over calcium chloride in the presence of sodium hydroxide. The chlorine analysis was carried out by reducing a sample with aqueous potassium iodide in the presence of acetic acid and calculating the chlorine from the amount of liberated iodine as titrated with 0.1 *N* sodium thiosulfate.

Anal. Calc'd for $C_8H_2Cl_4I_4O_4$: Cl, 17.47. Found: Cl, 19.08.

A direct chlorine determination was carried out as follows: a small sample was decomposed with dilute alkali at room temperature, acidified with acetic acid, filtered, and the chlorine in the filtrate determined with silver nitrate.

Anal. Calc'd for $C_8H_2Cl_4I_4O_4$: Cl, 17.47. Found: Cl, 16.82.

For reasons not yet known the chlorine derivative frequently decomposes completely on drying *in vacuo*.

Oxidation of triiodophthalic anhydride. In order to obtain consistent results the oxidation period had to be extended to about five hours. It was noted that two compounds invariably were formed, one separating spontaneously when the solution in concentrated acid was poured on ice, the other one crystallizing gradually from the dilute acid. Complete separation was effected by washing the first precipitate thoroughly with lukewarm water. The relative amount of the compounds was about 3:1, and the active oxygen content of the first derivative was invariably higher than that of the second.

Anal. Calc'd for $C_8H_3I_3O_7$: 3[O], 8.1.
Found first fraction: [O], 8.29, 7.82.
Calc'd for $C_8H_3I_3O_6$: 2[O], 5.56.
Found second fraction: [O], 6.21, 5.67.

If samples of these two fractions were reduced with potassium iodide, the eliminated iodine removed with sulfur dioxide, and the acids crystallized from acetic anhydride, the corresponding anhydrides were obtained, m.p. 217–224° (cor.) and 227–229° (cor.) respectively.

Anal. Calc'd for $C_8HI_3O_3$: I, 72.4. Found, both fractions: I, 72.5.

The second fraction obtained from another sample of triiodophthalic anhydride contained [O], 5.46, 5.69, and was converted to the corresponding acid by reduction as before.

Anal. Calc'd for $C_8H_3I_3O_4$: I, 71.85. Found: I, 71.87.

These data lead to the conclusion that the samples of triiodophthalic anhydride constitute a mixture of isomers.

OXIDATION OF LOWER IODINATED PHTHALIC ACIDS

3,6-Dichloro-4,5-diiodophthalic anhydride, m.p. 252° (uncor.) [literature value (1) 258° (cor.)]. This compound took up no active oxygen and starting material (m.p. 249–250°) was isolated.

3,4-Diiodophthalic acid, m.p. 211°. This compound took up two active oxygen atoms.

Anal. Calc'd for $C_8H_4I_2O_6$: 2[O], 7.11. Found: [O], 6.97.

4,5-Diiodophthalic acid, m.p. 222.5–223.5° (cor.). This substance did not take up any oxygen and no nitration occurred.

3,6-Diiodophthalic anhydride, m.p. 233.5–235.5° (cor.). This compound took up two oxygen atoms, although the mixture of concentrated acids did not show the temporary dark coloration usually noted. Pouring on to ice did not cause immediate precipitation, but the oxidation product gradually separated in white, shiny crystals.

Anal. Calc'd for $C_8H_4I_2O_6$: 2[O], 7.11. Found: [O], 6.70, 6.73.

3-Iodophthalic anhydride. This compound added one oxygen atom. After the oxidation was completed the concentrated acid solution was poured on to ice and the dilute solution cooled in an ice-salt mixture. The resulting precipitate was washed and dried *in vacuo*.

Anal. Calc'd for $C_8H_5IO_5$: 1[O], 5.19. Found: [O], 5.17, 5.05.

Similar titration results were obtained without the use of acetic acid.

4-Iodophthalic anhydride. This product did not take up any oxygen but was partly nitrated. The reaction product was fairly soluble in dilute acid but separated on cooling in an ice-salt mixture. The compound contained 3.58% N (calculated value for nitroiodophthalic acid, 4.18%).

OXIDATION OF IODOBENZOIC ACIDS

2,3-Diiodobenzoic acid. This compound took up two oxygen atoms, yielding a yellow substance.

Anal. Calc'd for $C_7H_4I_2O_4$: 2[O], 7.88.
Found, using acetic acid: [O], 7.76.
Found, without acetic acid: [O], 3.73, 4.11.

2-Iodo-3-chloro-, *2-iodo-3-bromo-*, and *2-bromo-3-iodo-benzoic acid*. Each of these compounds yielded resinous products in which no active oxygen could be detected with certainty.

m- and p-Iodobenzoic acid. These acids did not take up any oxygen. The former was partly, and the latter almost entirely nitrated under the reaction conditions.

o-Iodobenzoic acid. This product took up one oxygen atom.

Anal. Calc'd for $C_7H_5IO_3$: 1[O], 6.06.
Found, using acetic acid: [O], 5.87.
Found, without acetic acid: [O], 3.03.

For comparison, *o*-iodoxybenzoic acid was prepared by the method of Hartmann and Meyer (16) and analyzed for active oxygen.

Anal. Calc'd for $C_7H_5IO_4$: 2[O], 11.43; 1/2[O], 2.86.
Found, using acetic acid: [O], 11.62.
Found, without acetic acid: [O], 2.98.

PREPARATION OF STARTING MATERIALS

Tetraiodophthalic anhydride. In a 500-cc. 3-necked flask, fitted with stirrer, mercury seal, air-condenser, and gas absorption tower, were placed 29.5 g. of phthalic anhydride and 725 cc. of 7% fuming sulfuric acid. The temperature was maintained at 80° while 102 g. of iodine was gradually added. The mixture was then heated for 6 hours at 95°, 8 hours at 110–115°, and 12 hours at 135–145°. The heavy yellow precipitate was filtered, stirred into ice-water, washed, and dried. Yield, 119 g. (90%).

Anal. Calc'd for $C_8I_4O_3$: I, 77.90. Found: I, 77.2.

Mono- and di-methyl tetraiodophthalate. Tetraiodophthalic anhydride (20 g.) was heated under reflux for 6 hours with 250 cc. of absolute methanol to which 10 drops of concentrated

sulfuric acid had been added. In the course of the esterification the anhydride slowly dissolved. The solution was then concentrated *in vacuo* and poured into water giving a slightly gummy precipitate which soon became granular. It was purified by solution in 150 cc. of hot alcohol with the addition of hot water dropwise until a slight turbidity appeared, followed by crystallization.

The mono ester thus obtained was dissolved in about the theoretical amount of sodium hydroxide solution, the *p*H was adjusted to 6.0 with dilute nitric acid, and twice the calculated amount of 5% aqueous silver nitrate was added. The resulting yellow silver salt was filtered and dried. A portion of the dry salt (12.5 g.) was suspended in 80 cc. of dry benzene, 5 cc. of methyl iodide was added slowly and the mixture was refluxed for two hours. After distilling off the solvent, the residue was extracted with 250 cc. of boiling alcohol. Evaporation gave dimethyl tetraiodophthalate in a yield of 6.5 g. (60%). After crystallization from alcohol the alkali-insoluble ester melted at 166.5–167.5° (cor.).

3,6-Diiodo-4,5-dibromophthalic anhydride. This compound could not be obtained by iodination of 4,5-dibromophthalic anhydride. 4,5-Dibromophthalic acid was obtained as a by-product in the preparation of tetrabromophthalic anhydride; m.p. 203.5–205.5° (cor.) [literature value, 200° (11)]. This was converted to its anhydride by recrystallization from acetic anhydride, and then from benzene; m.p. 217–220° [literature value 208° (11)].

Anal. Calc'd for $C_8H_2Br_2O_3$: Br, 52.3. Found: Br, 52.4.

Iodination of the dibromo compound in 60% fuming sulfuric acid in the usual way gave a product which was freed of excess iodine and dried at 110°. It was soluble in cold benzene. Recrystallization from glacial acetic acid containing 1% acetic anhydride gave a product, m.p. 259–261° (uncor.).

Anal. Calc'd for $C_8Br_3IO_3$ (0.3260-g. sample): AgX, 0.5096 g.; Br, 47.0; I, 24.8.
Found: AgX, 0.5098 g.; Br, 49.2; I, 22.0.

Considering the inherent errors in the differential halogen determination, the above analyses indicate the formation of a tribromophthalic anhydride, presumably at the expense of other molecules of the starting dibromo compound.

This tribromo compound on oxidation did not take up any oxygen, but due to uncertainty as to its structure further work on this compound was discontinued.

3,6-Dichloro-4,5-diiodophthalic anhydride, m.p. 252° (uncor.). This compound was prepared by iodination of 3,6-dichlorophthalic anhydride (1), in 78% yield.

Anal. Calc'd for $C_8Cl_2I_2O_3$ (0.3838-g. sample): AgX, 0.6174 g.
Found: AgX, 0.6206 g.

Triiodophthalic anhydride, 4,5-diiodo-, and 3,6-diiodo-phthalic acid. These compounds were prepared by the method of Pratt and Perkins (1), in which phthalic anhydride is iodinated under suitable conditions.

3-Iodophthalic acid and 4-iodophthalic acid. Attempts to prepare the monoiodo compounds by direct iodination in sulfuric acid resulted in the formation of the diiodo compounds instead. When the method of Datta and Chatterjee (17) was followed, using iodine and nitric acid, only unreacted phthalic acid was recovered. Attempted direct reduction of 3-nitrophthalic acid to the corresponding amino compound with zinc dust and acetic acid by the method of Bernthsen and Semper (18) and Kenner and Mathews (19) gave a product which was not soluble in sulfuric acid and which was not the desired amino compound but was probably a polymer. Gisvold (20) reported the formation of much polymeric substance in the reduction of 3-nitrophthalic acid with platinum or Raney nickel at fifty pounds pressure, but reported some of the amine as well. In the present study, catalytic hydrogenation, using platinum and pressures of ten pounds, in 95% alcohol, 50% alcohol or water, invariably resulted in the theoretical uptake of hydrogen but yielded a brown product which could not be diazotized. The literature (21) shows 3-aminophthalic acid to be very unstable, being decomposed by water and alcohol even at room temperature. Our catalytic hydrogenation experiments with 4-nitrophthalic acid met with similar failure. In both cases preliminary esterification of the nitro acids eliminated this difficulty and catalytic hydrogenation to the amino esters went quite smoothly.

Attempts to prepare dimethyl 3-nitrophthalate from the mono ester with dimethyl sul-

fate in the usual manner met with failure. It was made in 83% yield by treating the silver salt of 3-nitrophthalic acid with methyl iodide (22). This dimethyl ester (8.6 g., m.p. 67–69°) was dissolved in 150 cc. of alcohol and hydrogenated over Adams' platinum oxide catalyst, 45 minutes being required for complete uptake of hydrogen. Most of the alcohol was allowed to evaporate to give a colorless oil, wt., 6.6 g., which was dissolved in 100 cc. of 17% sulfuric acid and diazotized as usual. Then 10 g. of potassium iodide in 10 cc. of water was added and the mixture warmed to about 90° for a short time. Extraction with ether and evaporation of the latter yielded 6.3 g. of crude dimethyl 3-iodophthalate, m.p. 77–79°. The ester was saponified by refluxing for two hours with a solution of 3.7 g. of potassium hydroxide in 50 cc. of absolute alcohol; the potassium salt was allowed to crystallize after concentration and cooling in ice. The salt was redissolved in a small amount of water, acidified with sulfuric acid, and the liquid extracted with ether. Vacuum sublimation (in the dark) of the ethereal residue gave 2 g. of slightly yellow needles of 3-iodophthalic anhydride, m.p. 159–161° [literature value (23), 153°].

In contrast to the above, esterification of 4-nitrophthalic acid with absolute methanol gave the desired dimethyl ester (24), m.p. 65°; the ester (5 g.) was hydrogenated catalytically in 100 cc. of alcohol with platinum oxide. Spontaneous evaporation of the solvent left a clear oil which crystallized on stirring. Recrystallization from alcohol gave 3 g. of dimethyl 4-aminophthalate, m.p. 81.5–83° [literature value, 84° (24)]; yield, 70%. The ester was dissolved in 100 cc. of 17% sulfuric acid, cooled to −2°, and a cold solution of 1 g. of sodium nitrite in 5 cc. of water added dropwise until the solution showed an excess of nitrous acid. The addition of 5 g. of potassium iodide in 5 cc. of water produced an oily precipitate which was dissolved in 50 cc. of absolute alcohol containing 2.5 g. of potassium hydroxide and refluxed for an hour. Concentration of the solution yielded a strawberry-colored precipitate. Acidification of a concentrated aqueous solution of the latter gave a precipitate which was washed with ice-water, dried, and sublimed in the dark at 120°/4 mm. Yield, 2.35 g. (60%) of 4-iodophthalic anhydride, m.p. 124.5–126.5° (cor.) [literature value, 123° (24)].

IODOBENZOIC ACIDS

2,3-Diiodobenzoic acid. Anhydro-2-hydroxymercuri-3-nitrobenzoic acid, prepared from 3-nitrophthalic acid according to Whitmore, Culhane, and Neher (25), was converted into 2-iodo-3-nitrobenzoic acid (26). Attempted catalytic hydrogenation of the latter with platinum resulted in decomposition, but the reduction was successfully carried out in the following manner. A solution of 17 g. of stannous chloride in 20 cc. of hydrochloric acid was added dropwise over an hour to a cooled, stirred solution of 5 g. of 2-iodo-3-nitrobenzoic acid in 100 cc. of glacial acetic acid. The white precipitate, presumably the tin chloride double salt of the amino acid, was filtered off after about 16 hours and washed with a little cold water, in which it was somewhat soluble. A solution of 3.3 g. of the dry compound in 100 cc. of 17% sulfuric acid was diazotized at 0°, and 5 g. of potassium iodide in 5 cc. of water added. The mixture was allowed to warm up to room temperature and then was heated to about 90° for 10 minutes. After standing in the ice box overnight, 2.5 g. of crude 2,3-diiodobenzoic acid had crystallized; yield, 75%. Sublimation in the dark at 4 mm. pressure gave long needles, m.p. 178–181° (cor.). The compound turns yellow on exposure to light.

Anal. Calc'd for $C_7H_4I_2O_2$: I, 67.9. Found: I, 68.3.

2-Iodo-3-chlorobenzoic acid. This acid was synthesized in a similar manner to the previous compound. However in this case the tin double salt was not isolated but the reduction mixture was diazotized directly. The diazotized solution from 10 g. of the corresponding iodonitrobenzoic acid was poured rapidly into a solution of cuprous chloride (27), then 15 cc. of concentrated hydrochloric acid was added, and the mixture was left overnight. After diluting with two parts of water it was cooled in the ice box, whereupon 5.3 g. of crude 2-iodo-3-chlorobenzoic acid separated as a light tan-colored product. The relatively low yield was due to the dissolving action of the acetic acid added in the initial stage of the process. It could be improved slightly by isolating the tin chloride complex and carrying out the Sand-

meyer reaction separately. In another experiment an attempt was made to dissolve the complex in 35% sulfuric acid by heating to 60° prior to diazotization, but this resulted in the elimination of iodine. 2-Iodo-3-chlorobenzoic acid was purified by vacuum sublimation (4 mm.), giving white needles, m.p. 135–138° (cor.).

Anal. Calc'd for $C_7H_4ClIO_2$, (0.2054-g. sample): Ag halide, 0.2792 g.
Found: Ag halide, 0.2742 g.

2-Iodo-3-bromobenzoic acid. To eliminate the possibility of an exchange of halogen atoms during the Sandmeyer reaction, the reduction of 2-iodo-3-nitrobenzoic acid was carried out with stannous bromide, (27), instead of stannous chloride. The tin bromide complex did not precipitate and the diazotization was carried out in the medium in which it was formed. The diazonium solution thus obtained was cooled and poured into a cuprous bromide solution (27), hydrobromic acid was added, the suspension was warmed to 50°, and left overnight in the ice box. After concentration *in vacuo* at 80° to about one-third of its volume the 2-iodo-3-bromobenzoic acid was filtered off from the chilled suspension and purified by sublimation (4 mm.). It formed white needles, m.p. 148–151° (cor.).

Anal. Calc'd for $C_7H_4BrIO_2$, (0.1513-g. sample): Ag halide, 0.1957 g.
Found: Ag halide, 0.1984 g.

2-Bromo-3-iodobenzoic acid. This compound was prepared from anhydro-2-hydroxymercuri-3-nitrobenzoic acid in one continuous operation by reduction with stannous chloride, diazotization, and the Sandmeyer reaction in the cold with potassium iodide. The mixture was finally heated to 70°, concentrated *in vacuo* and, after chilling, the crude acid was filtered off. Sublimation *in vacuo* gave white needles, m.p. 159–162.5° (cor.).

Anal. Calc'd for $C_7H_4BrIO_2$, (0.1984-g. sample): Ag halide, 0.2566.
Found: Ag halide, 0.2551.

Monoiodobenzoic acids. The *ortho* derivative was prepared by reduction of Eastman iodosobenzoic acid with potassium iodode, while the *m*- and *p*-iodobenzoic acids were obtained from the corresponding amino acids by diazotization in 17% sulfuric acid and application of the Sandmeyer reaction with potassium iodide.

SUMMARY

A comparative study has been made of the oxidation of iodinated phthalic and benzoic acids with nitric-sulfuric acids and some rules were derived from the experimental data.

2,3-Diiodobenzoic acid, 2-iodo-3-chlorobenzoic acid, 2-iodo-3-bromobenzoic acid, and 2-bromo-3-iodobenzoic acid were synthesized from 3-nitrophthalic acid by replacing in succession a carboxyl and a nitro group by the appropriate halogen atom.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

7-METHYLMERCAPTO-1-TETRALONE, AND ITS USE IN PREPARING SULFUR-CONTAINING CARBAZOLES AND ACRIDINES[1]

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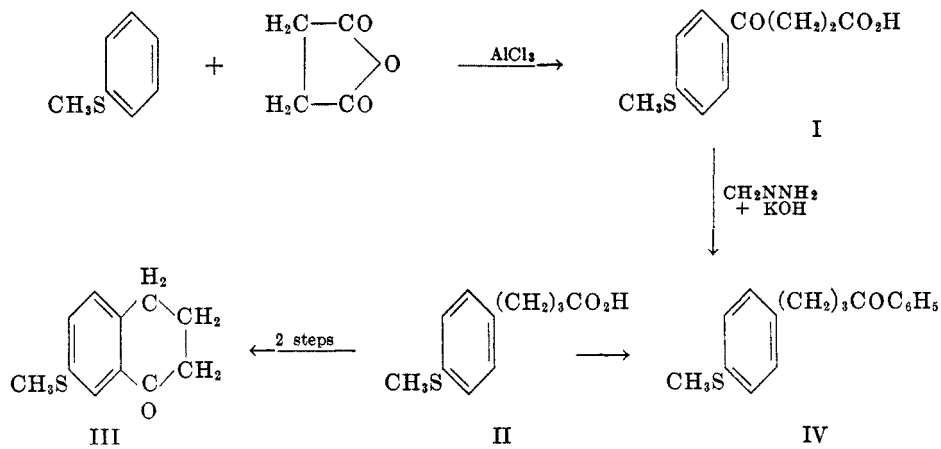
Sulfur-containing organic molecules have frequently been linked to the cancer problem, in respect either to the mechanism (1) or to the inhibition (2) of chemical carcinogenesis. In view of the activity of angular benzocarbazoles and dibenzocarbazoles as tumor-producing agents (3), derivatives of these bearing thioether groups have now been synthesized for biological investigation.[2]

From results published in previous papers of this series (4), 7-methylmercapto-1-tetralone (III) was deemed a particularly convenient intermediate for such syntheses. We prepared this hitherto unknown ketone very easily by the following sequence of reactions: (a) Friedel-Crafts' condensation of succinic anhydride with thioanisole, to give β-(4-methylmercaptobenzoyl)propionic acid (I); (b) reduction of the foregoing compound to γ-(4-methylmercaptophenyl)butyric acid (II) by the Wolff-Kishner reaction, using the convenient modified technique of Huang-Minlon (5); (c) conversion of the acid (II) into its *chloride* by thionyl chloride and cyclization of the latter with aluminum chloride into 7-methylmercapto-1-tetralone (III).

Each of these reactions was achieved with high yields, but it was found in the final stage that the use of benzene as a solvent for cyclization resulted in poor yields of the cyclic ketone (II), owing to the competitive formation of 4-(methylmercaptophenylbutyryl)benzene (IV). As no similar side-reaction was observed to any extent in the cyclization in benzene medium of γ-phenylbutyryl chloride

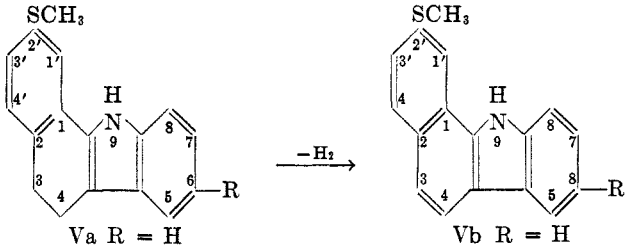


[1] This paper is Part V of a series of articles entitled: "Carcinogenic Derivatives of Carbazole."

[2] The substances described in this paper are under biological investigation in this Institute by Professor A. Lacassagne. The work here reported was carried out under a grant from the U. S. Public Health Service (Federal Security Agency). The authors convey their gratitude to the authorities concerned.

(6), it can be assumed that the thioether substituent exerted a deactivating influence on *meta* positions. This is parallel to what has already been observed in respect to the *meta*-deactivating effect of methoxyl groups (7). It may also be noted that the condensation of succinic anhydride with thioanisole apparently yielded none of the *ortho*-isomer.

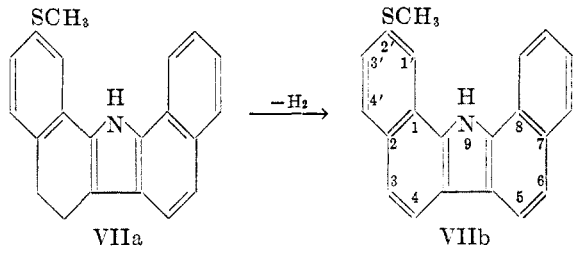
The indolization of 7-methylmercapto-1-tetralone phenylhydrazone was achieved as usual by hydrogen chloride in acetic acid; the 2′-methylmercapto-3,4-dihydro-1,2-benzocarbazole (Va) thus obtained was smoothly dehydrogenated into 2′-methylmercapto-1,2-benzocarbazole (Vb) with chloranil. From



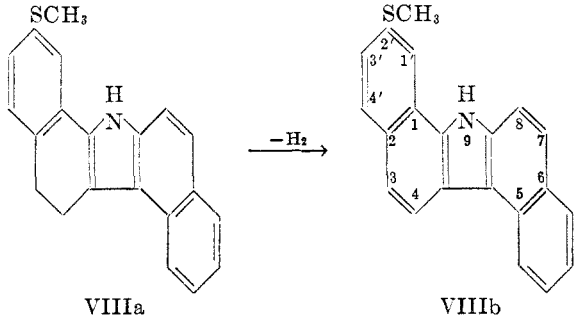
Va R = H
VIa R = CH_3

Vb R = H
VIb R = CH_3

7-methylmercapto-1-tetralone *p*-tolylhydrazone, 2′-methylmercapto-6-methyl-1,2-benzocarbazole (VIb) was similarly synthesized *via* the corresponding 3,4-dihydro intermediate (VIa). Indolization of the α and β-naphthylhydrazones of 7-methylmercapto-1-tetralone was also easily performed and yielded 2′-methylmercapto-3,4-dihydro-1,2,7,8-dibenzocarbazole (VIIa) and 2′-methylmercapto-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIIIa); these relatively stable



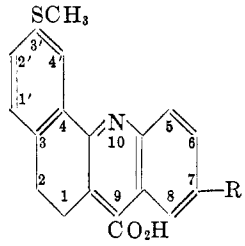
VIIa VIIb



VIIIa VIIIb

compounds were dehydrogenated by chloranil as usual into 2′-methylmercapto-1,2,7,8-dibenzocarbazole (Vb) and 2′-methylmercapto-1,2,5,6-dibenzocarbazole (VIIIb).

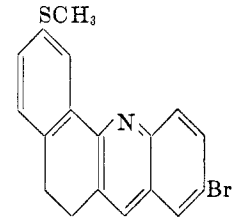
In view of the biological significance of certain 3,4-benzacridine derivatives either as carcinogens (8) or as strychnine-like drugs (9), some related compounds were prepared from 7-methylmercapto-1-tetralone. Pfitzinger condensation of the latter with isatin, 5-methylisatin, and 5-bromoisatin, readily yielded respectively, 3′-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (IX), and 7-methyl- (X) and 7-bromo-3′-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (XI); from the latter, 7-bromo-3′-methylmercapto-1,2-dihydro-3,4-benzacridine (XII) could be obtained by thermal decarboxylation.



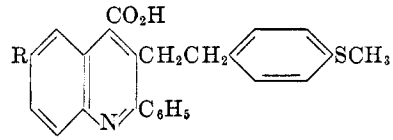
IX R = H

X R = CH_3

XI R = Br



XII



XIII R = H

XIV R = Br

4-(Methylmercaptophenylbutyryl)benzene (IV) responded also to the Pfitzinger reaction, giving 2-phenyl-3-[β-(*p*-methylmercaptophenyl)ethyl]cinchoninic acid (XIII) with isatin and the 7-bromo derivative (XIV) of the latter with 5-bromoisatin.

EXPERIMENTAL

β-(4-Methylmercaptobenzoyl)propionic acid (I). To an ice-cooled well-stirred mixture of 182 g. of freshly distilled thioanisole (prepared from thiophenol with dimethyl sulphate and potassium hydroxide) and 150 g. of succinic anhydride with 1000 ml. of dry nitrobenzene, 330 g. of powdered aluminum chloride was added in small portions. The mixture was kept overnight at room temperature, poured on to ice, and the nitrobenzene completely removed with steam. The hard crust formed after cooling was powdered and treated with a hot aqueous solution of sodium carbonate; after filtration and acidification with dilute hydrochloric acid, 235 g. of the solid crude acid (I) was obtained; recrystallization from xylene or chlorobenzene yielded shiny colorless needles, melting at 157°.

Anal. Calc'd for $C_{11}H_{12}O_3S$: C, 58.9; H, 5.3.

Found: C, 58.9; H, 5.6.

γ-(4-Methylmercaptophenyl)butyric acid (II). A solution of 100 g. of the foregoing acid in a mixture of 100 g. (very large excess) of 70% hydrazine hydrate, potassium hydroxide (90 g.), and diethylene glycol (300 ml.) was heated with removal of water until the temperature reached 190–195° (*circa* five hours); the greater part of the diethylene glycol was removed by vacuum-distillation. The residue was dissolved in water, and yielded on acidification with dilute hydrochloric acid an oil which quickly solidified. This was crystallized from boiling water; glistening colorless leaflets, m.p. 54°, were obtained (yield, 95%). This compound distilled *in vacuo* without decomposition and had an unpleasant odor reminiscent of γ-phenylbutyric acid.

Anal. Calc'd for $C_{11}H_{14}O_2S$: C, 62.8; H, 6.6.

Found: C, 62.5; H, 6.8.

7-Methylmercapto-1-tetralone (III). A mixture of 180 g. of the acid (II) and 120 g. of thionyl chloride was kept for two hours at room temperature, then gently heated on the water-bath for a further hour, and thionyl chloride in excess was removed *in vacuo*. To the ice-cooled solution of the crude γ-(4-methylmercaptophenyl)butyryl chloride in 400 ml. of dry thiophene-free benzene, 135 g. of powdered aluminum chloride was stirred in in small portions. The mixture was kept overnight at room temperature, then poured on to ice; the benzene layer was washed throughly with 5% aqueous sodium hydroxide, then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. Yield, 30 g. of the ketone (III) in the form of a thick, pale yellow oil, b.p. 202–205°/18 mm.

Anal. Calc'd for $C_{11}H_{12}OS$:C, 68.7; H, 6.2.

Found: C, 68.5; H, 6.3.

The *semicarbazone* crystallized from ethanol in fine colorless glistening prisms, melting at 215°.

4-(Methylmercaptophenylbutyryl)benzene (IV). The higher-boiling fractions from the preparation of the foregoing ketone consisted mainly of the ketone (IV), which had b.p. 250–260°/18 mm., and crystallized from benzene-ligroin in fine colorless needles melting at 70° (yield, 60 g.).

Anal. Calc'd for $C_{17}H_{18}OS$: C, 75.5; H, 6.6.

Found: C, 75.2; H, 6.5.

2'-Methylmercapto-3,4-dihydro-1,2-benzocarbazole (Va). A mixture of 2 g. of ketone (III), 2.2 g. of phenylhydrazine hydrochloride, and 3 g. of sodium acetate, was refluxed with 40 ml. of ethanol for one hour. After cooling, water was added, and the precipitate of the crude phenylhydrazone was washed with water, and dissolved in 20 ml. of a saturated solution of hydrogen chloride in acetic acid. After five minutes' heating on a water-bath, the mixture was poured into water, and the precipitate washed with water, dried, and crystallized from ligroin. Colorless needles m.p. 98°, extremely soluble in ethanol and benzene, and giving a yellow coloration with sulfuric acid and a violet *picrate*. The yield was 2 g.

Anal. Calc'd for $C_{17}H_{15}NS$: N, 5.2. Found: N, 5.0.

2'-Methylmercapto-1,2-benzocarbazole (Vb). A mixture of 1 g. of the foregoing dihydro compound, 1.2 g. of chloranil, and 25 ml. of dry xylene was gently refluxed for two hours. After cooling, the tetrachlorohydroquinone was filtered off and washed with a little xylene; the filtrate was shaken with 10% aqueous sodium hydroxide and then with water, and dried over calcium chloride. After evaporation of the solvent *in vacuo*, the solid residue was twice recrystallized from benzene; colorless prisms were obtained (0.8 g.), m.p. 149°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{13}NS$: N, 5.0. Found: N, 5.3.

2'-Methylmercapto-6-methyl-3,4-dihydro-1,2-benzocarbazole (VIa). Prepared as usual from 2 g. of ketone (III), 2 g. of *p*-tolylhydrazine hydrochloride, and 3 g. of sodium acetate in ethanol; crystallized from benzene in fine colorless prisms (2 g.), m.p. 145°, which gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{17}NS$: N, 5.0. Found: N, 4.8.

2'-Methylmercapto-6-methyl-1,2-benzocarbazole (VIb). Crystallized from benzene in glinting colorless needles, m.p. 189°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{15}NS$: N, 5.0. Found: N, 5.0.

2'-Methylmercapto-3,4-dihydro-1,2,7,8-dibenzocarbazole (VIIa). Prepared from 2 g. of ketone (III), 3 g. of α-naphthylhydrazine hydrochloride, and 4 g. of sodium acetate; crystallized from ligroin in fine yellowish needles, m.p. 138°, which gave an orange coloration with sulfuric acid. The yield was 1.5 g. The *picrate* was violet.

Anal. Calc'd for $C_{21}H_{17}NS$: N, 4.4. Found: N, 4.2.

2'-Methylmercapto-1,2,7,8-dibenzocarbazole (VIIb). Crystallized from benzene in microscopic yellowish needles, m.p. 154°, which gave an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NS$: N, 4.4. Found: N, 4.2.

2'-Methylmercapto-3,4-dihydro-1,2,5,6-dibenzocarbazole (VIIIa). Prepared from 2 g. of ketone (III), 3 g. of β-naphthylhydrazine hydrochloride, and 4 g. of sodium acetate; crystallized from benzene in microscopic colorless needles (2.2 g.), m.p. 169°, which gave an orange-yellow coloration with sulfuric acid, and a violet *picrate*.

Anal. Calc'd for $C_{21}H_{17}NS$: N, 4.4. Found: N, 4.4.

2'-Methylmercapto-1,2,5,6-dibenzocarbazole (VIIIb). Crystallized from benzene in glinting colorless leaflets, m.p. 180°, which gave a brown coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NS$: N, 4.4. Found: N, 4.2.

3'-Methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (IX). A mixture of 1.9 g. of ketone (III), 1.8 g. of isatin, and a solution of potassium hydroxide (1.8 g.) in water (2 ml.) and ethanol (12 ml.) was refluxed for 18 hours; after dilution with water, and removal of neutral impurities by ether-extraction, the aqueous layer was slightly acidified with acetic acid. The yellow precipitate (3 g.) obtained was recrystallized from methanol, yielding glinting yellow needles which softened at *circa* 160° and liquefied at 219°.

Anal. Calc'd for $C_{19}H_{15}NO_2S$: N, 4.3; Neut. equiv., 321.
Found: N, 4.0; Neut. equiv., 319.

7-Methyl-3'-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (X). From 1.9 g. of ketone (III), 2 g. of 5-methylisatin, and 1.8 g. of potassium hydroxide, 3.5 g. of the acid (X) was obtained, crystallizing from methanol in microscopic yellow needles which softened at *circa* 150° and liquefied at 212°.

Anal. Calc'd for $C_{20}H_{17}NOS$: N, 4.1; Neut. equiv., 335.
Found: N, 4.0; Neut. equiv., 331.

7-Bromo-3'-methylmercapto-1,2-dihydro-3,4-benzacridine-9-carboxylic acid (XI). Obtained in 90% yield from 1.9 g. of ketone (III), 2.5 g. of 5-bromoisatin, and 1.8 g. of potassium hydroxide; crystallized from ethanol in microscopic bright yellow needles melting at 231°.

Anal. Calc'd for $C_{19}H_{14}BrNOS$: N, 3.5; Neut. equiv., 400.
Found: N, 3.4; Neut. equiv., 402.

Dry distillation of the foregoing acid *in vacuo* yielded *7-bromo-3'-methylmercapto-1,2-dihydro-3,4-benzacridine* (XII), which formed from ethanol silky pale yellow needles, m.p. 108°, which gave a yellow coloration with sulfuric acid. Its *picrate* formed lustrous orange leaflets, m.p. 245°, from ethanol.

Anal. Calc'd for $C_{18}H_{14}BrNS$: N, 3.9; Br, 22.4.
Found: N, 3.7; Br, 22.0.

2-Phenyl-3-[β-(p-methylmercaptophenyl)ethyl]cinchoninic acid (XIII). From 1.2 g. of ketone (IV), 0.8 g. of isatin, and 1 g. of potassium hydroxide in 10 ml. of ethanol after 18 hours was obtained the acid (XIII) in 50% yield. It crystallized from ethanol in fine yellow prisms, m.p. 232° (decomp.).

Anal. Calc'd for $C_{25}H_{21}NO_2S$: N, 3.5; Neut. equiv., 395.
Found: N, 3.2; Neut. equiv., 390.

From 1.2 g. of the same ketone, 1 g. of 5-bromoisatin, and 1 g. of potassium hydroxide, 1.3 g. of *7-bromo-2-phenyl-3-[β-(p-methylmercaptophenyl)ethyl]cinchoninic acid* (XIV) was similarly obtained. It formed from acetic acid deep yellow prisms, m.p. 260° with decomposition.

Anal. Calc'd for $C_{25}H_{20}BrNO_2S$: N, 2.9; Neut. equiv., 474.
Found: N, 2.6; Neut. equiv., 470.

SUMMARY

1. The preparation of 7-methylmercapto-1-tetralone is described.

2. The use of the foregoing ketone for the synthesis of sulfur-containing carbazole and acridine derivatives is reported.

PARIS Ve, FRANCE

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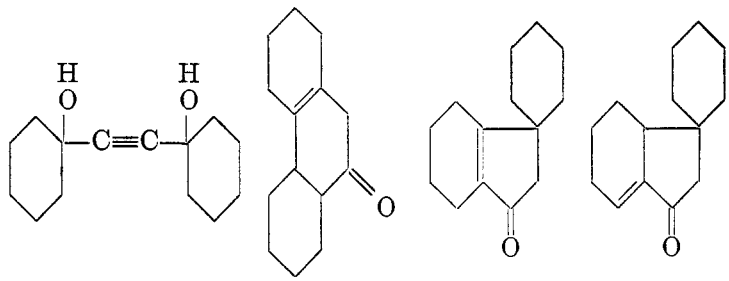
[EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

SYNTHESIS OF A SERIES OF COMPOUNDS CONTAINING A QUATERNARY CARBON ATOM[1]

LOUIS H. SCHWARTZMAN[2]

Received October 17, 1949

Recently, we became interested in a series of compounds which contain a quaternary carbon atom and a tertiary amine group, in order to study their analgesic activities. In the course of the investigation, it soon became evident that we had the key to a controversial problem. Pinkney, Nesty, Wiley, and Marvel (1) studied the dehydration and cyclization of 1,1′-ethynylene-*bis*-cyclohexanol (I), and they assumed their product to be Δ^{11}-dodecahydrophenanthrone-9 (II).



I II III IV

Linstead and Walpole (2), in a very meticulous manner, isolated two solid ketones (m.p. 38–39° and m.p. 93–94°) from the product of the cyclodehydration of 1,1′-ethynylene-*bis*-cyclohexanol (I). Both of these substances were α,β-unsaturated ketones as indicated by ultraviolet absorption spectra. In addition, Woodward, still uncertain of the spirane or phenanthrene structure, showed that the ketone melting at 39° contained an exocyclic carbon-carbon double bond, and the ketone melting at 94° contained α,β-unsaturation within the same ring (3). These ketones are designated as III (m.p. 94°) and IV (m.p. 39°).

Linstead and Doering (4) in their preparation of all of the isomeric perhydrodiphenic acids proved that the dibasic acid obtained from Marvel's cyclized ketones, III and IV, by reduction of the double bond and subsequent oxidation (2) was not the same as any of their diphenic acids. Levitz, Perlman, and Bogert (5) synthesized spiro[cyclohexane-1,1′-indane] in order to show that the cyclodehydration of 1-β-phenylethylcyclohexanol-1 could yield a spirane compound as well as a phenanthrene. In the course of their work, they synthesized spiro-[cyclohexane-1,1′-indanone-3′] (VI). However, in spite of the accumulation of evidence indicating that Marvel had a spirane instead of a phenanthrene type

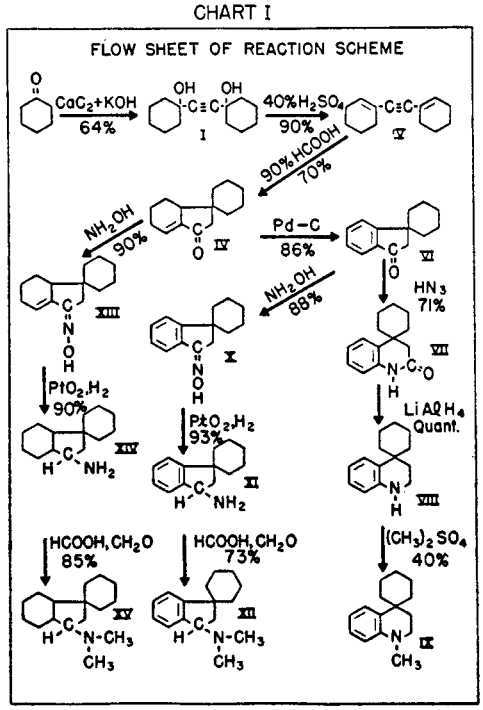
[1] Presented before the American Chemical Society, 116th meeting, Atlantic City, N. J., September 21, 1949.

[2] National Institutes of Health Postdoctoral Fellow.

compound, no one had shown conclusively that his ketonic product was a spiro-[cyclohexane-1,1′-tetrahydroindanone-3′] (III or IV).

With slight variations in procedure, Marvel's work was repeated and a ketonic product boiling at 130–132° (2 mm.) was isolated. Preparation of a 2,4-dinitrophenylhydrazone of the ketone produced a red substance melting at 224–225°. The oxime was prepared and yielded 90% of brilliant massive polyhedra melting at 183.5–184°. These compounds check very closely the derivatives made from the ketone melting at 39° (1, 2), and we shall therefore use structure IV in this paper to indicate the ketonic product of cyclodehydration.

CHART I



When this ketone was dehydrogenated over a palladium charcoal catalyst, spiro[cyclohexane-1,1′-indanone-3′] (VI) was produced in excellent yields. Since this compound is the same that Bogert and coworkers (5) synthesized by an alternate method, we conclude that Marvel was dealing with a spirane of proved carbon skeleton and not a phenanthrene, that the position of the carbonyl group is established, and that Woodward's formulations involving the relationship of the double bond and the carbonyl group are now valid in entirety.

The synthesis of a series of compounds containing a quaternary carbon atom and a tertiary, methylated amine proceeds as indicated in Chart I.

The Schmidt reaction on spiro[cyclohexane-1,1′-indanone-3′] (VI) could possibly lead to a dihydrocarbostyril compound (VII) or to a dihydroisocarbostyril compound, although from the experimental evidence on this reaction with

alkyl aryl ketones (6), one would expect to find the dihydrocarbostyril in the greater yield. Spiro[cyclohexane-1,1′-indanone-3′] (VI) when subjected to the Schmidt reaction with 90% sulfuric acid and powdered sodium azide produced the crystalline spiro[cyclohexane-1,4′-dihydrocarbostyril] (VII) in 71% yields. This compound was then reduced quantitatively with lithium aluminum hydride to spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] (VIII).

In order to prove that the amine was a tetrahydroquinoline and not a tetrahydroisoquinoline a comparison of the ultraviolet absorption spectra (Figure 1) of 1,2,3,4-tetrahydroquinoline, 1,2,3,4-tetrahydroisoquinoline and the synthetic amine, spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] (VIII) was made. These curves show conclusively that the Schmidt reaction produced the normal compound in which the amino group was injected adjacent to the aryl

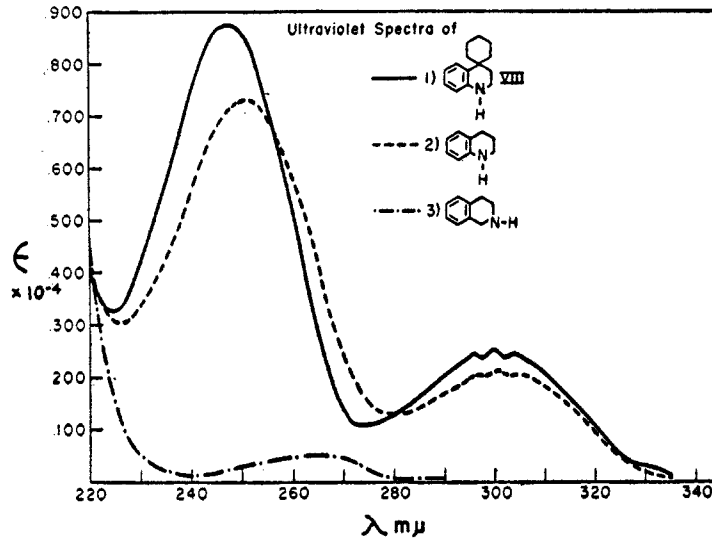


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA of 1,2,3,4-Tetrahydroquinoline, 1,2,3,4-Tetrahydroisoquinoline, and Spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline].

group in an aryl alkyl ketone and which subsequently was reduced to a tetrahydroquinoline type compound (VIII).

Chemically, the amine (VIII) reacts with formaldehyde and formic acid to produce a high molecular weight substance, which could not be characterized readily. A sample of 1,2,3,4-tetrahydroquinoline also gave a polymeric material when subjected to formaldehyde-formic acid treatment, but with 1,2,3,4-tetrahydroisoquinoline normal N-methylation resulted, and a good yield of isokairoline was obtained.

Since N-methylation of spiro[cyclohexane 1,4′-1′,2′,3′,4′-tetrahydroquinoline] using formaldehyde and formic acid was not successful, resort was had to dimethyl sulfate; the tertiary amine (IX) was obtained in 40% yield.

Oximination of spiro[cyclohexane 1,1′-indanone-3′] (VI) in pyridine and absolute alcohol gave (X) in excellent yields. Hydrogenation of this oxime at room

temperature and atmospheric pressure with Adams' catalyst produced spiro[cyclohexane-1,1′-3′-aminoindane] (XI), which upon subsequent methylation with formaldehyde and formic acid produced spiro[cyclohexane-1,1′-3′-dimethylaminoindane] (XII).

Reduction of the oxime (XIII) with Adams' catalyst in glacial acetic acid at room temperature and atmospheric pressure produced spiro[cyclohexane-1,1′-3′-aminohexahydroindane] (XIV). This amine was then methylated to give good yields of spiro[cyclohexane-1,1′-3′-dimethylaminohexahydroindane] (XV).

Analgesic testing on this series of compounds is being done by Dr. Nathan B. Eddy of this Institute. Preliminary results indicate that all the amine compounds, VIII, IX, XI, XII, XIV, and XV, exhibit analgesic activity. A more detailed report of these activities will be reported elsewhere after completion of the tests.

Acknowledgement. The author wishes to express his thanks to Drs. Lyndon F. Small, Erich Mosettig, and G. Forrest Woods for their suggestions during the course of this research. Microanalyses were performed by William Alford, Margaret Ledyard, and Evelyn Peake of this Institute.

EXPERIMENTAL

All melting points and boiling points given are uncorrected.

1,1′-Ethynylene-bis-cyclohexanol (I). This preparation is a modification of the ethynylation procedure of Kazarin (7). Into a mixture of 382 g. of calcium carbide, 240 g. of finely powdered technical potassium hydroxide, and 2500 ml. of anhydrous benzene cooled to 0–5°, 425 g. of cyclohexanone was added dropwise with vigorous stirring over a period of two hours; additional stirring was continued for four hours, and then the mixture left for 48 hours at room temperature. The congealed mass was decomposed at 0–5° with two liters of 50% hydrochloric acid and the filtered, crude, grey solid air-dried overnight. Recrystallization from boiling carbon tetrachloride yielded 295 g. or 64% of white, crystalline 1,1′-ethynylene-*bis*-cyclohexanol. An analytical sample, prepared by recrystallization from acetone and sublimation at 120° (1 mm.), melted at 109–110°; lit. m.p. 109–110°.

Anal. Calc'd for $C_{14}H_{22}O_2$: C, 75.6; H, 10.0.

Found: C, 75.6; H, 10.4.

Spiro[cyclohexane-1,1′-Δ⁹′-tetrahydroindanone-3′] (IV). The procedure for the dehydration and cyclization of the acetylenic glycol (I) is essentially that of Marvel and coworkers (1). Sixty-four grams (0.288 mole) of 1,1′-ethynylene-*bis*-cyclohexanol was refluxed for 2½ hours with 300 ml. of 40% sulfuric acid. The organic layer was separated from the cooled mixture, and the aqueous layer extracted with ether. The combined organic layer and ether extracts were washed until neutral, and the solvent removed under reduced pressure. The crude dieneyne V was then refluxed for 2½ hours with 450 ml. of 90% formic acid. The cooled mixture was extracted with ether, the ether extract washed until neutral, and then dried over magnesium sulfate. The solution was distilled under reduced pressure: spiro-[cyclohexane-1,1′-Δ⁹′-tetrahydroindanone-3′] (38 g., 64%) b.p. 130–132° (2 mm.), n_D^{20} 1.5326; lit. b.p. 130–132° (2 mm.), n_D^{20} 1.5315.

The red *2,4-dinitrophenylhydrazone* prepared in the usual manner melted at 224–224.5° after recrystallization from ethyl acetate; lit. m.p. 227–228°.

Anal. Calc'd for $C_{20}H_{24}N_4O_4$: C, 62.3; H, 6.3.

Found: C, 62.4; H, 6.5.

Spiro[cyclohexane-1,1′-Δ⁹′-tetrahydroindanone-3′] (IV) (6.2 g.) was added to a mixture of hydroxylamine hydrochloride (7.0 g.), pyridine (13 ml.), and absolute alcohol (33 ml.), and the solution refluxed for 3½ hours. After removal of the solvent under reduced pres-

sure, the resulting crystalline mass was recrystallized from an alcohol-water mixture to yield the *oxime* of spiro[cyclohexane-1,1'-$\Delta^{3'}$-tetrahydroindanone-3'] (XIII) (6.0 g. or 90%) which melted at 180–183°: the analytical sample was recrystallized very slowly from 70% petroleum ether (30–60°)-alcohol solutions to produce brilliant, massive polyhedra melting at 183.5–184.0°; lit. m.p. 183–184°.

Anal. Calc'd for $C_{14}H_{21}NO$: C, 76.7; H, 9.7.

Found: C, 76.7; H, 9.7.

Spiro[cyclohexane - 1,1' - indanone - 3'] (VI). Spiro[cyclohexane - 1,1' - $\Delta^{3'}$ - tetrahydro-indanone-3'] (IV, 25 g.) was added to 10 g. of a 5% Pd-C catalyst and 20 ml. of *p*-cymene. *p*-Cymene was distilled off until the temperature of the mixture reached 285–295°, then the distillation was discontinued, and the mixture refluxed for an additional four hours at this temperature range. The cooled mixture was filtered from the catalyst and distilled: spiro[cyclohexane-1,1'-indanone-3'] (VI) (21.1 g., 86%) boiled at 139–145° (4 mm.), n_D^{20} 1.5574. When several drops of the ketone were added to petroleum ether (30–60°) and the mixture scratched and chilled in a Dry Ice-bath, a copious white precipitate formed which was used to seed the rest of the ketone. An analytical sample, prepared by sublimation at 60° (0.5 mm.), melted at 53–54°; lit. m.p. 58–59°.

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.1.

Found: C, 84.0; H, 8.5.

Spiro[cyclohexane-1,1'-indanone-3'] (15 g.) was added to a mixture of hydroxylamine hydrochloride (17.5 g.), pyridine (32 ml.), and anhydrous alcohol (81 ml.), and the solution refluxed for 3½ hours. Removal of the solvent under reduced pressure, and recrystallization of the crystalline mass from alcohol-water mixture afforded the *oxime* of spiro-[cyclohexane-1,1'-indanone-3'] (X) (m.p. 127–129°, 14.1 g., 88%), which after further recrystallization from absolute alcohol melted at 138–139°; lit. m.p. 137–138°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0.

Found: C, 77.9; H, 7.9.

Semicarbazone. The ketone (1 ml.) was dissolved in alcohol (10 ml.) and water added until the solution became turbid, then a few additional drops of alcohol were added. To this mixture was added semicarbazide hydrochloride (1.0 g.) and sodium acetate (1.5 g.) and the mixture was shaken vigorously for 30 minutes and then put in boiling water and allowed to cool overnight. The white semicarbazone, recrystallized from an alcohol-water mixture, melted at 213–214°; lit. m.p. 211.5–212.5°.

Anal. Calc'd for $C_{15}H_{19}N_3O$: C, 70.0; H, 7.4.

Found: C, 70.0; H, 7.6.

Spiro[cyclohexane-1,4'-dihydrocarbostyril] (VII). Spiro[cyclohexane-1,1'-indanone-3'] (13.8 g.) was dissolved in benzene (125 ml.); water (3.3 ml.), and concentrated sulfuric acid (30.4 ml.), enough to make a 90% sulfuric acid solution, was then added and the mixture heated to 55°. Finely powdered sodium azide (6.8 g.) was added portion-wise with mechanical stirring over a period of 20 minutes. The mixture, kept at this temperature and stirred continuously for 30 minutes after the evolution of nitrogen had ceased, was cooled and the benzene layer decanted from the sulfuric acid layer. Ice was added, with efficient cooling and mechanical stirring, to the sulfuric acid layer. Continual stirring for one hour and the addition of small portions of ether caused the oily layer to crystallize. Yellow, solid spiro[cyclohexane-1,4'-dihydrocarbostyril] (10.5 g., 71%) so formed is pure enough for use in subsequent reactions. Recrystallization from alcohol-water mixture produced a white, analytical sample melting at 185–185.5°.

Anal. Calc'd for $C_{14}H_{17}NO$: C, 78.1; H, 8.0.

Found: C, 78.1; H, 8.2.

Spiro[cyclohexane-1,4'-1',2',3',4'-tetrahydroquinoline] (VIII). To 100 ml. of a cooled 1.2 molar (100% excess) solution of lithium aluminum hydride in ether, 26.6 g. of VII in 200 ml. of dry benzene was added dropwise over one hour; the reaction was vigorous. The ether was then removed by distillation and the mixture refluxed for 24 hours to produce a voluminous white precipitate. This complex was decomposed in the cold with just enough

water to precipitate all of the aluminum hydroxide. Then the benzene layer was decanted, and the gelatinous residue extracted with ether. The amine was isolated by acid-base extraction and the viscous, yellow oil distilled under nitrogen: b.p. 156–157° (1.5 mm.), 23.7 g., or 96%. It crystallized from petroleum-ether (30–60°) in a Dry Ice-bath and sublimed readily under reduced pressure to yield white crystals melting at 40–40.5°.

Anal. Calc'd for $C_{14}H_{19}N$: C, 83.5; H, 9.5.
Found: C, 83.5; H, 9.7.

The *N-acetyl* derivative formed by refluxing the amine (VIII) in acetic anhydride, recrystallized from water and sublimed at reduced pressure, melted at 99–100°.

Anal. Calc'd for $C_{16}H_{21}NO$: C, 79.0; H, 8.7.
Found: C, 79.0; H, 8.7.

The *N-benzoyl* derivative, made by treating the amine (VIII) (1 g.) with benzoyl chloride (1 g.) and 20% sodium hydroxide (5 ml.), was recrystallized from absolute alcohol and melted at 131–132°.

Anal. Calc'd for $C_{21}H_{23}NO$: C, 82.6; H, 7.6.
Found: C, 82.9; H, 7.7.

Spiro[cyclohexane-1,4'-N-methyl-1',2',3',4'-tetrahydroquinoline] (IX). A suspension of 2.7 g. of the amine VIII in 10 ml. of water was refluxed for four hours with 1.73 g. of dimethyl sulfate, and then allowed to stand for 48 hours at room temperature. Ammonium hydroxide was added and the basic solution extracted with ether. The amine (2.5 g.) was isolated in the usual manner. This oil was reacted with benzoyl chloride and dilute sodium hydroxide and the unreacted oil extracted with ether. Spiro[cyclohexane-1,4'-N-methyl-1',2',3',4'-tetrahydroquinoline] (1.25 g., 43%) isolated in the usual manner was distilled under nitrogen: b.p. 134–135° (1 mm.), n_D^{30} 1.5778.

Anal. Calc'd for $C_{15}H_{21}N$: C, 83.7; H, 9.8.
Found: C, 83.7; H, 9.8.

The *picrate* was formed in the usual manner and after several recrystallizations from absolute alcohol melted at 170–172°.

Anal. Calc'd for $C_{21}H_{24}N_4O_7$: C, 56.8; H, 5.4.
Found: C, 56.6; H, 5.5.

Spiro[cyclohexane-1,1'-3'-aminoindane] (XI). The oxime of spiro[cyclohexane-1,1'-indanone-3'] (X) (17.5 g.) was hydrogenated at room temperature and atmospheric pressure in a glacial acetic acid solution (100 ml.) using Adams' catalyst (1.0 g.). The theoretical amount of hydrogen was absorbed in four hours. After the catalyst was removed by filtration, the solvent was distilled off under reduced pressure to give the acetylated amine, which was hydrolyzed by refluxing in 20% sodium hydroxide (100 ml.) for three hours. The amine was isolated from the cooled solution by acid-base extraction. The dried ether solution was distilled under nitrogen to yield spiro[cyclohexane-1,1'-3'-aminoindane] (10.5 g., 64%): b.p. 115–117° (1 mm.), n_D^{30} 1.5512. The free amine is very hygroscopic, which is reflected in the analytical value.

Anal. Calc'd for $C_{14}H_{19}N$: C, 83.5; H, 9.5.
Found: C, 82.9; H, 10.1.

The *benzoyl* derivative was made in the usual manner and after recrystallization from alcohol melted at 164–165°.

Anal. Calc'd for $C_{21}H_{23}NO$: C, 82.6; H, 7.6.
Found: C, 82.3; H, 7.4.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XI, melted at 245–246° after recrystallization from an absolute alcohol-ether mixture.

Anal. Calc'd for $C_{14}H_{20}ClN$: C, 70.7; H, 8.5; Cl, 15.2.
Found: C, 70.3; H, 8.7; Cl, 15.3.

Spiro[cyclohexane-1,1'-3'-dimethylaminoindane] (XII). To a cooled solution of 3 g. of the amine (XI) and 3.5 g. of 90% formic acid, 3.5 g. of a 36% aqueous solution of formaldehyde was added (8). Upon warming this mixture to room temperature a vigorous evolution

of carbon dioxide ensued and lasted for one hour, after which the mixture was refluxed on a steam-bath overnight. Isolation of the amine was accomplished in the usual manner. This product was then treated with 30 ml. of 20% sodium hydroxide and 8 ml. of acetic anhydride. The tertiary amine (2.5 g. or 73%), isolated from this mixture in the usual manner, boiled at 123–124° (0.8 mm.), n_D^{35} 1.5400.

Anal. Calc'd for $C_{16}H_{23}N$: C, 83.8; H, 10.1.
Found: C, 83.4; H, 10.3.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XII, melted at 237–238° after recrystallization from absolute alcohol-ether mixtures.

Anal. Calc'd for $C_{16}H_{24}ClN$: C, 72.3; H, 9.1.
Found: C, 72.2; H, 9.2.

The *picrate*, formed in the usual manner and recrystallized from absolute alcohol, melted at 190–191°.

Anal. Calc'd for $C_{22}H_{26}N_4O_7$: C, 57.6; H, 5.7.
Found: C, 57.8; H, 5.9.

The *methiodide*, formed in the usual manner and recrystallized from absolute alcohol, melted at 187–189°.

Anal. Calc'd for $C_{17}H_{26}IN$: C, 55.0; H, 7.1.
Found: C, 54.7; H, 7.1.

Spiro[cyclohexane-1,1'-3'aminohexahydroindane] (XIV). This compound was prepared in 90% yields in the same manner as the corresponding aromatic amine (XI): b.p. 119–121° (1.8 mm.), n_D^{29} 1.5128.

The *N-benzoyl* derivative was made in the usual manner and after recrystallization from an alcohol-water mixture melted at 184–185°.

Anal. Calc'd for $C_{21}H_{29}NO$: C, 81.0; H, 9.4.
Found: C, 81.0; H, 9.4.

The *hydrochloride*, prepared by passing dry hydrogen chloride gas through an ether solution of the amine XIV, melted at 290–295° after recrystallization from alcohol-ether mixtures.

Anal. Calc'd for $C_{24}H_{26}ClN$: C, 69.0; H, 10.8.
Found: C, 68.9; H, 10.6.

Spiro[cyclohexane-1,1'-3'-dimethylaminohexahydroindane] (XV). The tertiary amine was prepared and isolated in the same manner as the corresponding aromatic amine XII, in 85% yield: b.p. 127–128° (1.8 mm.), n_D^{28} 1.5053.

Anal. Calc'd for $C_{16}H_{29}N$: C, 81.6; H, 12.4.
Found: C, 81.2; H, 12.4.

The *picrate* was formed in the usual manner, and after recrystallization from absolute alcohol melted at 168–170°.

Anal. Calc'd for $C_{22}H_{32}N_4O_7$: C, 56.9; H, 6.9.
Found: C, 57.0; H, 7.2.

The *methiodide*, prepared in the usual manner, was recrystallized from absolute alcohol and melted at 190–192°.

Anal. Calc'd for $C_{17}H_{32}IN$: C, 54.1; H, 8.6.
Found: C, 53.9; H, 8.6.

N-Methylation of 1,2,3,4-tetrahydroisoquinoline. 1,2,3,4-Tetrahydroisoquinoline was purified by recrystallization of its hydrochloride and subsequent regeneration and distillation: b.p. 82–82.5° (3 mm.) n_D^{23} 1.5790. The formic acid-formaldehyde methylation procedure was the same as that used in previous parts of this paper. Isokairoline [b.p. 81–86° (2 mm.)] was obtained in 80% yields and produced a *methiodide*, which after recrystallization from absolute alcohol, melted at 188–189° (Literature, m.p. 188–189°).

Ultraviolet absorption spectra. All measurements were made on a Beckman spectrophotometer on absolute alcohol solutions. Commercial 1,2,3,4-tetrahydroquinoline was redistilled and the fraction b.p. 68.0–68.5° (1.5 mm.), n_D^{25} 1.5910 used in this analysis. Cell length

was 1.007 cm. and concentration 8.2×10^{-5} molar. 1,2,3,4-Tetrahydroisoquinoline was purified as indicated previously. Cell length was 0.999 cm. and concentration 8.92×10^{-5} molar. The spectrum of spiro[cyclohexane-1,4′-1′,2′,3′,4′-tetrahydroquinoline] was taken on the analytical sample; 3.2×10^{-5} molar concentration with a 1.006-cm. cell being used.

SUMMARY

1. Strong evidence is presented which indicates that the cyclodehydration of 1,1′-ethynylene-*bis*-cyclohexanol produces a mixture of spirano-ketones and not a phenanthrone type compound.

2. A new series of compounds containing a quaternary carbon atom and a tertiary amine group has been synthesized.

3. These compounds were tested and each one showed analgesic activity.

BETHESDA 14, MD.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE ADDITION OF 1,3-BUTADIENE TO PROPIONITRILE[1]

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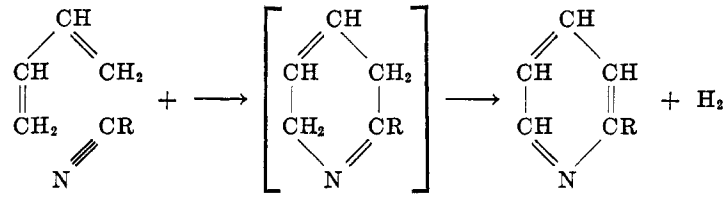
The addition of butadiene to cyanogen, hydrogen cyanide, acetonitrile, and benzonitrile at relatively high temperatures has been reported by Janz and his co-workers (1, 2). The products are α-substituted pyridines which apparently result from a Diels-Alder type addition between the diene and the —C≡N group followed by dehydrogenation.

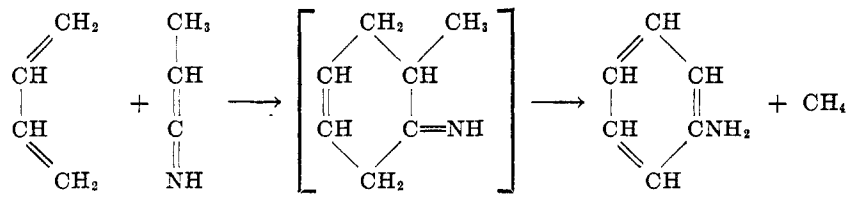


R = —CN, —H, —CH_3, —C_6H_5

This reaction seemed suited to the preparation of 2-ethylpyridine by use of propionitrile for the cyanogen derivative. Accordingly the reaction was carried out under the general conditions used before.

In our experiments with butadiene and propionitrile at 600° and atmospheric pressure reaction did occur, but the liquid product proved to be a mixture containing some butadiene dimer (vinylcyclohexene) and a basic fraction which contained a pyridine derivative first identified by the characteristic odor and later characterized as 2-ethylpyridine, and a primary amine which proved to be aniline. The pyridine derivative was formed in only about 0.5% yield and the aniline in 4.0% yield (based on the total butadiene employed) in one pass through the hot tube.

The formation of aniline in the reaction was extremely surprising. Further examination of the reaction products demonstrated that methane was also produced and this accounts for the carbon atom which is lost when butadiene and propionitrile yield aniline. We at first thought some acetonitrile might be formed in our hot tube by cracking propionitrile, but this was shown not to be the case. We have postulated the following probable intermediates to account for the pro-production of aniline.



[1] This work was done under the sponsorship of the Office of Rubber Reserve, Reconstruction Finance Corporation, in connection with the government synthetic rubber program.

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Under the same general reaction conditions acetonitrile adds butadiene to give aniline as the principal reaction product and very little, if any, pyridine derivative is formed. Acetyl cyanide at 315°, 400°, or 530° did not add butadiene.

Packing the hot tube with various catalysts such as calcium sulfate, steel wool, silica gel, chromic oxide, and cuprous oxide did not seem to change the course of the reaction. Fresh aluminum-oxide surfaces did suppress the yield of aniline, although the total amount of the basic addition product remained about the same as when no catalytic surface was present.

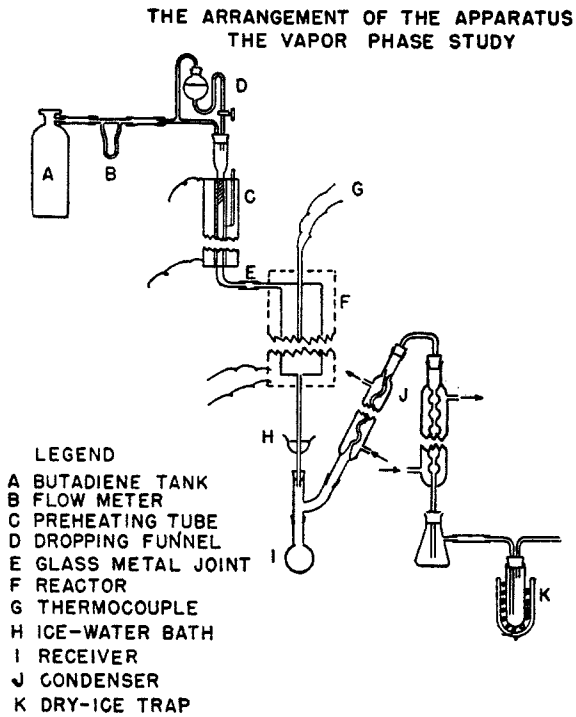

FIGURE 1.

EXPERIMENTAL

All melting points and boiling points reported are uncorrected. All microanalyses were done by the Clark Microanalytical Laboratory. We are indebted to Mrs. J. L. Johnson for the infrared spectra determinations and their interpretation.

Apparatus. The reaction tube was built on the plan outlined by Janz and his co-workers (1, 2) and the apparatus was assembled as in Figure 1.

Procedure. Before each run the whole system was swept out with nitrogen gas and after each run the hydrocarbon-nitrile vapors were again swept out of the apparatus with nitrogen in the interest of safety. When the temperature of the furnace was at the proper point, the flow of butadiene was started and propionitrile in excess was admitted from the dropping-funnel into the preheater which was maintained at 260–280°. Glass beads were placed in the upper part of the preheater to give heat transfer surface.

The dark liquid which gathered in flask I was fractionated in an 11-in. helices-packed column to separate unchanged propionitrile and the residue was extracted with three or four 10–20-ml. portions of 5% hydrochloric acid. The acid extract was washed with benzene and with ether and was heated to remove any dissolved solvent. It was then made alkaline with excess solid potassium hydroxide, the oil was separated, and the aqueous layer was extracted with ether. The combined oil and extract were dried over potassium carbonate and distilled.

TABLE I

REACTION OF BUTADIENE WITH PROPIONITRILE AT ELEVATED TEMPERATURES

RUN NO.	REACTANTS		EXPERIMENTAL CONDITIONS			RECOVERY[d]				YIELD[g]			
	Propionitrile,[a] g.	Butadiene,[b] g.	Temp. of Reactor, °C.	Time of Pass, Sec.[c]	Catalyst	Propionitrile[e]		Butadiene[f]		Aniline[h]		2-Ethylpyridine[h]	
						g.	%	g.	%	g.	%	g.	%
7	338	54	600	109	None	262	78	—	—	4.1	4.4	—	—
8	157	20	600	88	"	110	70	6.5	32	1.5	4.4	—	—
9	188	176	610	29	"	153	81	68	39	1.3	0.4	0.2	0.1
10	156	23	610	101	"	105	67	15.5	67	1.6	4.0	.2	.5
11[i]	141	169	600	99	"	96	68	62.5	37	1.1	0.4	.3	.1
12[i]	141	147	610	60	"	88	62	49.5	34	0.8	.3	.2	.1
15	[j]	[j]	700	100	"	—	—	—	—	Extensive pyrolysis			
16	81	82	300	30	Al_2O_3[k]	64	79	60	73	—	—	.5[l]	.3

[a] B.p. 96.9–97°, n_D^{20} 1.3651–1.3661. [b] Special purity grade, Phillips Petroleum Company, Bartlesville, Oklahoma. [c] Calculated assuming both reactants in the gaseous state are ideal gases. [d] The percentage recoveries of propionitrile and butadiene were based on the total amounts of the respective reagents employed in the reaction. [e] B.p. 95–97°, n_D^{20} 1.3667–1.3997. [f] The butadiene collected in a Dry-Ice trap during the reaction and during the fractionation of the reaction condensate, constitutes this total recovery. [g] The yields of aniline and 2-ethylpyridine in runs 7–10 were based on the total amount of butadiene employed whereas the yields in runs 11, 12, and 16 were based on the total amount of propionitrile employed in the reaction. [h] Estimated from the infrared absorption spectra and the indices of refraction of the distilled product. [i] The reaction condensate, after removal of unchanged propionitrile, was fractionated directly in an 8-in. helices-packed column. 2-Ethylpyridine and aniline were then isolated from the corresponding fractions. [j] Molar ratio of propionitrile to butadiene was 7.0:1. [k] Reaction conducted in a 23-in. pyrolysis tube packed with the catalyst (10-mesh Hydralo, 157 g.). The catalyst was heated at the reaction temperature for ½-1 hour before the reaction was started. [l] Picrate, m.p. 102–105.5°.

Table I is a summary of typical experiments.

Other runs were made with tube packings of anhydrous calcium sulfate (Drierite, blue indicator, 8 mesh), steel wool (Beaver grade No. 1), silica gel (6–16 mesh), chromic oxide, and cuprous oxide in an iron tube at 500° and 600°. Aniline and 2-ethylpyridine were found in approximately the same ratio as in the unpacked tube.

Identification of aniline. The crude base separated from run 7 was distilled under reduced pressure; the major portion boiled at 79–81° at 15 mm. This material gave a picrate, m.p. 188–189°, a salt with methyl *p*-toluenesulfonate, m.p. 227–229.5°; a benzenesulfonamide, m.p. 108.5–109.5°; an acetyl derivative, m.p. 113.5–114.5°; and a derivative with phenyl isothiocyanate, m.p. 150.7–151°. Since aniline was unsuspected, the salts with picric acid (A) and methyl *p*-toluenesulfonate (B) were analyzed.

Anal. Calc'd for (A) $C_{12}H_{10}N_4O_7$: C, 44.80; H, 3.13; N, 17.38.
Found: C, 45.27; H, 2.89; N, 17.23.

Anal. Calc'd for (B) $C_{14}H_{17}O_3S$: C, 60.30; H, 6.16; N, 5.02; S, 11.46.
Found: C, 59.01; H, 6.08; N, 4.48; S, 11.48.

With this clue to the composition, the other derivatives were analyzed and compared with the corresponding derivatives of authentic aniline. Benzenesulfonamide of aniline, m.p. 106–107°; mixed m.p. with benzenesulfonamide of unknown, 107–108.5°. Acetanilide, m.p. 113–114°; mixed m.p. with acetyl derivative of unknown, 112.5–114°. Diphenylthiourea, m.p. 150.5–151.5°; mixed m.p. with phenyl isothiocyanate derivative of unknown, 149.5–150.5°.

A micro boiling-point determination of the unknown base gave 184° at 740 mm.; $n_D^{24.2}$ 1.5772. The infrared pattern of the unknown and of aniline were identical showing characteristic bands at 1420, 1435, 1465, 1500, 1520, and 1540 cm.$^{-1}$.

Identification of methane. The gas evolved in run 11 was collected over water. It was then washed with saturated bromine water and 20% potassium hydroxide, and dried over calcium chloride, Ascarite, and Hydralo in sequence. This purified gas gave infrared absorption bands at about 1300 and 3000 cm.$^{-1}$ which are characteristic of methane (3).

Identification of 2-ethylpyridine. The condensate in run 11 was fractionated in an 8-in. helices-packed column and the fraction boiling at 87–95°/100 (n_D^{20} 1.5006) was collected (4.2 g.). The basic material in this fraction was dissolved in 5% hydrochloric acid and separated. Then the basic material was salted out by the additon of excess solid potassium hydroxide. About 0.3 ml. of base was obtained as a liquid. The aqueous alkali was extracted with ether and 2 ml. of the extract obtained. The characteristic pyridine odor was noted in these extracts.

To 1 ml. of the ether extract was added a saturated solution of picric acid in ether. The solid *picrate* which separated was twice recrystallized from water, m.p. 104–106.5°. A sample of authentic picrate of 2-ethylpyridine,[3] m.p. 108–109.5°, was mixed with the above in equal amounts and the mixture melted at 105.5–107.5°.

The remaining 1 ml. of ether extract was treated with 0.25 ml. of 10% hydrochloric acid, the ether layer was separated, and a solution of 0.20 g. of mercuric chloride in 1.5 ml. of hot water was added to the acid solution. The precipitate which formed was recrystallized twice from hot water, m.p. 102.5–106.5°. A mixture of this salt with authentic 2-ethylpyridine mercuric chloride salt (4), m.p. 102.5–106°, melted at 103.5–106°.

Addition of butadiene to acetonitrile. When 22.5 g. of butadiene and 206 g. of acetonitrile were allowed to react in the unpacked reactor at 600° and 60-seconds passage time, the basic condensate (0.4 g., 1% yield found on the total butadiene used) boiled at 186–187° at 740 mm.; n_D^{23} 1.5760; benezenesulfonyl derivative, m.p. 104–107°. These data support the view that this base was nearly all aniline.

Attempted pyrolysis of propionitrile at 600°. Passage of propionitrile through the unpacked reactor at 600° and 87-seconds passage time did not produce an appreciable amount of low-boiling material and no evidence of methane production was found.

Attempted addition of butadiene to acetyl cyanide. Acetyl cyanide prepared by the method of Migrdichian (5) was passed through the reactor with butadiene as described in the acetonitrile experiment at three different temperatures, 315°, 400°, and 530°. The product obtained in each case was the dimer of butadiene and the dimer of acetyl cyanide. No evidence of the formation of 2-acetylpyridine could be obtained.

SUMMARY

Butadiene and excess propionitrile in the vapor phase combine at 600° to give low yields of aniline and 2-ethylpyridine. In the presence of fresh aluminum-

[3] 2-Ethylpyridine was prepared by the catalytic hydrogenation of 2-vinylpyridine over Raney nickel in alcoholic solution at 25° and 2.5 atm., b.p. 147–148°, n_D^{21} 1.4964. Frank and Phillips, *J. Am. Chem. Soc.*, **71**, 2804 (1949), prepared 2-ethylpyridine from ethyllithium and pyridine; their picrate had m.p. 110–111° (private communication, March 1948). Gregg and Craig, *J. Am. Chem. Soc.*, **70**, 3138 (1948), report m.p. 108.5–110°. Furst, *J. Am. Chem. Soc.*, **71**, 3550 (1949) reports m.p. 107–107.5°.

oxide surfaces the ethylpyridine is formed and aniline is not produced in appreciable quantitites. Butadiene and acetronitrile also react at 600° to give aniline. No evidence of addition of butadiene to acetyl cyanide was found.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

LAURATES OF LACTIC ACID ESTERS

M. L. FEIN AND C. H. FISHER

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Because of their potential importance as plasticizers (1) and synthetic lubricants, the laurates of several lactic esters were prepared and studied. The preparation and physical properties of these lactate laurates [$H(CH_2)_{11}COOCH(CH_3)COOR$] are described in this paper.

The lactate laurates (Table I) were made conveniently in two steps: (a) the appropriate lactic ester was prepared by esterification of lactic acid or by the alcoholysis of methyl lactate (2–4), and (b) the lactic ester was then acylated with lauroyl chloride (5).

At room temperature, the lactate laurates were liquids having little or no color. Their boiling points at different pressures are given in Figures 1 and 2. For purposes of comparison, the boiling points of *n*-butyl, tetrahydrofurfuryl, and benzyl laurate were determined (Fig. 2). Comparison of the boiling points of the *n*-butyl, tetrahydrofurfuryl, and benzyl laurates at 1 and 4 mm. with the boiling points of the corresponding lactate laurates shows that the effect of the lactate segment in these compounds is to raise the boiling point approximately 30°.

The boiling points of the lactate laurates [$H(CH_2)_{11}COOCH(CH_3)COOR$] at 1 and 4 mm. are roughly proportional to the normal boiling points of ROH (Fig. 3). These relationships, which are useful for predicting the boiling points of other lactate laurates, are expressed by the following equations:

$$y(1\text{ mm.}) = 0.408\,X + 108$$
$$y(4\text{ mm.}) = 0.408\,X + 135$$

where y = b. p. of lactate laurate at 1 or 4 mm., and X = b. p. of ROH at 760 mm. Boiling points calculated by these equations agree moderately well (3° or better) with the experimental boiling points in Figures 1 and 2.

The lactate laurates have boiling points between those of *n*-butyl phthalate and *n*-octyl phthalate, two widely used commercial plasticizers (Figs. 1 and 2). Results obtained in an evaluation of the lactate laurates as plasticizers for vinyl chloride resins will be published elsewhere.

ACKNOWLEDGMENT

The authors are grateful to the Barrett Division of Allied Chemical and Dye Company for cyclohexyl lactate, Shell Development Company for methyl isobutyl carbinol, Dr. C. E. Rehberg of this laboratory for isobutyl lactate, Carbide and Carbon Chemicals Corporation for monoethers of glycol and diethylene glycol, and Arnold, Hoffman & Company, Inc. for *n*-butyl laurate. The authors are indebted also to Dr. C. L. Ogg, Miss Jane C. Dixon, and Miss Mary Jane

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

TABLE I

PROPERTIES OF LACTATE LAURATES [$H(CH_2)_{11}COOCH(CH_3)COOR$]

R	BOILING POINT		n_D^{20}	d_4^{20}	MOLECULAR REFRACTION		ESTER EQUIVALENT		C		H		VISCOSITY, 20°	
	°C.	mm.			Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found	Centi-stokes	Centi-poises
sec-Butyl	155	1.3	1.4360	0.9181	93.25	93.56	164.2	164.3	69.47	69.55	11.05	11.11	11.88	10.90
Isobutyl	153	1.0	1.4372	.9199	93.25	93.58	164.2	165.0	69.47	69.30	11.05	11.14	12.22	11.24
2-Ethylhexyl	193	2.0	1.4441	.9122	111.72	112.00	192.3	189.0	71.83	71.86	11.53	11.61	17.85	16.27
2-Ethoxyethyl	170	1.3	1.4399	.9510	94.89	95.45	172.2	170.2	66.24	66.89	10.53	10.63	14.01	13.32
2-Butoxyethyl	204	3.2	1.4412	.9411	104.13	104.57	186.3	185.0	67.70	68.00	10.82	10.78	15.28	14.38
2-(2-Ethoxyethoxy)ethyl	180	0.7	1.4450	.9716	105.77	106.43	194.3	194.0	64.91	64.81	10.38	10.67	25.66	24.93
2-(2-Butoxyethoxy)ethyl	205	1.2	1.4441	.9570	115.01	115.60	208.3	207.5	66.31	66.23	10.65	10.60	20.40	19.52
Benzyl	206	2.3	1.4774	.9865	103.50	103.90	181.3	181.2	72.89	72.90	9.45	9.56	22.16	21.86
Cyclohexyl	184	1.5	1.4530	.9514	100.29	100.71	177.3	177.0	71.14	71.40	10.80	11.00	26.56	25.27
Methyl isobutyl carbinyl	168	1.5	1.4373	.9093	102.49	102.79	178.3	178.1	70.74	70.70[a]	—	—	14.69	13.35
n-Butyl laurate[b]	145	3.0	1.4351	.8593	77.74	77.88	256.4	254.7	74.94	75.14	12.58	12.64	5.27	4.53
Benzyl laurate[b]	174	2.0	1.4820	.9375	88.00	88.31	290.4	292.1	78.57	78.55	10.41	10.37	8.90	8.34
Tetrahydrofurfuryl laurate[b]	154	1.2	1.4519	.9361	81.80	81.94	284.4	284.9	71.78	71.95	11.34	11.30	11.19	10.48

[a] *Carbon determined by wet oxidation.* [b] Properties of the simple laurates are given for comparison.

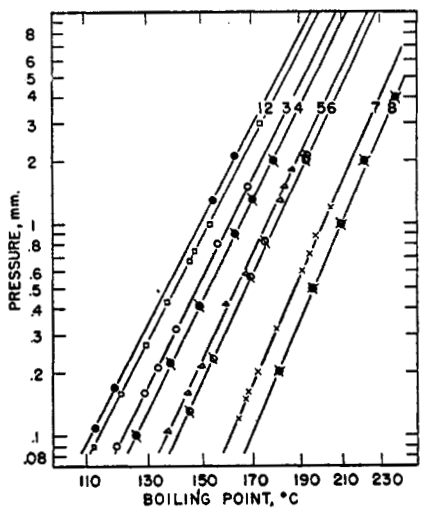

FIG. 1

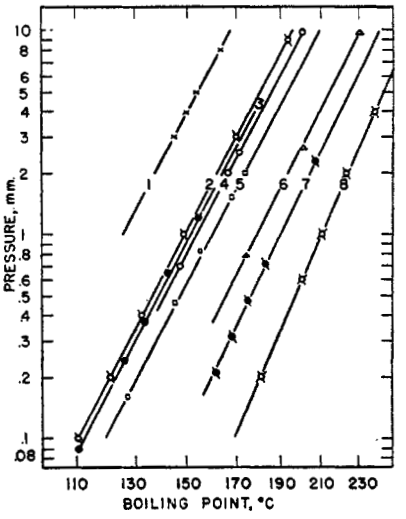

FIG. 2

FIG. 1. BOILING POINTS OF LACTATE LAURATES

1. *sec*-Butyl lactate laurate. 2. Isobutyl lactate laurate. 3. Methyl isobutyl carbinyl lactate laurate. 4. 2-Ethoxyethyl lactate laurate. 5. Cyclohexyl lactate laurate. 6. Ethylhexyl lactate laurate. 7. 2-(2-Butoxyethoxy)ethyl lactate laurate. 8. *n*-Octyl phthalate.

FIG. 2. BOILING POINTS OF LAURATES AND LACTATE LAURATES

1. *n*-Butyl laurate. 2. *n*-Butyl phthalate. 3. Tetrahydrofurfuryl laurate. 4. *n*-Butyl lactate laurate. 5. Benzyl laurate. 6. Tetrahydrofurfuryl lactate laurate. 7. Benzyl lactate laurate. 8. *n*-Octyl phthalate.

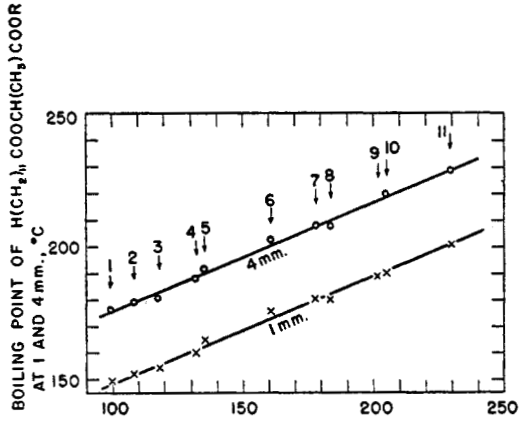

FIG. 3. RELATION BETWEEN BOILING POINTS OF ROH AND THOSE OF THE CORRESPONDING $H(CH_2)_{11}COOCH(CH_3)COOR$

R = 1, *sec*-Butyl; 2, Isobutyl; 3, *n*-Butyl; 4, Methyl isobutyl carbinyl; 5, 2-Ethoxyethyl; 6, Cyclohexyl; 7, Tetrahydrofurfuryl; 8, 2-Ethylhexyl; 9, 2-(2-Ethoxyethoxy)ethyl; 10, Benzyl; 11, 2-(2-Butoxyethoxy)ethyl.

Welsh, of the Analytical and Physical Chemistry Division of this Laboratory, for analytical data.

EXPERIMENTAL

Lactic esters. The 2-ethoxyethyl, 2-butoxyethyl, and 2-(2-butoxyethoxy)ethyl lactates were prepared by previously described methods (2, 3). Benzyl lactate was prepared by alcoholysis of methyl lactate: A mixture of 7 moles of benzyl alcohol, 3 moles of methyl lactate, and 6 g. of aluminum isopropoxide was refluxed under a 2-foot Vigreux column, through which methanol was removed as it was formed. When the reaction was complete, the excess benzyl alcohol and then the benzyl lactate were distilled. A center cut of benzyl lactate distilled at 114°/3 mm., and the index of refraction at 20° was 1.5142. This compound has been reported to boil at 134°/4 mm. (6) and 103–104°/1.3 mm. (7). *sec*-Butyl lactate, 2-ethylhexyl lactate, and methyl isobutyl carbinyl lactate were prepared by alcoholysis of methyl lactate. In each case, one mole of methyl lactate was reacted with 4 moles of the alcohol, 2 to 5 g. of *p*-toluenesulfonic acid being used as the catalyst. The procedure was that described above, except that the catalyst was neutralized before distillation. The physical constants observed for these three lactates were: *sec*-Butyl (8), b.p. 60.5°/8 mm., n_D^{20} 1.4160, d_4^{20} 0.9729; 2-ethylhexyl (8), b.p. 97–98°/3.0 mm., n_D^{20} 1.4357, d_4^{20} 0.9399; methyl isobutyl carbinyl, b.p. 52°/1 mm., 59.5°/1.8 mm., n_D^{20} 1.4220. 2-(2-Ethoxyethoxy)ethyl lactate could not be prepared readily as a pure derivative[2] because of the presence of glycol in the alcohol (9). The crude ethoxyethoxyethyl lactate contained a considerable amount of glycol monolactate, which was separated later as the dilaurate (see below).

Lactate laurates. These were prepared, as described previously (5), by treating the lactic esters with lauroyl chloride in the presence of dry pyridine. Commerical lauroyl chloride was redistilled through a 2-foot Vigreux column; the fraction boiling over the range 137–139°/11 mm., n_D^{20} 1.4452, was used in most acylations. Reagent grade (Eastman White Label) lauroyl chloride was used in several preparations. Ether, 200 ml. per mole of lactic ester, was used as a diluent. The yields ranged from 64–92% of the theoretical. These yields were influenced by losses due to emulsions, sometimes persistent, that formed during washing prior to distillation.

In the case of 2-(2-ethoxyethoxy)ethyl lactate laurate, a high-boiling fraction was isolated, which solidified when cooled. This material, recrystallized three times from ethanol, melted at 44.5–45°. From the analysis, this solid appears to be *glycol monolactate dilaurate.*

Anal. Calc'd: C, 69.84; H, 10.91; Ester equivalent, 166.24.

Found: C, 70.51; H, 10.43; Ester equivalent, 166.0.

These analytical values are quite different from those of glycol dilaurate, 2-(2-ethoxyethoxy)ethyl laurate, or glycol dilactate dilaurate, which might have been formed.

Benzyl and tetrahydrofurfuryl laurates. These esters were made in 95% yield by the reaction of 2 moles of the alcohol with one mole of lauric acid,[3] with 200 ml. of toluene as entrainer, and 2 g. of *p*-toluenesulfonic acid (monohydrate) as catalyst. This mixture was heated in a flask fitted with a 2-foot Vigreux type column topped by a water-cooled Barrett moisture (modified Dean and Stark) trap. In each case, 2 hours were required to complete the esterification (18 ml. of water collected in trap). After the flask had cooled, 1 g. of sodium acetate (anhydrous) was added to neutralize the catalyst. The entrainer was distilled under a water-pump vacuum, and then the excess alcohol and the desired product were distilled under higher vacuum (oil pump). A commercial sample of *n*-butyl laurate was redistilled prior to determination of its physical constants.

Data for the boiling-point curves were obtained by distillation through a modified alembic still [an improved tensimeter-still (10)]. Other physical data were determined with carefully distilled, narrow-boiling fractions, as described previously (5). The boiling points

[2] Since this work was completed, a pure sample of 2-(2-ethoxyethoxy)ethanol was obtained, and the pure lactate was prepared by reaction with methyl lactate. Physical constants and analytical data for this lactate are: B.p. 117°/3.0 mm.; n_D^{20} 1.4390; d_4^{20} 1.0786; *Anal.* Calc'd: C, 52.41; H, 8.80. Found: C, 52.28; H, 8.87.

[3] A commercial grade was used; average analysis given by the manufacturer: mean molecular weight, 203; lauric acid, 90%; myristic acid, 9%; and oleic acid, 1%.

of various alcohols at atmospheric pressure (Fig. 3) were taken from the literature (11–13). Boiling points of butyl and octyl phthalates (Fig. 2) were taken from reference (14).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. II. PRIMARY ALIPHATIC AMINES[1, 2]

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In the first paper of this series (1) the production of cyanoformamidines from cyanogen and secondary amines was described.

$$R_2NH + (CN)_2 \rightarrow R_2NC(=NH)CN$$

The reaction was most satisfactory when *anhydrous* solvents such as ethyl acetate, benzene or toluene were employed, and no compounds were isolated in which both CN groups of cyanogen had undergone amine addition.

It was interesting to discover, therefore, in extending the reaction to primary aliphatic amines, that in this case both CN groups reacted simultaneously with the production of symmetrically substituted oxamidines.

$$2\ RNH_2 + (CN)_2 \rightarrow RNHC(=NH)\text{—}\text{—}C(=NH)NHR$$

A similar reaction for aniline was described by Hoffmann (2) in 1848 and for benzylamine by Strakosch (3) in 1873, but no reaction of cyanogen with purely aliphatic amines has hitherto been reported.

Depending on the amine, the oxamidines were obtained by us in one of two ways, either directly by saturation of an *aqueous* solution of the amine with purified cyanogen, or indirectly by neutralizing the hydrochloride salt. The latter was produced by saturating an alcoholic solution of the amine first with cyanogen, then with anhydrous hydrogen chloride. The substituted oxamidine hydrochlorides are less soluble in alcohol than the hydrochlorides of the amines from which they are made. There is no difficulty, therefore, in separating the oxamidine salts from amine impurities. Whether or not the direct method gives good results depends on the water-solubility and the melting point of the product, those having both high solubility and low melting point being best obtained through their hydrochlorides.

The reaction has been investigated for all the primary amines up to and including normal amyl. In the case of *tert*-butyl amine no product could be obtained in spite of many attempts which were made with varying reaction conditions. A Hirschfelder model of the desired substance indicated that it would be sterically very difficult for such a molecule to form.

[1] From the research program followed by Chen Ming Chih in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

[2] This work was supported by the Office of Naval Research under Contracts N7 ONR-445 and N8 ONR-69200.

[3] Present address: Fabrics and Finishes Department, E. I. du Pont de Nemours and Co., Philadelphia, Pa.

The eight oxamidines described in this paper are white crystalline solids or colorless liquids. Their solubility in water decreases with increasing molecular weight and becomes very small at C_4. In organic solvents the lower members are less soluble than the higher ones. The hydrochloric or nitric acid salts are often more suitable for storage than the free bases since the latter hydrolyze slowly on standing. Cold aqueous solutions, especially if small amounts of alkylamine are present, hydrolyze to disubstituted oxamides. Refluxing, with or without amine, causes complete breakdown to unsubstituted oxamide.

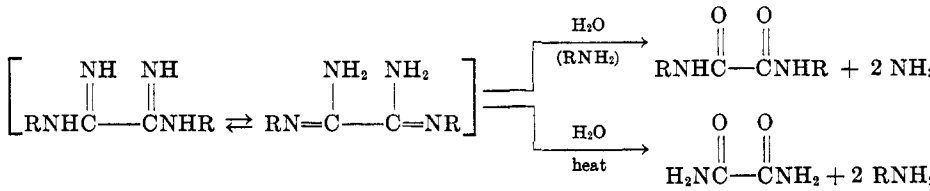


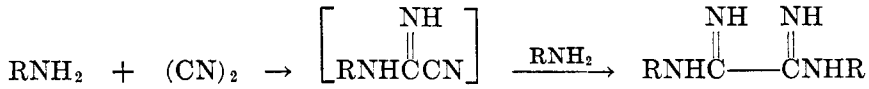
TABLE I

PROPERTIES OF RNHC(=NH)—C(=NH)NHR

R	M.P., °C.	B.P., °C.	M.P., °C., HCl SALT	M.P.°C., HNO_3 SALT
CH_3	103–104		289–290 dec.	215–216 dec.
C_2H_5	53		274–276 dec.	226–228 dec.
n-C_3H_7		95 dec.	272–274 dec.	207–210 dec.
iso-C_3H_7		80	285–287 dec.	222–224 dec.
n-C_4H_9	63		270–272 dec.	206–208 dec.
iso-C_4H_9	79		300–302 dec.	220–223 dec.
sec-C_4H_9		140 dec.	295–297 dec.	220–224 dec.
n-C_5H_{11}	dec. above 100		278–279 dec.	208–209 dec.

The comparison by mixed melting point of the oxamides resulting from hydrolysis, with the same compounds made by an alternative procedure (4), together with analyses of the original compounds, constitute the chief arguments for the oxamidine structure used in this paper, since we have not yet been able to synthesize the compounds by other methods. The action of ammonia on symmetrically substituted oxamides or on oximidic chlorides has failed, but other investigations reported in the succeeding paper (5) leave no reason to doubt the accuracy of the formulas.

The isolation of cyanoformamidines as the reaction product of secondary amines (1), while oxamidines resulted from primary amines suggested that the course of the cyanogen-amine reaction might be through initial formation of cyanoformamidine with further addition sterically hindered in the secondary amines.



Experiments were, therefore, run with secondary amines which involved changes in the original procedures (1) as to solvent, cyanogen-amine ratio, and mode of recovery, with the result that a di-addition compound of cyanogen and dimethylamine, $(CH_3)_2NC(NH)—C(NH)N(CH_3)_2$, was finally isolated in the form of its hydrochloride, together with the expected cyanoformamidine. No other secondary amine has as yet yielded such a product.

Attempts were also made to isolate a cyanoformadine precursor from the primary amine reaction mixture. Results have thus far been completely negative.

EXPERIMENTAL

Analyses were carried out as described in the first paper of this series (1). Melting and boiling points are uncorrected. An improvement in the method of purifying the cyanogen was made by replacing the calcium chloride tower by one filled with activated alumina. Under these circumstances water was so completely removed that no noticeable heat developed in the succeeding sodium hydroxide tower and the tendency for cyanogen to polymerize and contaminate the reaction mixture with tar was greatly decreased.

sym-Dimethyloxamidine. (*a*) A 25% aqueous solution of methylamine containing 31 g. of amine (1.0 mole) was treated with purified cyanogen gas (0.5 mole) at 0°. The resulting light yellow liquid was kept in an ice-chest for 24 hours and then frozen solid in Dry Ice; (when the reaction mixture was not allowed to stand, but frozen solid immediately the yield of desired product was much lower). It was then placed in an ice-salt bath until enough had melted to form a slush, which consisted of a mixture of ice and crystalline product. Filtration gave an 8.5% yield of white crystlas. It was essential to have rapid and efficient filtration of the melting ice as the product was extremely soluble in water. Recrystallization from ether gave white crystals melting at 103–104°. The substance was unstable and changed upon standing to dimethyloxamide (m.p. 212°).

The *hydrochloric acid salt* was prepared by saturating an alcoholic solution of *sym*-dimethyloxamidine with dry hydrogen chloride. Recrystallization from ethyl alcohol yielded white crystals, m.p. 289–290° with decomposition.

Anal. Calc'd for $C_4H_{10}N_4 \cdot 2\ HCl$: C, 25.7; H, 6.4; N, 29.9; Molecular weight, 187.
Found: C, 25.8; H, 6.6; N, 29.9; Molecular weight, 187.

The *nitric acid salt* was prepared by neutralizing an ether solution of the free base with concentrated nitric acid. Recrystallization from an alcohol-ether solution gave white crystals, m.p. 215–216° with decomposition.

(*b*) A solution of 12.4 g. (0.4 mole) of anhydrous methylamine in 200 ml. of 95% ethyl alcohol was reacted with purified cyanogen gas (0.2 mole) at 0°. The reaction mixture was saturated immediately with dry hydrogen chloride forming a solid product. Recrystallization from ethyl alcohol gave a 27% yield of white crystals, m.p. 289–290° with decomposition.

sym-Diethyloxamidine. A 33% aqueous solution of ethylamine containing 45 g. of amine (1.0 mole) was treated as in (*a*) above. Recrystallization of the product from ether gave a 35% yield of white solid, m.p. 53°.

The *hydrochloric acid salt* prepared as above melted at 274–276° with decomposition.

Anal. Calc'd for $C_6H_{14}N_4 \cdot 2\ HCl$: C, 33.5; H, 7.4; N, 26.1; Molecular weight, 215.
Found: C, 33.8; H, 7.8; N, 26.1; Molecular weight, 215.

The *nitric acid salt* prepared as above melted at 226–228° with decomposition.

sym-Di-n-propyloxamidine. (*a*) A 33% aqueous solution of *n*-propylamine containing 29.6 g. (0.5 mole) of amine was reacted with purified cyanogen gas (0.25 mole) at 0°. Since

freezing with Dry Ice did not lead to the isolation of a product, the reaction mixture was extracted with ether. Addition of an equal volume of ethyl alcohol followed by saturation with dry hydrogen chloride produced white crystals of the *hydrochloride* which after recrystallization from ethyl alcohol melted at 272–274° with decomposition. The yield was 22%.

Anal. Calc'd for $C_8H_{18}N_4 \cdot 2$ HCl: C, 39.5; H, 8.2, N, 23.1; Molecular weight, 243.
Found: C, 39.7; H, 8.5; N, 23.3; Molecular weight, 247.

(*b*) A 50% alcoholic solution of *n*-propylamine containing 29 g. (0.5 mole) of amine was treated with purified cyanogen gas (0.25 mole) at 0°. Saturation of the reaction mixture with dry hydrogen chloride formed white crystals which on recrystallization from ethyl alcohol melted at 272–274° with decomposition. The percentage yield of *hydrochloride* was slightly larger than that obtained by the previous method.

The *free base* was formed by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether yielded a colorless liquid, b.p. 95° with decomposition.

The *nitric acid salt* prepared from the free base melted at 207–210° with decomposition.

sym-Diisopropylamine. A 50% alcoholic solution of isopropylamine containing 59.1 g. (1 mole) of amine was treated with purified cyanogen gas (0.5 mole) at 0°. The reaction mixture was saturated with dry hydrogen chloride forming a solid product. Recrystallization from ethyl alcohol gave a 22% yield of *the hydrochloride*, white crystals melting at 285–287° with decomposition.

Anal. Calc'd for $C_8H_{18}N_4 \cdot 2$ HCl: C, 39.5; H, 8.2; N, 23.1; Molecular weight, 243.
Found: C, 39.5; H, 8.9; N, 23.3; Molecular weight, 241.

The *free base* was formed by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless liquid boiling at 80°.

The *nitric acid salt* prepared from the free base melted at 222–224° with decomposition.

sym-Di-n-butyloxamidine. A 33% aqueous solution of *n*-butylamine containing 73.1 g. (1.0 mole) of amine was treated with purified cyanogen gas *until the solution started to turn milky* (slightly less than 0.5 mole). If the reaction was not stopped at this point the mixture separated into two layers and isolation of a pure product was difficult. After the reaction mixture was cooled in an ice-chest for 24 hours, a crystalline solid formed. Recrystallization from ether gave a 30% yield of white crystals, m.p. 63°.

The *hydrochloride* was formed by saturating an ether solution of the oxamidine with dry hydrogen chloride. Recrystallization from ethyl alcohol yielded white crystals, m.p. 270–272° with decomposition.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2$ HCl: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 44.3; H, 9.0; N, 20.2; Molecular weight, 276.

The *nitric acid salt* prepared as above melted at 206–208° with decomposition.

sym-Diisobutyloxamidine. A 33% aqueous solution of isobutylamine containing 18.5 g. (0.25 mole) of amine was treated as above with 0.12 mole of cyanogen. Recrystallization from ether gave an 11% yield of white crystals, m.p. 79°.

The *hydrochloric acid salt* prepared by saturating the ether filtrate with anhydrous hydrogen chloride gave 11 g. of the hydrochloride, m.p. 300–302° with decomposition, corresponding to an additional 32% yield of free base.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2$ HCl: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 44.4; H, 8.9; N, 20.6; Molecular weight, 277.

The *nitric acid salt* melted at 220–223° with decomposition.

sym-Di-sec-butyloxamidine. A 33% aqueous solution of *sec*-butylamine containing 18.5 g. (0.25 mole) of amine was treated with purified cyanogen gas (0.12 mole) at 0°. After standing in an ice-chest for 24 hours an oil separated.

The *hydrochloride* was formed by saturating an alcoholic solution of the oil with dry hydrogen chloride. Recrystallization from ethyl alcohol gave a 13% yield of white crystals, m.p. 295–297° with decomposition.

Anal. Calc'd for $C_{10}H_{22}N_4 \cdot 2$ HCl: C, 44.3; H, 8.9; N, 20.7; Molecular weight, 271.
Found: C, 43.8; H, 8.8; N, 20.7; Molecular weight, 272.

The *free base* was obtained by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless liquid boiling at 140° with decomposition.

The *nitric acid salt* melted at 220–224° with decomposition.

sym-Diamyloxamidine. A solution of 30 g. (0.35 mole) of *n*-amylamine in 20 ml. of 95% ethyl alcohol and 60 ml. of water was treated with 0.5 mole of purified cyanogen at 0°. Increase in weight indicated that only about 0.25 mole of cyanogen was absorbed. Cooling in Dry Ice caused a separation of two layers but no crystals had formed after two days.

The organic layer was, therefore, separated, washed with water, and extracted with ether. Addition of an equal volume of ethyl alcohol followed by saturation with dry hydrogen chloride produced white crystals of the *hydrochloride salt.* After recrystallization from ethyl alcohol the crystals melted at 278–279° with decomposition; yield, 27%.

Anal. Calc'd for $C_{12}H_{26}N_4 \cdot 2$ HCl: C, 48.2; H, 9.4; N, 18.7; Molecular weight, 299.
Found: C, 48.5; H, 9.4; N, 18.5; Molecular weight, 300.

The *free base* was obtained by neutralizing an aqueous solution of the hydrochloride with a solution of sodium hydroxide. Extraction with ether gave a colorless, oily liquid of high viscosity. It decomposed quickly even though stored in the ice-chest.

The *nitric acid salt* was prepared by neutralizing an ether solution of the free base with concentrated nitric acid. It was a fine, white powder, m.p. 208–209° with decomposition.

Hydrolysis of sym-disubstituted oxamidines. (*a*) *sym*-Dimethyloxamidine (10 g.) was dissolved in 25% aqueous methylamine and allowed to stand in the ice-chest for two days Needle-like crystals separated which, after recrystallization from ethanol, melted at 212°. No depression of melting point resulted from admixture with *dimethyloxamide.* The yield of hydrolyzed product was 3 g.

(*b*) *sym*-Diethyloxamidine dissolved in 33% aqueous ethylamine was allowed to stand in the ice-chest for one week. The solid product, recrystallized from ethanol, melted at 179° and gave no melting point depression with *sym-diethyloxamide.*

(*c*) A water solution containing 6 g. of *sym*-Diethyloxamidine was heated to boiling in an open beaker. A strong ammoniacal odor was noted. After one-half hour the mixture was cooled in ice. A white powder separated which was insoluble in organic solvents and only slightly soluble in water. It did not melt but sublimed above 360°. The compound was evidently *oxamide.* Two grams was recovered.

The same material resulted when *sym*-dibutyloxamidine was boiled with water, with a water-alcohol mixture or with a water-butylamine mixture.

N,N-Tetramethyloxamidine. A 25% aqueous solution of dimethylamine containing 27.5 g. (0.5 mole) of amine was treated with purified cyanogen gas (0.25 mole) at 0°. The reaction mixture was then allowed to stand at room temperature for 24 hours after which it was extracted with ether to remove any cyanoformamidine that had formed or amine that had not reacted. To the water layer was added an excess of conc'd hydrochloric acid and the solution was evaporated carefully on a steam-bath until a thick slush remained. Ethyl alcohol was then introduced to throw out additional solid and after filtration the crystals were purified by recrystallization from hot alcohol. The yield of *hydrochloride* was 11%; white crystals melting at 280° with decomposition.

Anal. Calc'd for $C_6H_{14}N_4 \cdot 2$ HCl: C, 33.5; H, 7.4; N, 26.1; Molecular weight, 215.
Found: C, 33.3; H, 7.7; N, 26.0; Molecular weight, 219.

The free *base* liberated from the hydrochloride by neutralization with sodium hydroxide was extracted from the aqueous solution with ether and without isolation was converted to the *nitric acid salt* by the addition of conc'd nitric acid. White crystals melting at 170° with decomposition resulted.

The ether extract from the original cyanogenation mixture, saturated with dry hydrogen chloride gas, gave a 4% yield of white crystals of *dimethylcyanoformamidine hydrochloride,* m.p. 197–198°.

SUMMARY

The reaction of cyanogen with the aliphatic primary amines from C_1 through n-C_5 to produce symmetrically disubstituted oxamidines is described.

BUFFALO 14, NEW YORK

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF BUFFALO]

THE REACTION OF CYANOGEN WITH ORGANIC COMPOUNDS. III. SUBSTITUTION AND EXCHANGE REACTIONS OF DIALKYLOXAMIDINES[1,2]

HENRY M. WOODBURN, BEACHLEY A. MOREHEAD,[3] AND CHEN MING CHIH

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During our investigation of the behavior of primary aliphatic amines with cyanogen (1) we isolated several times from the ethylamine reaction mixture a product whose analysis, molecular weight, and chemical properties pointed to the structure $C_2H_5NHC(=C_2H_5N)-CNHC_2H_5$ instead of to the expected disubstituted oxamidine. Although we have as yet been unable to discover conditions under which this compound can be obtained without fail directly from ethylamine and cyanogen, its isolation proved that tetrasubstituted oxamidines can exist and led us to study the possibility of converting disubstituted oxamidines into tetrasubstituted compounds by reaction with aliphatic amines.

Two aspects of the problem were investigated, first the possible formation of symmetrical tetrasubstituted oxamidines by the interaction of compounds containing the same alkyl group throughout,

$$RNHC(=HN)-CNHR(=NH) + 2\,RNH_2 \rightarrow RNHC(=RN)-CNHR(=NR) + 2\,NH_3$$

and second, the possible formation of mixed substitution products by the use of an amine containing an alkyl group different from that present in the oxamidine.

$$RNHC(=HN)-CNHR(=NH) + 2\,R'NH_2 \rightarrow RNHC(=R'N)-CNHR(=NR') + 2\,NH_3$$

The first possibility was realized by the isolation in yields of 20–80% of tetramethyl-, tetraethyl-, tetra-*n*-propyl-, tetra-*n*-butyl, and tetraisobutyl-oxamidines from reaction mixtures containing the corresponding disubstituted oxamidines and primary amines.

When amines with different alkyl groups were used, however, instead of replacement of hydrogen by alkyl, interchange of alkyl groups between amine and

[1] From the research program followed by Chen Ming Chih in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

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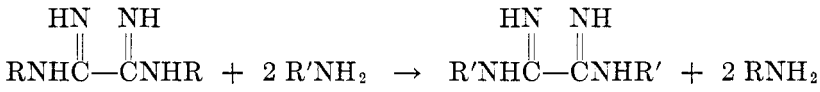
oxamidine occurred in every case where the formula weight of the alkyl group in the amine was greater than that in the oxamidine.



Thus from diethyloxamidine and isopropylamine there was obtained a 40% yield (as hydrochloride) of diisopropyloxamidine, and from diethyloxamidine and aniline there was isolated diphenyloxamidine, the "cyanoaniline" reported by Hoffmann in 1848 (2).

In many cases the exchange of groups was followed by conversion of the new oxamidine to a tetrasubstituted derivative of the heavy alkyl group.

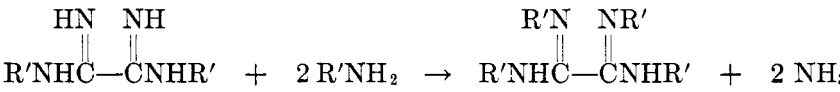
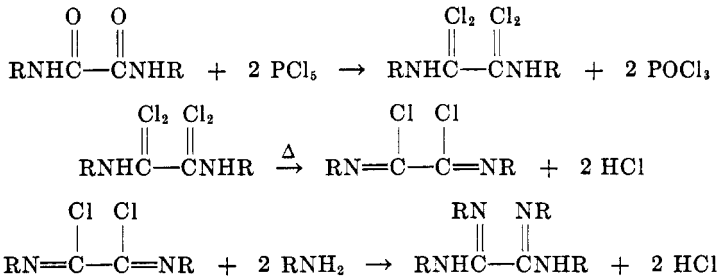


Table I lists the results of 27 reactions. In all cases except those noted, the oxamidines were used in the form of their hydrochlorides since the yield of product was considerably better under those conditions than when the free base was used.

Carbon, hydrogen, and nitrogen analyses were carried out on all tetra compounds. In addition the tetraethyl and tetrapropyl derivatives were synthesized for comparison by treatment of the corresponding imidic chlorides with the alkyl amine.



This is an application to aliphatic compounds of a reaction discovered by Bauer (3) for the preparation of tetraaryloxamidines.

Disubstituted compounds formed by exchange reactions were identified by mixed melting point with compounds produced directly from cyanogen and amine (1).

Reactions 26 and 27 were carried out in the hope of obtaining secondary amine derivatives either by substitution or exchange. The reactants were recovered without change in both cases.

Generally speaking, the tetraalkyloxamidines were obtained in the form of white, silky or fibrous crystals. The two lower members were extremely soluble in water, less so in ethanol, and only slightly soluble in ether and petroleum ether. The water-solubility decreased with increasing molecular weight; the ether solubility increased.

All the compounds were stable to moderate heating (100°), could be boiled for short periods with water without decomposition, and in the one case investigated would not undergo ammonolysis on prolonged boiling with alcoholic ammonia.

TABLE I

REACTIONS OF OXAMIDINES WITH AMINES

REACTANTS		YIELD, %	PRODUCT	M.P., °C.
Oxamidine hydrochloride	Amine			
1. Dimethyl	Methyl	70	Tetramethyloxamidine	243–245 dec.
2. Diethyl	Ethyl	21	Tetraethyloxamidine	150
3. Di-*n*-propyl	*n*-Propyl	83	Tetrapropyloxamidine	110
4. Diisopropyl	Isopropyl	0	Oxamidine recovered	
5. Di-*n*-butyl	*n*-Butyl	76	Tetrabutyl oxamidine	86
6. Di-*sec*-butyl	*sec*-Butyl	0	Oxamidine recovered	
7. Diisobutyl	Isobutyl	V. low	Tetraisobutyloxamidine	79–80
8. Di-*n*-amyl	*n*-Amyl	[a]		
9. Diethyl (base)	Ethyl	V. low	Tetraethyloxamidine	150
10. Di-*n*-propyl (base)	*n*-Propyl	V. low	Tetrapropyloxamidine	110
11. Di-*n*-butyl (base)	*n*-Butyl	18	Tetrabutyloxamidine	86
12. Diisobutyl (base)	Isobutyl	V. low	Tetraisobutyloxamidine	79–80
13. Dimethyl	Ethyl	25	Tetraethyloxamidine	150
14. Diethyl	*n*-Propyl	33	Tetrapropyloxamidine	110
15. Diethyl	Isopropyl	40	Diisopropyloxamidine hydrochloride	287–290 dec.
16. Diethyl	*n*-Butyl	90	Tetrabutyloxamidine	86
17. Di-*n*-propyl	*n*-Butyl	90	Tetrabutyloxamidine	86
18. Dimethyl	Isobutyl	32	Tetraisobutyloxamidine	79–80
19. Diethyl	Isobutyl	17[b]	Diisobutyloxamidine hydrochloride	290 dec.
20. Diethyl	Isobutyl	43[c]	Tetraisobutyloxamidine	79–80
21. Diethyl	*sec*-Butyl	V. low	Di-*sec*-butyloxamidine hydrochloride	295 dec.
22. Diethyl	*n*-Amyl		Tarry mass	
23. Di-*n*-amyl	*n*-Propyl		Tarry mass	
24. Diethyl	Aniline	73	Diphenyloxamidine	210
25. Di-*n*-amyl	Aniline	V. low	Diphenyloxamidine	210
26. Diethyl	Diethyl	0	Oxamidine recovered	
27. Diethyl	Di-*n*-butyl	0	Oxamidine recovered	

[a] The product was impossible to purify. The physical appearance of the impure material resembled that of other tetra compounds. [b] Reaction time, five minutes. [c] Reaction time, one hour.

The tetramethyl derivative differed from the remainder of the series in possessing an unusually high melting point and in the granular appearance of its crystals. The latter property may have resulted from the fact that it was the only compound that was purified by ethanol recrystallization.

It is noteworthy that in certain cases the yield of tetra compound was better from an exchange reaction than from a substitution process.

EXPERIMENTAL

SUBSTITUTION REACTIONS

sym-Tetramethyloxamidine. An excess of methylamine was introduced into a pressure bottle containing 3.0 g. (0.016 mole) of *sym*-dimethyloxamidine dihydrochloride and allowed to stand at room temperature for 24 hours. The bottle was cooled in a Dry-Ice chest until the contents became solid, whereupon 20 ml. of ethanol was added to dissolve methylamine hydrochloride and the mixture filtered. The solid residue was recrystallized from hot ethanol resulting in granular crystals, m.p. 243–245° with decomposition; yield, 1.6 g. or 70%.

Anal. Calc'd for $C_6H_{14}N_4$: C, 50.7; H, 9.9; N, 39.4.
Found: C, 50.7; H, 10.3; N, 39.8.

sym-Tetraethyloxamidine. (*a*) An excess of ethylamine was introduced into a pressure bottle containing 2.5 g. (0.012 mole) of *sym*-diethyloxamidine dihydrochloride and allowed to stand at room temperature for 12 hours. Cooling in an ice-bath caused the separation of a solid which was filtered and extracted with ether, leaving a residue of ethylamine hydrochloride. The ether extract on evaporation gave white crystals, which were taken up in ether and recovered by slow evaporation several times to remove traces of ethylamine. The final product was in the form of white, silky, fibrous crystals melting at 150°, easily soluble in ether, alcohol, and water. The yield of pure material was 0.5 g. or 21%.

Anal. Calc'd for $C_{10}H_{22}N_4$: C, 60.6; H, 11.1; N, 28.3.
Found: C, 60.0; H, 11.1; N, 28.2.

(*b*) An excess of ethylamine was reacted in a pressure bottle at room temperature with 4.3 g. (0.03 mole) of *sym*-diethyloxamidine to give a very small yield of silky, fibrous crystals melting at 150°.

sym-Tetra-n-propyloxamidine. (*a*) An excess of *n*-propylamine was refluxed with 3 g. (0.013 mole) of *sym*-di-*n*-propyloxamidine dihydrochloride for five hours. The mixture was cooled, filtered to remove precipitated propylamine hydrochloride, and poured into 200 ml. of water. An oily mass of crystals separated which was dried and recrystallized from petroleum ether. The product in the form of white, silky, fibrous crystals, melted at 110° and weighed 2.5 g., an 80% yield.

Anal. Calc'd for $C_{14}H_{30}N_4$: C, 66.2; H, 11.8; N, 22.0.
Found: C, 66.1; H, 12.3; N, 22.1.

(*b*) An excess of *n*-propylamine refluxed with 3 g. (0.018 mole) of *sym*-di-*n*-propyloxamidine for five hours gave a very small yield of silky, fibrous crystals melting at 110°.

sym-Tetra-n-butyloxamidine. (*a*) An excess of *n*-butylamine was refluxed with 3 g. (0.011 mole) of *sym*-di-*n*-butyloxamidine dihydrochloride for three hours and the product worked up as described above (see *n*-propyl). A 76% yield of white, silky, fibrous crystals melting at 86° resulted.

Anal. Calc'd for $C_{18}H_{38}N_4$: C, 69.7; H, 12.3; N, 18.1.
Found: C, 69.7; H, 12.4; N, 18.4.

(*b*) An excess of *n*-butylamine was refluxed with 4.9 g. (0.025 mole) of *sym*-di-*n*-butyloxamidine in 200 ml. of ether for 24 hours. After removal of the ether by distillation the liquid residue was poured into 200 ml. of water producing a mass of fibrous crystals. Recrystallization from ether gave an 18% yield of material melting at 86°.

sym-Tetraisobutyloxamidine. (*a*) An excess of isobutylamine was refluxed with 3.0 g. (0.011 mole) of *sym*-diisobutyloxamidine dihydrochloride for 12 hours. After cooling, the mixture was poured into ice-water and the heavy, yellow mass which separated was filtered off. Recrystallization from petroleum ether gave fine white needles, m.p. 79–80°; but the yield of pure material was very low.[4]

[4] Better yields of this compound were obtained by the exchange reactions 18 and 20.

Anal. Calc'd for $C_{18}H_{38}N_4$: C, 69.7; H, 12.3; N, 18.1.
Found: C, 69.5; H, 12.7; N, 18.3.

(*b*) An excess of isobutylamine refluxed for two hours with 2.0 g. (0.007 mole) of *sym*-diisobutyloxamidine gave a very low yield of material melting at 79–80°.

UNSUCCESSFUL REACTIONS

Sym-diisopropyloxamidine dihydrochloride with isopropylamine. An excess of isopropylamine was refluxed with 2 g. (0.01 mole) of *sym*-diisopropyloxamidine dihydrochloride for 20 hours. Crystals of isopropylamine hydrochloride were recovered from the cooled mixture. The filtrate, allowed to evaporate slowly, gave a heavy, oily residue which would not crystallize. It was taken up in alcohol and treated with dry hydrogen chloride. The solid formed, melted with decomposition at 290° and gave no depression of melting point when mixed with *sym*-diisopropyloxamidine dihydrochloride. The recovery of the oxamidine was about 90%.

Sym-di-sec-butyloxamidine dihydrochloride with sec-butylamine. An excess of *sec*-butylamine refluxed with *sym*-di-*sec*-butyloxamidine dihydrochloride for 3 hours gave crystals of *sec*-butylamine hydrochloride but no tetra-substitution product. The filtrate, treated with alcohol and hydrogen chloride was found to contain only *sym*-di-*sec*-butyloxamidine dihydrochloride.

Sym-di-n-amyloxamidine dihydrochloride with n-amylamine. An excess of *n*-amylamine was refluxed with 3 g. (0.01 mole) of *sym*-di-*n*-amyloxamidine dihydrochloride for 12 hours. The mixture was poured into ice-water and the tarry mass which resulted was extracted with ether. Evaporation gave a solid made up of crystals and tar. Repeated attempts at purification failed to give a product sufficiently clean to justify analysis or the measurement of physical constants.

EXCHANGE REACTIONS

Tetraethyloxamidine from dimethyloxamidine hydrochloride and ethylamine. An excess of ethylamine was placed in a pressure bottle containing 1.1 g. (0.006 mole) of *sym*-dimethyloxamidine dihydrochloride and allowed to stand at room temperature for 24 hours. Cooling in ice caused the separation of crystals which on recrystallization from ether melted at 150°. A mixed melting point determination proved them to be tetraethyloxamidine; yield, 0.3 g. or 25%.

Tetrapropyloxamidine from diethyloxamidine hydrochloride and n-propylamine. An excess of *n*-propylamine was refluxed with 2 g. (0.01 mole) of *sym*-diethyloxamidine dihydrochloride for 3 hours. The mixture was cooled, separated from crystals of amine hydrochloride which deposited, and poured into water. The solid which was produced was recrystallized from petroleum ether giving crystals that melted at 110°. No depression of melting point resulted by admixture with *sym*-tetra-*n*-propyloxamidine. The yield was 33%.

Diisopropyloxamidine hydrochloride from diethyloxamidine hydrochloride and isopropylamine. An excess of isopropylamine was refluxed with 1 g. (0.005 mole) of *sym*-diethyloxamidine dihydrochloride for 12 hours. The reaction mixture was cooled in an ice-bath, filtered to remove amine hydrochlorides, and allowed to evaporate. Attempts to crystallize the oily residue were ineffective, consequently, it was taken up in alcohol and treated with anhydrous hydrogen chloride. A 40% yield of *sym*-diisopropyloxamidine dihydrochloride melting with decomposition at 287–290° was obtained.

Tetrabutyloxamidine from diethyloxamidine hydrochloride and n-butylamine. An excess of *n*-butylamine refluxed for 5 hours with 2 g. (0.01 mole) of *sym*-diethyloxamidine dihydrochloride gave a 90% yield of *sym*-tetrabutyloxamidine (m.p. 86°) when the reaction mixture was worked up in the usual way. Identification was made by mixed melting point.

Tetrabutyloxamidine from dipropyloxamidine hydrochloride and n-butylamine. A 90% yield of *sym*-tetrabutyloxamidine was obtained from the refluxing of *sym*-di-*n*-propyloxamidine dihydrochloride with excess *n*-butylamine.

Tetraisobutyloxamidine from dimethyloxamidine hydrochloride and isobutylamine. An

excess of isobutylamine was refluxed with 2.0 g. (0.01 mole) of *sym*-dimethyloxamidine dihydrochloride for two hours and the mixture poured into cold water. The yellow solid which separated was recrystallized from petroleum ether giving fine, white needles melting at 79–80° which gave no melting point depression with a sample of tetraisobutyloxamidine. The yield was 32%.

Diisobutyloxamidine hydrochloride from diethyloxamidine hydrochloride and isobutylamine. An excess of isobutylamine was refluxed with 2.5 g. (0.012 mole) of *sym*-diethyloxamidine dihydrochloride for *five minutes*. The resulting mixture was diluted with ether and the insoluble amine hydrochlorides filtered off. Evaporation of the filtrate left an oily liquid which was taken up in alcohol and saturated with anhydrous hydrogen chloride. White crystals melting at 290° with decomposition, and giving no melting point depression with *sym*-diisobutyloxamidine dihydrochloride were obtained. The yield was 17%.

Tetraisobutyloxamidine from diethyloxamidine hydrochloride and isobutylamine. An excess of isobutylamine was refluxed with 3.0 g. (0.015 mole) of *sym*-diethyloxamidine dihydrochloride *for one hour*. The resulting mixture was poured into cold water and a heavy yellow mass separated weighing about 2 g. (43% yield). Recrystallization from petroleum ether gave fine white needles melting at 79–80° and giving no melting point depression with a sample of tetraisobutyloxamidine.

Di-sec-butyloxamidine hydrochloride from diethyloxamidine hydrochloride and sec-butylamine. Sym-diethyloxamidine dihydrochloride refluxed for 2 hours with excess *sec*-butylamine gave a very low yield of *sym*-di-*sec*-butyloxamidine isolated as the hydrochloride.

Diphenyloxamidine from diethyloxamidine hydrochloride and aniline. Three grams (0.014 mole) of *sym*-diethyloxamidine dihydrochloride in 80 ml. of alcohol was refluxed for 3 hours with 3 g. (0.032 mole) of aniline. Crystals were formed as the solution cooled. These, recrystallized from benzene, melted at 210° and gave no melting point depression when mixed with *sym*-diphenyloxamidine prepared from cyanogen and aniline (2). The yield was 73%.

Diphenyloxamidine from diamyloxamidine hydrochloride and aniline. A mixture of *sym*-diamyloxamidine dihydrochloride, alcohol, and aniline was refluxed as above. Three-days standing was required before crystals of *sym*-diphenyloxamidine (m.p. 210°) appeared. The yield was very low.

Unsuccessful reactions. The following combinations gave tarry masses from which no crystalline product could be isolated: *sym*-diethyloxamidine dihydrochloride and *n*-amylamine, *sym*-di-*n*-amyloxamidine dihydrochloride and *n*-propylamine. The original oxamidine was recovered when *sym*-diethyloxamidine dihydrochloride was refluxed (*a*) for 12 hours with excess of the secondary amine, di-*n*-butylamine and (*b*) for 2 days with the secondary amine, diethylamine.

sym-Tetraethyloxamidine from diethyloxamide (3). Into a flask fitted with a fractionating-column was introduced 200 ml. of dry toluene, 3.6 g. (0.025 mole) of *sym*-diethyloxamide, and 10.4 g. (0.05 mole) of phosphorus pentachloride. Hydrogen chloride was evolved slowly and the mixture turned yellow. After about one-half hour a water aspirator was attached to the apparatus and heat was applied gradually until the distillation temperature was reached; most of the phosphorus oxychloride and toluene was removed in this way. (The presence of toluene allowed the phosphorus oxychloride to be distilled off at a temperature below the decomposition temperature of the imidic chloride.)

The residue was cooled in Dry Ice and an excess of anhydrous ethylamine was introduced. A tarry crystalline mass formed as the mixture came to room temperature and the unreacted ethylamine evaporated. Triethylamine proved to be the best medium for the separation of the product from tarry impurities, first by simple agitation and decantation, later by extraction of the tarry residue with hot solvent. A 34% yield of silky, fibrous crystals melting at 150° was obtained.

sym-Tetrapropyloxamidine from dipropyloxamide. Treatment of *sym*-di-*n*-propyloxamide with phosphorus pentachloride and *n*-propylamine in the manner described above gave a low yield of a product melting at 110°.

SUMMARY

Symmetrically disubstituted oxamidines react with primary amines either to yield *sym*-tetrasubstituted oxamidines by substitution of alkyl for hydrogen or to yield a second disubstituted oxamidine by exchange of alkyl groups.

BUFFALO 14, NEW YORK

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CONTRIBUTION NO. 153 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

HYDROLYSIS OF ARYLACETONITRILES

WILHELM WENNER

Received October 31, 1949

Arylacetic acids are generally prepared by hydrolysis of the corresponding nitriles (7). Almost every text-book of organic chemistry describes this important reaction for the special case of phenylacetic acid (1, 3).

Difficulties encountered when the known methods for saponification were applied to large scale manufacture prompted the following investigation, which resulted in a simple method for the hydrolysis of arylacetonitriles.

It was found that *rapid stirring with aqueous conc'd hydrochloric acid* at moderate temperatures readily leads to hydrolysis of the arylacetonitriles without the use of an organic solvent as solubilizer. Depending upon the conditions, free arylacetic acids or their amides may thus be prepared in high yields.

Rapid stirring of benzyl cyanide with conc'd hydrochloric acid leads to the formation of a clear solution of phenylacetamide. The reaction takes place even at temperatures as low as 10°. However, the hydrochloric acid has to be at least of about 30% strength to effect conversion of the nitrile into the amide. Hydrobromic acid will not lead to saponification under similar conditions. Up to temperatures of 50° the resulting phenylacetamide is not easily saponified further. To prepare phenylacetamide, therefore, the homogeneous solution obtained by stirring benzyl cyanide with conc'd hydrochloric acid is simply diluted with water, whereupon the amide crystallizes.

Further hydrolysis to free phenylacetic acid proceeds rather slowly when the initial homogeneous solution is heated higher. However, the formation of phenylacetic acid is speeded up considerably when the amide is heated with more dilute acid. In order to prepare free phenylacetic acid, the original solution of the amide is, therefore, diluted with water and is then refluxed. In a few hours hydrolysis is complete.

Homologs of benzyl cyanide likewise form the corresponding amides when they are stirred with conc'd hydrochloric acid at temperatures below 100°. Up to about 60° the amide is formed, which in these cases remains undissolved. At higher temperatures the corresponding acids result. Several polynuclear arylacetonitriles were saponified in the same way without difficulty.

Alkoxy substituted nitriles yield the corresponding amides under the conditions specified if the reaction temperature does not exceed 50–60°. At higher temperatures the conc'd hydrochloric acid will lead to cleavage of the alkoxy groups. Saponification of the amides to the free acids is accomplished by diluting the mixture after formation of the amides and subsequent boiling of the mixture.

The method is a striking illustration of the usefulness and importance of stirring in chemical reactions. It provides a simple procedure for the technical preparation of several commercially important arylacetic derivatives, and it has been found to be superior to the known saponification methods in the course of our research work in numerous instances.

EXPERIMENTAL

The melting points are uncorrected. The periods of time given to effect solution apply to stirrer speeds of about 700–1000 r.p.m.

1. *Phenylacetamide:* Benzyl cyanide (100 g.) and 200 cc. of conc'd hydrochloric acid were stirred (starting at 30°) for 2 hours. The temperature rose to 40° during the first hour and remained there. Homogeneity resulted about 10 minutes later. Ice-cooling and slow addition of 400 cc. of water gave 100 g. of crude phenylacetamide. The mother liquor contained small amounts of phenylacetic acid.

When carried out at +4–6° the reaction requires about 10 hours; at 60–65° it is complete in about 25–30 minutes.

2. *Phenylacetic acid:* Stirring 200 g. of benzyl cyanide with 800 cc. of conc'd hydrochloric acid at 40–50° yields a homogeneous solution about 1–2 hours later. When this solution is heated to 80–90° for 10 more hours, phenylacetic acid is formed and separates as an oil which solidifies on cooling. About 200 g. of crude acid, m.p. 72–75°, is obtained.

When the homogeneous solution of phenylacetamide, formed from 200 g. of benzyl cyanide and 800 cc. conc'd hydrochloric acid by stirring at 50°, is diluted with 800 cc. of water (precipitating most of the phenylacetamide) and refluxed for about 4 hours, a yield of about 200 g. of phenylacetic acid is obtained.

3. *4-Methylphenylacetic acid:* 4-Methyl-α-tolunitrile (50 g.) and 200 cc. of conc'd hydrochloric acid is stirred at 50° for 8 hours. The mixture is cooled, and 200 cc. of water is added. A solid forms which is filtered and washed with water and ether. It is practically pure 4-methylphenylacetamide. Recrystallization from benzene gives the pure amide of m.p. 180–182°

4. *4-Isopropylphenylacetic acid:* 4-Isopropyl-α-tolunitrile (20 g.) (2) and 200 cc. of conc'd hydrochloric acid are stirred for 10 hours at 90–100°. The mixture, which does not become homogeneous, is then diluted with 200 cc. of water, cooled to room temperature, and extracted with ether. 4-Isopropyl-α-toluic acid is extracted with sodium carbonate solution from the ether solution. The acid is liberated by the addition of hydrochloric acid, extracted with ether, and the ether solution distilled to dryness; yield 20 grams. Vacuum distillation gives the pure acid of $b.p._{14}$ 170–174°, m.p. 38–40°.

5. *4-Isopropylphenylacetamide:* 4-Isopropyl-α-tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred for 8 hours at 50–55°. Water (100 cc.) is added, and the mixture is cooled; twenty grams of crude 4-isopropylphenylacetamide is obtained. Recrystallization from toluene yields the pure compound of m.p. 156–157°.

6. *1-Naphthaleneacetic acid:* 1-Naphthaleneacetonitrile (20 g.) is stirred with 100 cc. of conc'd hydrochloric acid for 5 hours at 60–70°. Water (50 cc.) is then added, and the mixture is refluxed with stirring for 10 hours. After cooling, ether is added. The ether layer is separated and extracted with sodium carbonate solution. The extract is acidified and extracted with benzene. The benzene layer is concentrated to a small volume, and ligroin is added. Yield, 14 g. of 1-naphthaleneacetic acid, m.p. 111–113°.

7. *1-Naphthaleneacetamide:* 1-Naphthaleneacetonitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred for 10 hours at about 40°. Shortly after the start of the reaction crystals of the amide appear. At the end of 10 hours about 200 cc. of water is added, and the amide is filtered, weight 12 g. Recrystallization from benzene or alcohol yields the pure compound of m.p. 175°.

The mother liquor contains some free acid which is isolated as described in Experiment 6.

8. *5,6,7,8-Tetrahydro-2-naphthaleneacetic acid:* 5,6,7,8-Tetrahydro-2-naphthaleneacetonitrile (6 g.) is stirred with 60 cc. of conc'd hydrochloric acid at 70–80° for 8 hours. Water is added after cooling, and the mixture is extracted with ether. The ether solution is extracted repeatedly with sodium carbonate solution. The combined sodium carbonate extracts are acidified and extracted with ether. The ether solution is evaporated, leaving 6 g. of crude 5,6,7,8-tetrahydro-2-naphthaleneacetic acid. It is obtained pure by crystallization from benzene-petroleum ether and melts at 95–97° (6).

9. *5,6,7,8-Tetrahydro-2-naphthaleneacetamide:* 5,6,7,8-Tetrahydro-2-naphthaleneacetonitrile (15 g.) is stirred with 75 cc. of conc'd hydrochloric acid at 25°. The temperature is raised after 1 hour to 50° for 4 more hours. An oil separates which solidifies upon the addition of 150 cc. of water. The crude amide (15 g.) is recrystallized from benzene, yielding pure 5,6,7,8-Tetrahydro-2-naphthaleneacetamide of m.p. 142°.

10. *4-Methoxyphenylacetic acid:* 4-Methoxy-α-tolunitrile (50 g.) and 250 cc. of conc'd hydrochloric acid are stirred at room temperature for 15 hours. Water (250 cc.) is added, and the mixture is heated with stirring to 70° for 15 hours. After cooling, the solution is extracted with ether. The ether solution is evaporated, and the residue is distilled *in vacuo* to give 43 g. of 4-methoxy-α-toluic acid, b.p. 184–186°. The acid solidifies on cooling and on recrystallization from benzene-petroleum ether melts at 84–86°.

11. *4-Methoxyphenylacetamide:* 4-Methoxy-α-tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred and heated to 50° for 3 hours. Water (200 cc.) is added; the amide crystallizes and is filtered. It is extracted with dilute sodium carbonate solution to remove a small amount of free acid (about 2 g.). Yield, 17 g. of amide, m.p. 188°.

12. *3,4-Dimethoxyphenylacetic acid (homoveratric acid):* 3,4-Dimethoxy-α-tolunitrile (100 g.) is stirred with 200 cc. of conc'd hydrochloric acid, the temperature being kept below 40°. After about 3 hours, when the nitrile is dissolved, the temperature is raised to 50° for 2 more hours. Water (700 cc.) is added, and the mixture is refluxed with stirring. A short time later the solution becomes turbid, and an oil separates. After 7 hours the mixture is cooled to 0°. The oil solidifies and is filtered. Crude homoveratric acid, containing one molecule of water of crystallization, is obtained in about 95% yield. Recrystallization from benzene yields the pure acid, m.p. 99°.

13. *3,4-Dimethoxyphenylacetamide:* 3,4-Dimethoxy-α-tolunitrile (500 g.) is stirred with 1000 cc. of conc'd hydrochloric acid at room temperature. The nitrile dissolves slowly, the temperature rising about 5°. About 2–3 hours later the amide starts to crystallize. In the course of about 3 more hours a thick slurry is formed. About 2000 cc. of water is added, and the mixture is filtered, yielding 470–500 g. of homoveratramide. It contains small amounts of homoveratric acid which can be removed with sodium carbonate. The amide is crystallized from water and melts then at 142°.

14. *2,3-Dimethoxyphenylacetic acid (o-homoveratric acid):* 2,3-Dimethoxy-α-tolunitrile (20 g.) and 100 cc. of conc'd hydrochloric acid are stirred at room temperature. After 3 hours 300 cc. of water is added, and the mixture is heated with stirring to 80° for 10 hours. An oil separates which is extracted with ether after cooling. The ether layer is extracted with sodium carbonate solution. The aqueous extract is acidified, and the free acid is dissolved in ether. Evaporation of the ether layer leaves 21 g. of crude 2,3-dimethoxyphenylacetic acid which crystallizes on standing. Vacuum distillation yields the pure acid, b.p. 235–240°/20 mm. and m.p. 82–83°.

15. *2,3-Dimethoxyphenylacetamide:* 2,3-Dimethoxybenzyl cyanide (20 g.) is stirred with 100 cc. of conc'd hydrochloric acid for 4 hours at 20–30°. The solution is diluted with 300 cc. of water. The amide remains in solution and is extracted with chloroform. The chloroform extract is distilled to dryness, yielding 20 g. of crude 2,3-dimethoxyphenylacetamide. Recrystallization from benzene gives the pure amide, m.p. 109–111°.

Anal. Calc'd for $C_{10}H_{13}NO_3$: C, 61.52; H, 6.71.
Found: C, 61.79; H, 6.63.

16. *4-Phenoxyphenylacetic acid:* 4-Phenoxybenzyl chloride (4) is refluxed with sodium cyanide in aqueous alcohol, yielding 4-phenoxy-α-tolunitrile of $b.p._{0.15}$ 155–160°.

Twenty grams of the nitrile is stirred with 200 cc. of conc'd hydrochloric acid at 80–90° for 16 hours. After cooling, 300 cc. of water is added, and the mixture is extracted with ether. The acid is extracted from the ether with dilute sodium carbonate solution, precipitated with dilute hydrochloric acid, and is taken up in ether. Evaporation of the ether gives 20 g. of 4-phenoxyphenylacetic acid. Recrystallization from dilute acetic acid gives the pure acid, m.p. 55–56°.

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.67; H, 5.30.
Found: C, 73.94; H, 5.22.

17. *2-Dibenzofuranacetic acid:* Ten grams of 2-cyanomethyldibenzofuran (5), m.p. 89–90°, is stirred with 150 cc. of conc'd hydrochloric acid for 15 hours at 80–90°. Water (200 cc.) is added, the crystals are filtered, and then stirred with sodium carbonate solution. Most of the material dissolves. The solution is filtered and acidified with hydrochloric acid. The precipitated acid is filtered and washed with water. Recrystallization from 70% acetic acid yields pure 2-dibenzofuranacetic acid, m.p. 162–163°; yield, 8 g.

Anal. Calc'd for $C_{14}H_{10}O_3$: C, 74.33; H, 4.46.
Found: C, 74.23; H, 4.84.

Acknowledgment. I am indebted to Dr. Al Steyermark for the microanalyses.

SUMMARY

Vigorous stirring with aqueous conc'd hydrochloric acid at low temperatures converts arylacetonitriles into the corresponding amides. These amides are easily saponified further to the free acids by heating with dilute hydrochloric acid.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. IX. ADDITIONAL DERIVATIVES OF TRICHLOROSILANE AND THEIR ALKALINE HYDROLYSIS[1, 2]

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INTRODUCTION

This work continues the investigation which has already been partially reported by Jenkins, Lavery, Guenther, and Post (1). The emphasis here was placed on the preparation of certain trisubstituted derivatives of trichlorosilane by the conventional Grignard method, then the careful repetition of these processes with different proportions of reactants to prepare partially substituted products. Data covering these products are shown in Table I.

Physical properties of compounds prepared incidental to the identification of the above, or for their own value but which have previously been prepared will be found in Table II.

DISCUSSION

The compounds listed in Table I and some of those in Table II were prepared by the action of trichlorosilane on the proper Grignard reagent as outlined in the Experimental part. Grignard reagents were prepared from chlorides to eliminate possible halogen interchange between unused Grignard reagent and the desired silicon compound. Two Grignard reagents were used in series to prepare compounds with more than one kind of radical per molecule.

The well known reaction of a compound containing silane hydrogen with alkali by which hydrogen is evolved was also studied. It was felt that if a quaternary ammonium hydroxide was used there might be a possibility that the hydrogen anion, instead of forming a hydrogen molecule with a hydrogen cation, might possibly form a hydrocarbon. No tertiary amines or hydrocarbons were isolated in any of the three runs made with these compounds. The only isolable gas was hydrogen. The reaction could be represented as before, by the following equations:

$$HSi(C_2H_5)_3 + (OH)^- \rightarrow (C_2H_5)_3SiOH + (H)^+$$
$$(H)^+ + (H)^- \rightarrow H_2$$
$$2\ (C_2H_5)_3SiOH \rightarrow HOH + (C_2H_5)_3SiOSi(C_2H_5)_3$$

These results were obtained by the treatment of triethylsilane with tetramethylammonium hydroxide, triethylsilane with tetraethylammonium hydroxide, and tribenzylsilane with tetraethylammonium hydroxide.

[1] This paper represents a portion of the thesis presented by the first author in partial fulfillment of the requirements of the degree of Doctor of Philosophy at the University of Buffalo.

[2] The work on which this paper is based comprises a portion of the program of research being carried out under contract with the Office of Naval Research.

EXPERIMENTAL

Triethylsilane was prepared in accordance with methods already in the literature (2), b.p. 107° (755 mm.) [literature (2) 106.8–107.2° (760 mm.)].

n-Butyldichlorosilane. *n*-Butylmagnesium chloride (0.35 mole) was added to 38 cc. (0.38 mole) of trichlorosilane in 200 cc. of anhydrous ether with cooling and stirring. The reaction mixture was refluxed for 17 hours, magnesium salts were removed by filtration, and the filtrate distilled. n-$C_4H_9SiHCl_2$, b.p. 130–139° (745 mm.), d_{27}^{27} 1.0066, n_D^{20} 1.4275, yield 4%.

TABLE I

NEW COMPOUNDS

COMPOUND	B.P., °C. (MM.)	$d_{t°}^{t°}$	$n_D^{t°}$
$C_4H_9SiHCl_2$	140–139 (745)	1.0066_{27}^{27}	1.4275^{20}
$(C_4H_9)_2SiHCl$	50– 51 (2)	$0.9940_{21.5}^{21.5}$	1.4372^{20}
$HSi(C_4H_9)_3$	86– 87 (2.5)	0.9312_{25}^{25}	1.4400^{20}
iso-$C_4H_9SiHCl_2$	121–124 (760)	1.0009_{26}^{26}	1.4249^{25}
(iso-$C_4H_9)_2SiHCl$	160–167 (749.4)	0.9945_{24}^{24}	1.4340^{20}
iso-$C_5H_{11}SiHCl_2$	143–148 (760)	1.0005_{26}^{26}	1.4304^{28}
(iso-$C_5H_{11})_2SiHCl$	199–202 (741)	0.9944_{28}^{28}	1.4420^{15}
$HSi(C_6H_{11})_3$	170–176 (4)	0.9981_{24}^{24}	1.4968^{20}
$C_6H_5CH_2SiH(CH_3)Cl$	76– 83 (6)	1.0020_{27}^{27}	1.5160^{20}
$C_6H_5CH_2SiH(CH_3)_2$	53– 55 (3)	0.9486_{20}^{20}	1.5040^{20}
$(C_6H_5CH_2)_2SiHCH_3$	131–140 (3)	0.9936_{20}^{20}	1.5650^{20}

TABLE II

KNOWN COMPOUNDS

COMPOUND	B.P., °C.	MM.	M.P., °C.	$d_{t°}^{t°}$	n_D^{20}
$HSi(C_2H_5)_3$[a]	107	755			
$(C_2H_5)_3SiOH$[b]	154	760		0.8647_4^{20}	1.4329
$[(C_2H_5)_3Si]_2O$[c]	231	760		$.8590^0$	1.4340
$HSi(CH_2C_6H_5)_3$[d]			91		
$(C_6H_5CH_2)_3SiOH$[e]			106		
$[(C_6H_5CH_2)_3Si]_2O$[f]			205		

[a] B.p. 106.8–107.2° (2). [b] d_4^{20} 0.8647; n_D^{20} 1.4363 (3); d_4^{20} 0.8638, n_D^{20} 1.4329 (5). [c] B.p. 231° (760 mm.), d^0 0.8590 (8); n_D^{20} 1.4340, 1.4332 (4). [d] M.p. 90–91° (1). [e] M.p. 106° (7). [f] M.p. 205° (6).

Anal. Calc'd for $C_4H_{10}Cl_2Si$: Cl, 45.25. Found: Cl, 45.20.

Di-n-butylchlorosilane. The above procedure was repeated but with 0.4 mole of Grignard and 0.2 mole of trichlorosilane. (n-$C_4H_9)_2SiHCl$, b.p. 50–51° (2 mm.), $d_{21.5}^{21.5}$ 0.9940, n_D^{20} 1.4372.

Anal. Calc'd for $C_8H_{19}ClSi$: Cl, 19.89. Found: Cl, 19.65.

Tri-n-butylsilane. The above procedure was again repeated using 0.5 mole of Grignard and 0.1 mole of trichlorosilane. $HSi(C_4H_9$-$n)_3$, b.p. 86–87° (2.5 mm.), d_{25}^{25} 0.9312, n_D^{20} 1.4400, yield 5%.

Anal. Calc'd for $C_{12}H_{28}Si$: Mol. wt., 200. Found: Mol. wt. (cryoscopic in benzene) 206.

Isobutyldichlorosilane. The Grignard to trichlorosilane molar ratio in this preparation

was 0.25 to 0.30. iso-$C_4H_9SiHCl_2$, b.p. 121–124° (760 mm.), d_{26}^{26} 1.0009, n_D^{25} 1.4249, yield 3.5%.

Anal. Calc'd for $C_4H_{10}Cl_2Si$: Cl, 45.25. Found: Cl, 45.20.

Diisobutylchlorosilane. This preparation was carried out using 0.3 mole of Grignard reagent and 0.15 mole of trichlorosilane. (iso-$C_4H_9)_2SiHCl$, b.p. 160–167° (749.4 mm.), d_{24}^{24} 0.9945, n_D^{20} 1.4340, yield 2%.

Anal. Calc'd for $C_8H_{19}ClSi$: Cl, 19.89. Found: Cl, 19.80.

Isoamyldichlorosilane. Isoamylmagnesium chloride (350 cc., 0.35 mole) was added to 40 cc. (0.4 mole) of trichlorosilane in 500 cc. of anhydrous ether with cooling to 0° and stirring. The reaction mixture was allowed to stand for 16 hours, then refluxed for 2 hours. After removal of solid inorganic products the filtrate was distilled. iso-$C_5H_{11}SiHCl_2$, b.p. 143–148° (760 mm.), d_{26}^{26} 1.0005, n_D^{28} 1.4304.

Anal. Calc'd for $C_5H_{12}Cl_2Si$: Cl, 41.55. Found: Cl, 41.55, 41.50.

Diisoamylchlorosilane. The procedure outlined above was again followed save that the molar amounts of Grignard and trichlorosilane were 0.30 and 0.15 respectively. (iso-$C_5H_{11})_2SiHCl$, b.p. 199–202° (741 mm.), d_{28}^{28} 0.9944, n_D^{15} 1.4420, yield 1.5%.

Anal. Calc'd for $C_{10}H_{23}ClSi$: Cl, 17.20. Found: Cl, 17.00.

Tricyclohexylsilane. Trichlorosilane (20 cc., 0.2 mole) in 100 cc. of anhydrous ether was added to 0.8 mole of cyclohexylmagnesium chloride in 1200 cc. of the same solvent. Addition was spread through one hour with cooling to 0° and stirring, then refluxing for 4 hours. As before, solid products were filtered off and the filtrate fractionated. Tricyclohexylsilane, b.p. 170–176°, d_{24}^{24} 0.9981, n_D^{20} 1.4968, yield 4.4%.

Anal. Calc'd for $C_{18}H_{34}Si$: Mol. wt., 278. Found: Mol. wt. (cryoscopic in benzene), 274.

Benzylmethylchlorosilane. Benzylmagnesium chloride (175 cc., 0.5 mole) was added to 50 cc. (0.5 mole) of trichlorosilane in 400 cc. of anhydrous ether at 0° with stirring. The mixture was refluxed for 4 hours after which an additional 300 cc. of anhydrous ether was added. Methylmagnesium chloride (167 cc., 0.5 mole) was then added dropwise to the reaction mixture and refluxed for 16 hours. Solid material was filtered off and the filtrate fractionated. Benzylmethylchlorosilane, b.p. 76–83° (6 mm.), d_{27}^{27} 1.002, n_D^{20} 1.5160, yield 2.4%.

Anal. Calc'd for $C_8H_{11}ClSi$: Cl, 20.78; Silane hydrogen, 0.587.

Found: Cl, 20.80; Silane hydrogen 0.572.

Benzyldimethylsilane. Benzylmagnesium chloride (0.8 mole) was added to 80 cc. (0.8 mole) of trichlorosilane in 800 cc. of anhydrous ether at 0° with stirring. The mixture was refluxed for 1 hour, and 400 cc. of dry ether and 1.6 moles of methylmagnesium chloride were added. It was refluxed for 6 hours, acidulated ice-water (200 cc.) was slowly added, and the ether layer separated. The latter was dried over calcium chloride and fractionated. Benzyldimethylsilane, b.p. 53–55° (3 mm.), d_{20}^{20} 0.9486, n_D^{20} 1.5040, yield 16.5%.

Anal. Calc'd for $C_9H_{14}Si$: Mol wt., 150.0; Silane hydrogen, 0.666.

Found: Mol. wt. (cryoscopic in benzene), 145.5; Silane hydrogen, 0.645.

Dibenzylmethylsilane. Benzylmagnesium chloride (0.9 mole) was added to 45 cc. (0.45 mole) of trichlorosilane in 600 cc. of anhydrous ether with cooling to 0° and stirring. The mixture was refluxed for 3 hours, methylmagnesium chloride (167 cc., 0.5 mole) was added with stirring, refluxed for 4 hours, and 600 cc. of acidulated ice-water slowly added. The ether was dried over calcium chloride for 16 hours, and fractionation gave dibenzylmethylsilane, b.p. 131–140° (3 mm.), d_{20} 0.9936, n_D^{20} 1.5650, yield 22.1%.

Anal. Calc'd for $C_{15}H_{18}Si$: Mol. wt., 226; Silane hydrogen, 0.4425.

Found: Mol. wt. (cryoscopic in benzene), 220; Silane hydrogen, 0.425.

Tribenzylsilane was prepared according to the method already in the literature (1); m.p. 91° [literature, (1) 90–91°].

Interaction of triethylsilane and tetramethylammonium hydroxide. Aqueous tetramethylammonium hydroxide (80 cc., 0.15 mole) dissolved in 50 cc. of 96% ethanol was added to 23.3 cc. (0.15 mole) of triethylsilane. The reaction mixture was stirred. A glass tube led from the top of the reflux condenser to a trap immersed in Dry Ice and acetone, with an outlet arranged for gas collection. As the base was added, the flask was gently heated until

the ethanol refluxed. A gas was evolved. After the addition of 60 cc. of the hydroxide, no more gas was observed coming off. No trimethylamine was collected in the trap. The material in the reaction flask consisted of two layers; the top layer was fractionated, yielding *triethylhydroxysilane*, b.p. 154° (760 mm.), d_4^{20} 0.8647 [literature, 0.8647 (3), 0.8638 (5)]; n_D^{20} 1.4329 [literature, 1.4363 (3), 1.4329 (5)]. *Hexaethyldisiloxane* was also isolated from this layer, b.p. 231° (760 mm.) *cf.* (8), d^0 0.8590 (8), n_D^{20} 1.4342 [literature, 1.4340, 1.4332 (4)]. The gas evolved was *hydrogen*, unmixed with *methane* because (a) on contact with hot copper oxide, the latter was reduced to copper, (b) no portion of the gas underwent liquefaction in liquid nitrogen (about −196°), and (c) on combustion, the water formed gave no precipitate with calcium hydroxide.

Interaction of triethylsilane and tetraethylammonium hydroxide. The procedure in this experiment was approximately the same as in the preceding, save that 0.1-molar quantities were used. Refluxing was carried out at 100° for 3 hours, after which the system was allowed to stand at room temperature for 16 hours. A second reflux period at 70° for 2 hours followed. The upper layer yielded triethylhydroxysilane and hexaethyldisiloxane. As before, the gas was shown to contain only hydrogen.

Interaction of tribenzylsilane and tetraethylammonium hydroxide. Reactants were mixed using 0.05 mole of each and the experiment carried out as above, with 4 hours of refluxing. A gas came off during the first 30 minutes only. The only silicon compound isolable was *hexabenzyldisiloxane*, m.p. 205°, *cf.* (6).

SUMMARY

1. By interaction of the proper Grignard reagent and trichlorosilane in regulated ratios, there have been prepared butyldichlorosilane, dibutylchlorosilane, tributylsilane, isobutyldichlorosilane, diisobutylchlorosilane, isoamyldichlorosilane, diisoamylchlorosilane, and tricyclohexylsilane.

2. By successive action of benzylmagnesium chloride and methylmagnesium chloride in regulated ratios, benzylmethylchlorosilane, benzyldimethylsilane, and dibenzylmethylsilane have also been prepared.

3. Contact between (a) triethylsilane and tetramethylammonium hydroxide, (b) triethylsilane and tetraethylammonium hydroxide, and (c) tribenzylsilane and tetraethylammonium hydroxide produced no evidence of hydrocarbon formation. The products of these reactions were hydrogen, triethylhydroxysilane, hexaethyldisiloxane, tribenzylhydroxysilane, and hexabenzyldisiloxane.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. X. THE CHEMICAL PROPERTIES OF TRISUBSTITUTED SILANES[1,2]

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INTRODUCTION

The properties of trisubstituted silanes, containing one hydrogen atom connected to silicon, have already been studied from both the chemical (1) and the physical (2) point of view. It seems to be the concensus of opinion that silane hydrogen shows considerable evidence of being electronegative in character and this work was undertaken with the purpose of further exploring the field to obtain more evidence on this point.

Five halogenations were carried out with good yields. Thus tribenzylchlorosilane, and triethylchlorosilane were prepared by the action of chlorine on the proper silane and in a similar manner bromination resulted in the formation of tribenzylbromosilane, tricyclohexylbromosilane, and triethylbromosilane. An analogous reaction, the bromination of triphenylsilane, was carried out by Kipping and Murray in 1929 (12). Hydrolytic reactions were successfully carried out on all of these products except tribenzylchlorosilane.

Halogenation, in itself, is no evidence of the positive, negative, or non-polar character of the silane hydrogen. It might be assumed however that a polar nature is favored by the ease with which these halogenations were carried out.

It was desired to find some reagent with a reactive halogen which could quite definitely be considered negative halogen and which would effect interchange between that halogen and silane hydrogen. Such compounds were found in the benzoyl halides and certain of their derivatives.

The following reactions were carried out with moderate success:

I. $C_6H_5COCl + HSi(CH_2C_6H_5)_3 \rightarrow C_6H_5CHO + (C_6H_5CH_2)_3SiCl$
II. $C_6H_5COBr + HSi(C_2H_5)_3 \rightarrow C_6H_5CHO + (C_2H_5)_3SiBr$
III. $C_6H_5COBr + HSi(CH_2C_6H_5)_3 \rightarrow C_6H_5CHO + (C_6H_5CH_2)_3SiBr$
IV. $p\text{-}C_2H_5OC_6H_4COCl + HSi(C_2H_5)_3 \rightarrow p\text{-}C_2H_5OC_6H_4CHO + (C_2H_5)_3SiCl$
V. $p\text{-}C_2H_5OC_6H_4COCl + HSi(CH_2C_6H_5)_3 \rightarrow p\text{-}C_2H_5OC_6H_4CHO + (C_6H_5CH_2)_3SiCl$
VI. $p\text{-}C_2H_5OC_6H_4COBr + HSi(CH_2C_6H_5)_3 \rightarrow p\text{-}C_2H_5OC_6H_4CHO + (C_6H_5CH_2)_3SiBr$

o-Chlorobenzoyl chloride did not react with triethylsilane save in the presence of aluminum chloride. The reaction of benzoyl chloride with triethylsilane was also carried out in the presence of aluminum chloride.

These results in general seem to bear out the assumption that the silane hydrogen is electronegative in character.

[1] This paper represents a portion of the thesis presented by the first author in partial fulfillment of the requirements of the degree of Doctor of Philosophy at the University of Buffalo.

[2] The work on which this paper is based comprises a portion of the program of research being carried out under contract with the Office of Naval Research.

Physical data relative to products and derivatives will be found in Table I.

Certain other combinations were attempted without success, namely with tribenzylsilane: acetic anhydride, propionic anhydride, benzyl bromide, *p*-nitrobenzoyl chloride, *p*-chlorobenzoyl chloride, and *o*-chlorobenzoyl chloride, and with triethylsilane: triphenylchlorosilane and benzoyl chloride.

EXPERIMENTAL PART

Chlorination reactions. Chlorine gas was passed into a solution of 15.5 cc. (0.1 mole) of triethylsilane in 50 cc. of carbon tetrachloride for one hour at room temperature, under anhydrous conditions. The product, *triethylchlorosilane*, was isolated in 60% yield, b.p. 143–144° (760 mm.); literature, m.p. 144–145° (760 mm.) (3); n_D^{20} 1.4320; literature, n_D^{20} 1.4321 (3). In similar manner, 15.1 g. (0.05 mole) of tribenzylsilane in 125 cc. of anhydrous carbon tetrachloride was converted to *tribenzylchlorosilane* in lower yield, m.p. 141–142°; literature, m.p. 141° (4). Triethylsilane and tribenzylsilane were prepared in accordance with procedures already in the literature (5).

TABLE I

PHYSICAL CONSTANTS

	B.P., °C.	M.P, °C.	n_D^{20}
$(C_2H_5)_3SiCl$[a]	143–144		1.4320
$(C_2H_5)_3SiBr$[b]	162–163		
$(C_2H_5)_3SiOH$[c]	153–154		
$[(C_2H_5)_3Si]_2O$[d]	231		
$(C_6H_{11})_3SiBr$[e]		114–115	
$[(C_6H_{11})_3Si]_2O$[e]		176–178	
$(C_6H_5CH_2)_3SiCl$[f]		141–142	
$(C_6H_5CH_2)_3SiOH$[g]		105–106	
$(C_6H_5CH_2)_3SiBr$[e]		144–145	

[a] B.p. 144–145° (729 mm.), n_D^{20} 1.4311 (3). [b] B.p. 162–163° (760 mm.) (6). [c] B.p. 154° (760 mm.) (9). [d] B.p. 231° (760 mm.) (9). [e] New compound. [f] M.p. 141° (4). [g] M.p. 106° (7).

Bromination reactions. Bromine (5.13 cc., 0.1 mole) in 200 cc. of anhydrous carbon tetrachloride was added dropwise to 15.45 cc. (0.1 mole) of triethylsilane in 35 cc. of the same solvent. The reaction was slightly exothermic. The mixture was refluxed for 90 minutes. The product was *triethylbromosilane* in 30% yield, b.p. 162–163° (760 mm.); literature, b.p. 162–163° (760 mm.) (6). In similar manner, *tricyclohexylbromosilane* was also prepared though in lower yields, m.p. 114–115° (recrystallized).

Anal. Calc'd for $C_{18}H_{33}BrSi$: Br, 22.39. Found: Br, 22.09.

Tricyclohexylbromosilane was dissolved in aqueous ethanol and boiled for 15 minutes with water. Crystals separated, probably *hexacyclohexyldisiloxane*, m.p. 176–178°.

Anal. Calc'd for $C_{36}H_{66}OSi_2$: C, 75.73; H, 11.58.

Found: C, 73.52; H, 11.33.

By the same procedure, *tribenzylbromosilane* was also prepared from 0.5 mole of tribenzylsilane, m.p. 144–145°.

Anal. Calc'd for $C_{21}H_{21}BrSi$: Br, 20.98. Found: Br, 20.60.

Hydrolysis with heated 50% ethanol resulted in the formation of tribenzylhydroxysilane, m.p. 105–106°; literature, m.p. 106° (7). Mixture melting point with tribenzylchlorosilane, 135–138°; reddish purple in carbon tetrachloride with chlorine water.

Reactions with benzoyl chloride. Benzoyl chloride (5.33 cc., 0.05 mole) in 20 cc. of anhydrous ether was added to 13 g. (0.043 mole) of tribenzylsilane in 80 cc. of anhydrous ether

with stirring. The mixture was refluxed for 5 hours. Benzaldehyde (2 cc.) was isolated, b.p. 175–179°, positive test with Tollens reagent. A smaller amount of tribenzylchlorosilane was isolated, m.p. 141–142°. Benzoyl chloride, alone, did not react with triethylsilane. However, when 23 cc. of triethylsilane (0.15 mole) in 60 cc. of anhydrous ether was mixed with 17.98 cc. (0.15 mole) of benzoyl chloride and aluminum chloride (0.2 g.) was added, reaction took place during a 6-hour reflux period. Triethylchlorosilane (7 cc.) was isolated, b.p. 141–144°, n_D^{20} 1.4312; approximately 30% yield. Benzaldehyde was identified as the 2,4-dinitrophenylhydrazone, m.p. 237°; literature, m.p. 235° (8).

Reactions with benzoyl bromide. Benzoyl bromide (23.6 cc., 0.2 mole) was added to 31.0 cc. (0.2 mole) of triethylsilane in 100 cc. of dry ether with stirring. The mixture was refluxed for 19 hours. Triethylsilane (17 cc.) was recovered. Triethylbromosilane (6 cc.) was isolated, b.p. 165–167° (760 mm.), in approximately 15% yield. Triethylbromosilane was refluxed with 50% ethanol for 30 minutes, forming hexaethyldisiloxane, b.p. 231° (760 mm.); literature, b.p. 231° (9). As before, benzaldehyde was identified by precipitation as the 2,4-dinitrophenylhydrazone, m.p. 238–239°. In a similar manner, 0.1 mole of benzoyl bromide was allowed to react with 0.1 mole of tribenzylsilane in 200 cc. of anhydrous ether. The mixture was refluxed for four hours. Tribenzylbromosilane was isolated, m.p. 141–143°. Tribenzylbromosilane was refluxed for 15 minutes with 50% ethanol with the formation of tribenzylhydroxysilane, m.p. 103°; literature, m.p. 106° (7). Benzaldehyde was identified by its boiling point, 175–185° and by its positive test with Tollens reagent.

Reaction with o-chlorobenzoyl chloride. *o*-Chlorobenzoyl chloride did not react with tribenzylsilane, nor did the *para*-isomer. *o*-Chlorobenzoyl chloride reacted with triethylsilane only in the presence of aluminum chloride. Triethylsilane (23 cc., 0.15 mole), *o*-chlorobenzoyl chloride (15 cc., 0.15 mole), and 0.4 g. of aluminum chloride were heated gently to initiate reaction, then cooled in an ice-bath. At the end of five minutes the reaction had subsided and the system was refluxed for four hours. Triethylchlorosilane (6 cc.) was isolated; 3 cc. had b.p. 140–142° (760 mm.), n_D^{20} 1.4311 and 3 cc. had b.p. 142–143° (760 mm.), n_D^{20} 1.4314. *o*-Chlorobenzaldehyde, 5 cc., was also isolated, b.p. 210–215° (760 mm.); literature, b.p. 208° (760 mm.) (10).

Reactions with p-ethoxybenzoyl chloride. *p*-Ethoxybenzoyl chloride (18.45 g., 0.1 mole) was added to 15.5 cc. (0.1 mole) of triethylsilane in 75 cc. of anhydrous ether and refluxed for 19 hours. Triethylchlorosilane, 3 cc., was isolated, b.p. 144–146° (760 mm.), n_D^{20} 1.4311. When triethylchlorosilane was refluxed with 50% ethanol, triethylhydroxysilane was formed, b.p. 153–154° (760 mm.); literature, b.p. 154° (760 mm.) (9). The residue from the original reaction yielded a small amount of *p*-ethoxybenzaldehyde, b.p. 141–143° (20 mm.); literature, b.p. 140° (20 mm.) (11). *p*-Ethoxybenzoyl chloride was prepared by the action of phosphorus trichloride on *p*-ethoxybenzoic acid (11), b.p. 130–139° (16 mm.). In similar manner, *p*-ethoxybenzoyl chloride reacted with tribenzylsilane in 0.1-molar quantities yielding tribenzylchlorosilane, m.p. 139–140°, identified by mixture melting point. *p*-Ethoxybenzaldehyde, 6 cc., was also identified, b.p. 135–141° (19.5 mm.).

Reaction with p-ethoxybenzoyl bromide. *p*-Ethoxybenzoyl bromide did not react with triethylsilane. However, reaction occurred when 28 g. (0.122 mole) of *p*-ethoxybenzoyl bromide was added to 23.7 g. (0.0785 mole) of tribenzylsilane in 75 cc. of anhydrous ether; the mixture was refluxed eight hours. Tribenzylbromosilane, m.p. 144°, and 10 cc. of *p*-ethoxybenzaldehyde, b.p. 139–145° (20 mm.) were isolated. Tribenzylsilane was further identified by conversion to tribenzylhydroxysilane as before, m.p. 104–106°.

SUMMARY

1. By direct halogenation in carbon tetrachloride, the following have been prepared: triethylchlorosilane, tribenzylchlorosilane, triethylbromosilane, tricyclohexylbromosilane, and tribenzylbromosilane.

2. Benzoyl chloride has been found to react with tribenzylsilane to form benzaldehyde and tribenzylchlorosilane. With triethylsilane a comparable reaction

was brought about but only with the catalytic aid of aluminum chloride. Benzoyl bromide reacted with triethylsilane to form triethylbromosilane, identified by conversion to hexaethyldisiloxane. Similarly tribenzylbromosilane was prepared and converted to tribenzylhydroxysilane.

3. *o*-Chlorobenzoyl chloride did not react with tribenzylsilane nor did the *para*-isomer. However, the *ortho* compound reacted with triethylsilane in the presence of aluminum chloride to form triethylchlorosilane and *o*-chlorobenzaldehyde.

4. *p*-Ethoxybenzoyl chloride reacted with triethylsilane to form triethylchlorosilane and with tribenzylsilane to form tribenzylchlorosilane. Triethylchlorosilane was identified by conversion to triethylhydroxysilane. *p*-Ethoxybenzaldehyde was also formed in each case.

5. *p*-Ethoxybenzoyl bromide did not react with triethylsilane, but with tribenzylsilane it gave tribenzylbromosilane and *p*-ethoxybenzaldehyde. Tribenzylbromosilane was identified by conversion to tribenzylhydroxysilane.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

DIETHYLENE GLYCOL *BIS*-CARBONATES OF LACTIC ESTERS[2]

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The acylation of several alkyl lactates with diethylene glycol *bis*-chloroformate (I) and the properties of the resulting diethylene glycol *bis*-carbonates (II)

$O[CH_2CH_2OCOCl]_2$ (I) $\qquad$ $O[CH_2CH_2OCOOCH(CH_3)COOR]_2$ (II)

were reported in a previous paper from this Laboratory (1). Because of the commercial availability of the *bis*-chloroformate (I) and the potential value of the *bis*-carbonates (II) as plasticizers and resin intermediates (2–4), several additional *bis*-carbonates were made. They (Table I) were prepared as before (1) by acylating appropriate lactic esters with diethylene glycol *bis*-chloroformate.

The distilled *bis*-carbonates (II) were colorless and relatively viscous liquids having densities greater than one (Table II). The less viscous *bis*-carbonates were characterized by relatively long straight chains, such as those made from 2-ethoxyethyl, 2-butoxyethyl, and 2-(2-butoxyethoxy)ethyl lactates. The previously described (1) *bis*-carbonates made from *n*-alkyl lactates also were relatively fluid. The *bis*-carbonates having branched alkyl groups and rings were relatively viscous (Table II). The *bis*-carbonates (II) were thermally stable below about 225 to 250°.

It has been shown (1) that a straight line relationship[3] exists between the normal boiling points of ROH and the boiling points at 4 mm. of the corresponding *bis*-carbonates (II). The *sec*-alkyl and branched alkyl compounds of the present paper also fit moderately well into this relationship. The boiling points (Figures 1 and 2) at 4 mm. of the 2-alkoxyethyl, cyclohexyl, and methylcyclohexyl compounds, however, were about 10° higher than those predicted from the relationship.[3]

In agreement with earlier work on esters having two or more allyl groups (5, 6) the *bis*-carbonate made from allyl lactate (II, R = allyl) polymerized when heated in the presence of benzoyl peroxide. The polymer, presumably cross-linked, was transparent, colorless, hard, insoluble and infusible. The *bis*-carbonate made from allyl lactyllactate (II, R = $-CH(CH_3)COOCH(CH_3)COOCH_2CH{:}CH_2$) polymerized sluggishly when heated with benzoyl peroxide, the product being a soft, sticky, semisolid. Since the monomeric ester was not distilled (molecular weight too high), possibly impurities inhibited polymerization.

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

[2] Some of the material in this paper was presented before the Division of Paint, Varnish and Plastics Chemistry at the New York Meeting of the American Chemical Society, September 1947.

[3] B.p. (°C.) of ester at 4 mm. = 0.534 (b.p. of ROH at 760 mm.) + 187.

TABLE I

PREPARATION AND ANALYSES OF DIETHYLENE GLYCOL *bis*-CARBONATES OF LACTIC ESTERS

LACTATE USED	CONVERSION, %	C		H		CARBONATE AS CO_2, %		SAPN. EQUIV.	
		Calc'd	Found	Calc'd	Found	Calc'd	Found	Calc'd	Found
4-Methyl-2-pentyl[a]	—	56.9	57.2	8.4	8.5				
2,6-Dimethyl-4-heptyl	47					14.9	16.8	98.5	94.6
Cyclohexyl[a]	—	57.4	57.7	7.6	7.5				
Methylcyclohexyl[a]	—	58.9	59.1	8.0	8.1				
2-Methoxyethyl	71					19.4	19.7	75.7	76.1
2-Ethoxyethyl	67					18.2	18.2	80.4	80.4
2-Butoxyethyl	97					16.3	16.6	89.8	89.8
2-(2-Chloroethoxy)ethyl[b]	80					16.0	15.9	68.9	73.3
2-(2-Butoxyethoxy)ethyl[b]	95	53.7	53.4	8.0	8.3				
Tetrahydrofurfuryl	80	52.2	51.9	6.8	6.8	17.4	17.2	84.4	85.4
Allyl[a]	—					20.0	21.0	69.7	69.4
1-Carballyloxyethyl[b,c]	72	51.2	51.0	6.1	6.6	15.7	14.6	70.3	76.0
Isobutyl[d]	53					20.8	20.6	70.4	70.4

[a] Technical grades of these esters, kindly supplied by Franklin Strain and associates of the Columbia Chemicals Division of the Pittsburgh Plate Glass Company, were distilled and examined by the authors. [b] Undistilled. [c] Allyl lactyllactate. [d] Glycolate instead of lactate.

TABLE II

PROPERTIES OF DIETHYLENE GLYCOL *bis*-CARBONATES OF LACTIC ESTERS

LACTATE USED	n_D^{20}	n_D^{40}	d_4^{20}	d_4^{40}	MOL. REFRACTION			VISCOSITY, CPS.	
					Calc'd	Found at			
						20°	40°	20°	40°
4-Methyl-2-pentyl	1.4408	1.4340	1.0719	1.0560	124.6	124.8	124.9	593	96
2,6-Dimethyl-4-heptyl	1.4450	1.4380	1.0461	1.0294	152.3	150.3	150.6	1313	169
Cyclohexyl	1.4658	1.4590	1.1566	1.1392	120.2	120.3	120.6	22565	1092
Methylcyclohexyl	1.4630	1.4564	1.1254	1.1085	129.4	129.8	130.2	16240	832
2-Methoxyethyl	1.4480	1.4402	1.2167	1.1968	100.2	100.0	100.1	742	127
2-Ethoxyethyl	1.4462	1.4395	1.1776	1.1575	109.4	109.3	109.8	432	88
2-Butoxyethyl	1.4468	1.4400	1.1268	1.1104	128.9	127.6	127.9	330	78
2-(2-Chloroethoxy)ethyl	1.4622	1.4553	1.2645	1.2460	119.1	119.9	120.1	822	155
2-(2-Butoxyethoxy)ethyl	1.4485	1.4419	1.1146	1.0978	149.6	150.6	151.0	136	143
Tetrahydrofurfuryl	1.4660	1.4590	1.2297	1.2148	114.2	114.1	114.0	4440	516
Allyl	1.4550	1.4480	1.1873	1.1696	95.9	95.6	95.8	263	63
1-Carballyloxyethyl	1.4542	1.4437	1.1924	1.1721	127.0	127.8	127.4	1630	115
Isobutyl[a]	1.4440	1.4372	1.1620	1.1433	96.9	96.6	96.8	472	94

[a] Glycolate instead of lactate.

The diethylene glycol *bis*-carbonate of isobutyl glycolate was prepared for purposes of comparison. This glycolate boiled about 6° higher at 1 mm. than the corresponding isobutyl lactate derivative (1). This is in agreement with the boiling points of previously prepared derivatives of glycolic and lactic acid.

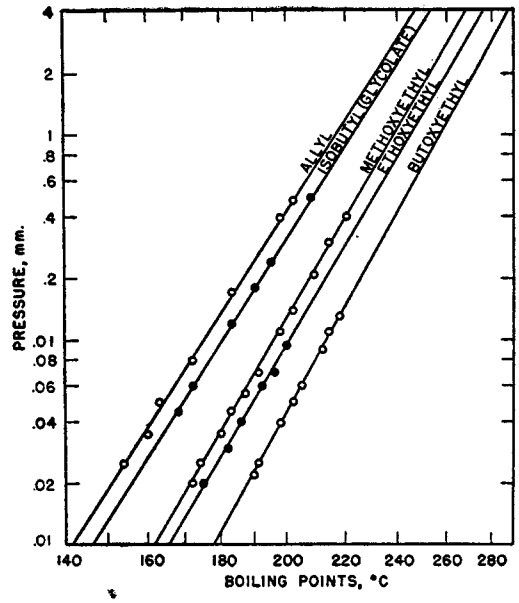

FIG. 1 BOILING POINTS OF DIETHYLENE GLYCOL BIS-CARBONATES OF LACTIC ESTERS

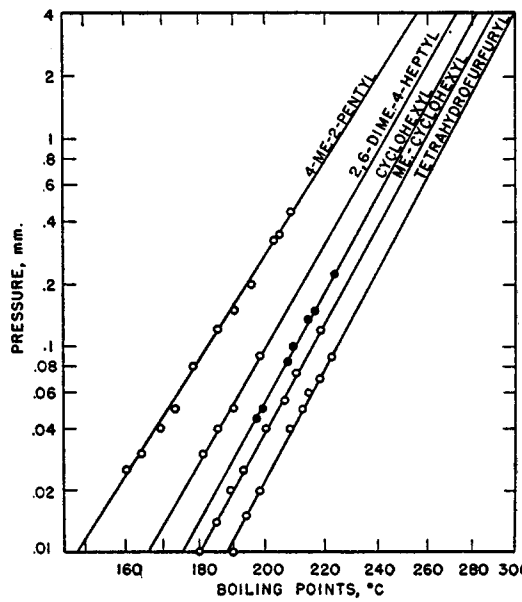

FIG. 2 BOILING POINTS OF DIETHYLENE GLYCOL BIS-CARBONATES OF LACTIC ESTERS

Acknowledgment. The authors are indebted to C. O. Willits and C. L. Ogg of this laboratory for analytical data; to Franklin Strain of Columbia Chemicals

Division of the Pittsburgh Plate Glass Company for diethylene glycol *bis*-chloroformate and technical, undistilled samples of some of the *bis*-carbonates (II); to R. L. Bateman, Carbide and Carbon Chemicals Corporation for the glycol monoethers; to K. R. Edlund, Shell Chemical Corporation for diisobutyl carbinol; and to the Barrett Division, Allied Chemical and Dye Corporation for cyclohexyl and methylcyclohexyl lactate.

EXPERIMENTAL

The lactic esters were prepared by previously described methods (2, 7). Table III gives data on the new lactates. Allyl lactylactate ($HOCH(CH_3)COOCH\cdot(CH_3)COOCH_2CH{:}CH_2$), was obtained as a by-product in the preparation of allyl lactate (7). Commercial diglycol *bis*-chloroformate was used as received. The lactic esters were acylated (1, 2)

TABLE III

PREPARATION AND PROPERTIES OF LACTIC ESTERS

PROPERTY		4-METHYL-2-PENTYL	2,6-DIMETHYL-4-HEPTYL	1-CARBALLYLOXY-ETHYL
Conversion, %		69	86	22
Boiling point °C., (mm.)		55 (1)	54 (0.1)	105 (1)
n_D^{20}		1.4220	1.4298	1.4448
d_4^{20}		0.9359	0.9166	1.1172
Mol. Refraction,	Calc'd	46.94	60.80	48.13
	Found	47.30	60.93	48.15
Sapn. Equiv.,	Calc'd	174.2	216.3	101.1
	Found	179.0	220.9	100.9
Carbon, %	Calc'd	62.0	66.6	53.5
	Found	61.9	67.6	53.5
Hydrogen, %	Calc'd	10.4	11.2	7.0
	Found	10.6	11.4	7.0

with the *bis*-chloroformate in the presence of pyridine and ether at about 0°. The products were washed successively with dilute acid and with water; most of the carbonates were then distilled at reduced pressure. The washed products, however, were light amber or almost colorless.

The distillations and boiling-point determinations were conducted in an improved tensimeter still (8), which was continuously agitated by a mechanical shaker. Refractive indices, densities, and viscosities were determined with an Abbé type refractometer, Sprengel type pycnometer, and modified Ostwald tube (9), respectively. For these measurements, a constant-temperature bath (10) set with a precision of 0.1° was used to maintain the temperature within ±0.02°.

SUMMARY

Several diethylene glycol *bis*-carbonates of lactic esters [R = 4-methyl-2-

$$O[CH_2CH_2OCOOCH(CH_3)COOR]_2$$

II

pentyl; 2,6-dimethyl-4-heptyl; cyclohexyl; methylcyclohexyl; 2-methoxyethyl; 2-ethoxyethyl; 2-butoxyethyl; 2-(2-chloroethoxy)ethyl; 2-(2-butoxyethoxy)

ethyl; tetrahydrofurfuryl; allyl; and 1-carballyloxyethyl] were made by acylation of the appropriate lactic ester with diethylene glycol *bis*-chloroformate ($O[CH_2CH_2OCOCl]_2$). The boiling points at different pressures, densities, refractive indices, and viscosities of the *bis*-carbonates (II) were determined. Some of these high-boiling esters are potentially useful as plasticizers and resin intermediates.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

MIXED ESTERS OF LACTIC AND CARBONIC ACIDS. *n*-ALKYL CARBONATES OF METHYL AND BUTYL LACTATES, AND BUTYL CARBONATES OF *n*-ALKYL LACTATES

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The first paper of this series (1) described a group of esters made by acylating various esters of α-hydroxy acids with alkyl chloroformates. Several of these compounds were of special interest because their low volatility and their compatibility with various resins indicated that they might be useful as plasticizers. In a subsequent paper (2), which included some of the data presented in the present paper, additional carbonates of lactates were described, and their suitability as plasticizers for vinyl chloride polymers indicated. To facilitate a more systematic study of esters of this type, additional ones were prepared so that families of homologous compounds could be examined and various physical properties could be correlated with the number of carbon atoms in the compounds. Data on the use of these esters as plasticizers will be published elsewhere.

The compounds in the present study (Table I) fall into three series of homologs: (a) *n*-alkyl carbonates of methyl lactate, (b) *n*-alkyl carbonates of *n*-butyl lactate, and (c) *n*-butyl carbonates of *n*-alkyl lactates. The third series consists of five members, of which the butyl carbonates of methyl and butyl lactate are common to the first and second series, respectively. The members of the second and third series are isomeric and differ only in that their alkyl radicals are interchanged. As might be expected, the physical properties of the isomeric members of these two series are nearly identical. Since in most cases the differences are within or near the estimated experimental error, and all the relationships developed for the physical constants of the second series fit the third series almost as well, the two series are treated herein as one family.

Boiling points and vapor pressures. Figures 1 and 2 show the boiling points of the esters as a function of the pressure. The temperature scales are laid off as a linear function of $1/(t + 193)$, where t = °C. The usual form of the Cox chart, where the temperature scale is determined by $1/(t + 273)$ was unsatisfactory because the data fell on lines which were convex upward instead of straight. Charts whose scales were derived from $1/(t + 230)$ were better, but the curvature was still present. The scales determined by $1/(t + 193)$ gave straight lines, and charts having this scale were conveniently prepared from commercial Cox chart paper having a scale $1/(t + 273)$ by adding 80° to each temperature designated on the chart. The mathematical proof of this transformation will be published elsewhere (3). The boiling points of the butyl carbonates of alkyl lactates were generally within 1° of those of the isomeric alkyl carbonates of butyl lactate; hence, separate lines for them are not shown in Figure 2.

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

TABLE I

n-ALKYL CARBONATES OF *n*-ALKYL LACTATES ROCOOCH(CH$_3$)COOR'

R	R'	YIELD, %	C		H		n_D^{20}	n_D^{40}	d_4^{20}	d_4^{40}	VISCOSITY, CPS.,		MOL. REFRACTION, 20°		SOLUBILITY IN WATER AT 25°, g./100 cc.
			Calc'd	Found	Calc'd	Found					20°	40°	Calc'd[a]	Found	
Methyl	Methyl[b]	58	44.5	44.5	6.2	6.4	1.4100	1.4020	1.1586	1.1363	5.42	2.90	34.86	34.68	4.07
Ethyl	"	34	47.7	47.9	6.9	7.1	1.4110	1.4035	1.1125	1.0913	4.78	2.63	39.48	39.32	1.65
Propyl	"	68	50.5	50.3	7.4	7.5	1.4163	1.4072	1.0820	1.0626	5.47	3.06	44.10	44.14	0.52
Butyl	"	61	52.9	52.6	7.9	7.9	1.4196	1.4112	1.0604	1.0411	5.99	3.26	48.71	48.64	.18
Amyl	"	41	55.0	55.2	8.3	8.5	1.4227	1.4150	1.0426	1.0231	7.30	3.78	53.33	53.26	.05
Hexyl	"	68	56.9	56.9	8.7	8.6	1.4255	1.4178	1.0229	1.0047	8.07	4.08	57.95	58.13	.01
Octyl	"	63	60.0	60.5	9.3	9.5	1.4304	1.4228	1.0010	0.9829	11.38	5.25	67.19	67.22	—
Decyl	"	66	62.5	62.7	9.8	9.7	1.4346	1.4273	0.9830	.9664	15.65	7.35	76.42	76.48	—
Methyl	Butyl	54	52.9	53.0	7.9	7.5	1.4170	1.4092	1.0575	1.0373	5.40	2.99	48.71	48.57	0.18
Ethyl	"	54	55.0	54.8	8.3	8.3	1.4181	1.4102	1.0325	1.0138	5.16	2.95	53.33	53.28	.07
Propyl	"	66	56.9	56.3	8.7	8.8	1.4218	1.4140	1.0189	0.9993	6.24	3.40	57.95	57.91	.01
Butyl	"	73	58.5	59.1	9.0	9.2	1.4240	1.4162	1.0049	.9864	6.51	3.64	62.57	62.55	—
Amyl	"	73	60.0	59.8	9.3	9.4	1.4263	1.4188	0.9943	.9763	7.49	3.90	67.19	67.13	—
Hexyl	"	65	61.3	61.3	9.6	9.7	1.4288	1.4212	.9823	.9647	8.96	4.64	71.80	71.97	—
Octyl	"	70	63.5	63.5	10.0	10.3	1.4332	1.4260	.9554	.9387	10.78	5.59	81.04	82.29	—
Decyl	"	66	65.4	65.4	10.4	10.8	1.4362	1.4290	.9551	.9391	15.19	7.46	90.28	90.51	—
Dodecyl	"	76	67.0	67.1	10.7	10.9	1.4394	1.4317	.9460	.9309	19.05	9.15	99.51	99.75	—
Butyl	Octyl	86	63.5	63.6	10.0	10.2	1.4324	1.4247	.9687	.9516	11.60	5.82	81.04	81.04	—
Butyl	Decyl	97	65.4	65.6	10.4	10.7	1.4358	1.4284	.9565	.9399	14.78	7.27	90.28	90.31	—
Butyl	Dodecyl	98	67.0	66.8	10.7	10.6	1.4390	1.4320	.9461	.9304	17.92	8.55	99.51	99.66	—

[a] Eisenlohr's constants were used because they gave slightly better agreement with observed values than did those of Vogel, *J. Chem. Soc.*, 1833 (1948). The two sets of constants gave the same calculated values for the compounds of highest molecular weight, but differed by 0.4 for the compounds of lowest molecular weight, Eisenlohr's being the higher. [b] This compound has been reported by Ritchie, *J. Chem. Soc.*, 1054 (1935).

Straight lines were obtained by plotting the logarithm of the vapor pressure of either family of esters, at any fixed temperature, *versus* the number of carbon

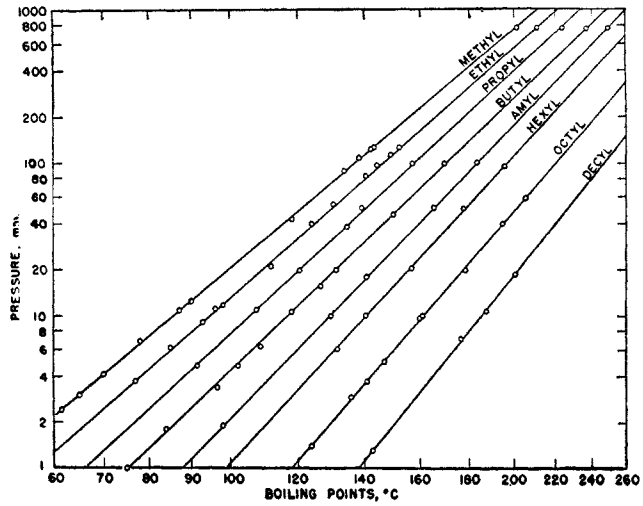

FIG. 1 BOILING POINTS OF n-ALKYL CARBONATES OF METHYL LACTATE

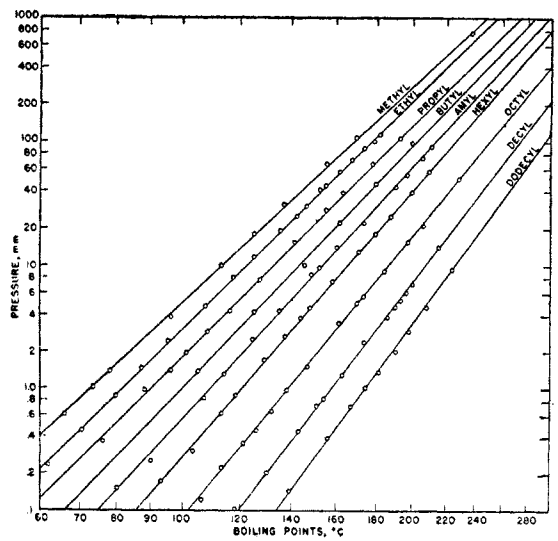

FIG. 2 BOILING POINTS OF n-ALKYL CARBONATES OF BUTYL LACTATE

atoms in the compounds. These lines, equations for which are shown in Table II, had a common point of intersection for each family. For the carbonates of methyl lactate, this point was where Log P = 6.78 and x = −13.6; for the butyl lactate derivatives, it was where Log P = 6.3 and x = −12. Also, within each family, the slopes (a) of these lines varied with the temperature:

TABLE II

EQUATIONS RELATING VAPOR PRESSURE (P) AT VARIOUS TEMPERATURES TO THE NUMBER OF CARBON ATOMS (x) IN *n*-ALKYL CARBONATES OF METHYL AND BUTYL LACTATES

$\log P = a x + b$

TEMP., °C.	a	b	DEVIATIONS,[a] %	
			Max.	Average
CARBONATES OF METHYL LACTATE				
100	−0.274	3.055	11	4
150	− .225	3.680	10	3
200	− .192	4.160	11	4
250	− .166	4.550	4	2
CARBONATES OF BUTYL LACTATE				
100	−0.270	3.240	10	5
150	− .214	3.697	7	3
200	− .181	4.145	4	2
250	− .154	4.480	5	2

[a] Deviations from the pressures read from Figures 1 and 2; methyl carbonates are excluded. A deviation of 5% corresponds to a difference in boiling point of about 1°.

TABLE III

EQUATIONS RELATING BOILING POINTS (T = °K) AT VARIOUS PRESSURES TO THE NUMBER OF CARBON ATOMS (x) IN *n*-ALKYL CARBONATES OF METHYL AND BUTYL LACTATES

$10^{-4} T^2 = a x + b$

PRESSURE, MM.	a	b	DEVIATIONS[a]	
			Max.	Average
CARBONATES OF METHYL LACTATE				
760	1.51	12.35	4	2.0
100	1.18	9.10	2	1.0
10	0.93	6.87	2	1.1
1	.78	5.23	2	.8
CARBONATES OF BUTYL LACTATE				
760	1.54	11.33	3	1.6
100	1.18	8.42	2	.7
10	0.93	6.20	2	.8
1	.75	4.95	2	1.1
0.1	.627	4.02	1	.4

[a] Deviations from boiling points read from Figures 1 and 2; methyl carbonates excluded.

For the methyl lactate series: $a = 0.048 - \frac{94}{t + 193}$

For the butyl lactate series: $a = 0.053 - \frac{92}{t + 193}$

By use of these equations for the slopes, and the common points given above, equations similar to those in Table II are readily calculated for any desired temperature.

TABLE IV

RELATIONSHIP OF REFRACTIVE INDEX AND DENSITY TO NUMBER OF CARBON ATOMS (x) IN *n*-ALKYL CARBONATES OF METHYL AND BUTYL LACTATES

EQUATIONS	DEVIATIONS[a] × 10^4	
	Max.	Average
CARBONATES OF METHYL LACTATE		
$\frac{x+5}{n_D^{20}} = 0.68x + 3.742$	5	2.4
$\frac{x+5}{n_D^{40}} = 0.6826x + 3.7755$	6	2.4
$\frac{x+3}{d_4^{20}} = 1.167x + 0.819$	27[b]	11
$\frac{x+3}{d_4^{40}} = 1.184x + 0.880$	22[b]	8
CARBONATES OF BUTYL LACTATE		
$\frac{x+6}{n_D^{20}} = 0.678x + 4.504$	6	2.4
$\frac{x+6}{n_D^{40}} = 0.681x + 4.537$	6	2.5
$\frac{x+2}{d_4^{20}} = 1.167x - 0.069$	19[c]	8[c]
$\frac{x+2}{d_4^{40}} = 1.183x$	14[c]	6[c]

[a] Difference between calculated and observed values of refractive index or density. Methyl carbonates excluded. [b] Maximum deviation was shown by the hexyl carbonate. [c] Octyl carbonate excluded; its deviation was 122 and 123 at 20° and 40°, respectively.

Table III consists of a set of equations relating boiling points, at certain fixed pressures, to the number of carbon atoms in the esters. Within each family, these lines pass through a common point as follows:

For the methyl lactate series: $10^{-4}T^2 = -2.3$, $x = -9.7$

For the butyl lactate series: $10^{-4}T^2 = -1.0$, $x = -8.0$

The slopes (a) of the lines are related to the pressure by the following equations:

For the methyl lactate series: $\text{Log } P = -4.61/a + 5.93$

For the butyl lactate series: $\text{Log } P = -4.11/a + 5.50$

These equations for the slope, together with the common points given above,

enable one to derive equations, similar to those in Table III, for boiling points at any desired pressure.

Densities and refractive indices. These constants were determined at 20° and 40°, and are recorded in Table I. Table IV shows empirical equations relating these constants to the number of carbon atoms in the compounds.

The last two equations in Table IV, which relate the densities of the carbonates of butyl lactate to the number of carbon atoms in the esters, yield calculated densities which show only small and random deviations from the observed values, with the exception of the octyl ester. The deviations of the calculated densities of this ester are 15 to 20 times the average deviations of the other esters; hence no weight was given this ester in the derivation of the equations. The reason for this large aberration is unknown. The ester was prepared twice, different lots of reagents being used. Each product was fractionally distilled until all determined

TABLE V

RELATION OF VISCOSITY (η = CPS.) TO NUMBER OF CARBON ATOMS IN *n*-ALKYL CARBONATES OF METHYL AND BUTYL LACTATES

$\text{Log } \eta_t = a\,x + b$

t, °C.	a	b	DEVIATIONS, CPS.[a]	
			Max.	Average
CARBONATES OF METHYL LACTATE				
20	0.062	0.242	0.80	0.25
40	0.054	0.036	0.34	0.20
CARBONATES OF BUTYL LACTATE				
20	0.055	0.176	0.60	0.31
40	0.049	−0.023	0.23	0.12

[a] Methyl carbonates excluded.

physical properties were constant. The two products had virtually identical properties and analyses. The boiling points, refractive indices, and viscosities had about the expected values; only the densities showed large deviations. The hexyl carbonate of methyl lactate showed a similar but smaller aberration.

Viscosities. Viscosities were determined at 20° and 40° (Table I). When plotted logarithmically *versus* the number of carbon atoms in the esters, straight lines were obtained, the equations of which are shown in Table V.

Solubilities. Table I shows the solubilities of the esters in water at 25°, determined by the method of Fordyce and Meyer (4). When the two alkyl groups in the esters contained a total of more than seven carbon atoms, the solubility was less than 0.01% and was too small to measure. The solubility of the carbonates of methyl lactate followed the equation $\text{Log } S = 3.81 - 0.513x$. The solubilities of the butyl lactate derivatives, when large enough to measure, were approximately equal to those of the isomeric methyl lactate carbonates.

Acknowledgment. The authors are grateful to C. O. Willits and C. L. Ogg and their associates for analyses; to H. L. Fisher, U. S. Industrial Chemical Co., for hexyl, octyl, decyl, and dodecyl chloroformates; and to the Carbide and Carbon Chemicals Corp., for *n*-hexanol.

EXPERIMENTAL

Materials. The chloroformates up to the hexyl ester are commercially available. The higher ones were supplied by the U. S. Industrial Chemical Company. All were used as received.

Commercial methyl and butyl lactates were used after a fractional distillation. The higher lactates were prepared by the alcoholysis of methyl lactate (5). The lactates were treated with the chloroformates in the presence of pyridine as described in the first paper of this series (1).

Physical constants. Boiling points used in the construction of Figures 1 and 2 were determined by use of an improved tensimeter-still (6).

Refractive indices were measured with an Abbé type refractometer. Densities were determined with a Sprengel type pycnometer holding about 10 cc. Viscosities were measured with modified Ostwald pipettes calibrated with standard oils furnished by the Bureau of Standards. The constant temperature bath used for all these measurements was set to $\pm 0.1°$ and controlled to $\pm 0.02°$ (7).

SUMMARY

Three homologous series of esters, comprising twenty compounds, were prepared: (a) *n*-alkyl carbonates of methyl lactate, (b) *n*-alkyl carbonates of butyl lactate, and (c) butyl carbonates of *n*-alkyl lactates. The two latter series differ only in that their alkyl groups are interchanged, and their isomeric members have almost identical physical properties.

Equations were developed which relate vapor pressures, boiling points, refractive indices, densities, viscosities, and solubilities to the number of carbon atoms in the members of each series of esters.

PHILADELPHIA 18, PA.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE JOHNS HOPKINS UNIVERSITY AND MIDDLEBURY COLLEGE]

THE OXIDATION OF TETRONIC ACIDS. I. STRUCTURAL CRITERIA FOR THE FORMATION OF 1,2-DIKETONES

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No satisfactory mechanism has been devised for the production of 2,3-butanedione by the acid oxidation of 3-methyltetronic acid (I). Wolff proposed (1) an intermediate 3-hydroxytetronic acid (II) whose hydroxylic hydrogen atom was assumed to rearrange to the 5-position with simultaneous loss of carbon dioxide. This hypothesis was based upon his observation that 3-bromo-3-methyltetronic acid (III) was slowly hydrolyzed by base to form a solution from which 2,3-butanedione and carbon dioxide were liberated on acidification. To date no further work has appeared on this remarkable reaction.

In order to explore the limits of the oxidation reaction, and at the same time to gain information regarding its nature, we have prepared and studied various types of tetronic acids from which α-diketones might arise. These fall into three structural classes. In class (a) are acids carrying only 5-substituents, while in (b) the substitution is entirely on the 3-carbon atom, and in (c) both 3- and 5-substitution are present. These compounds and the results of their oxidation are shown in Fig. 2 where, for the sake of uniformity, non-enolic structures are used.

It is apparent that the formation of α-diketones is not a general reaction, but is dependent upon certain structural features in the parent tetronic acid. The first and most important of these is the presence of methylene hydrogen to permit enolization. Second, if the 3-carbon is monosubstituted, α-diketones are produced regardless of substitution on the 5-carbon atom. On the other hand, if the 3-carbon is unsubstituted, the 5-carbon must carry one and only one substituent group. Significant differences also appear with respect to the natu e of the diketones produced. Thus, if the tetronic acid carries one 3-substituent, then regardless of 5-substitution, the over-all oxidation process results in decarboxylation with *reduction* of the 5- and *oxidation* of the 3-carbon atoms.[3] However, in the case of monosubstitution on the 5-carbon, this rule is exactly reversed. These cases, and also that of tetronic acid itself, will be considered later in this paper.

It is necessary at this point to consider the possibility of α-diketones arising from the oxidation of the hydrolysis products of tetronic acids. Previous work (1, 2) has shown that ketols result from hydrolysis of tetronic acids, and in both the earlier oxidation by Wolff (1) and the present investigation, ketols accom panied α-diketones. Moreover, it has been established that ketols are capable

[1] From the doctoral dissertation of Robert B. Fortenbaugh, The Johns Hopkins University, 1949. Grateful acknowledgement is here made of receipt of a grant-in-aid from the Hynson, Westcott, and Dunning Fund.

[2] From the M. S. thesis of Mrs. Helen R. Patterson, Middlebury College, 1946.

[3] The rule has been substantiated for a 3,5-disubstituted tetronic acid containing dissimilar groups. This will appear in a later communication.

of acid-catalyzed isomerizations (3), and of oxidation by air (4) to the corresponding α-diketones. Of special significance in this context is the report (5) that α-hydroxybutyraldehyde isomerizes in hot acid solution to 3-hydroxy-2-butanone, with simultaneous formation of 2,3-butanedione and polymeric products.

We thus turned our attention to the acid hydrolysis of several tetronic acids. The experiments were conducted under nitrogen to protect the products, and the amounts of carbon dioxide evolved furnished a guide to the completion of the hydrolysis. From 3-ethyltetronic acid [Class (b)(I)], 1-hydroxy-2-pentanone was obtained, and oxidation of this ketol under the normal conditions failed to furnish any 2,3-pentandione. The products were carbon dioxide, formic acid, and butyric acid.

Surprising results attended our studies of 3,5-dimethyltetronic acid [Class (c)(I)], and 5-methyltetronic acid [Class (a) (I)]. The former, on hydrolysis, slowly formed the expected 2-hydroxy-3-pentanone, but oxidation of this ketol

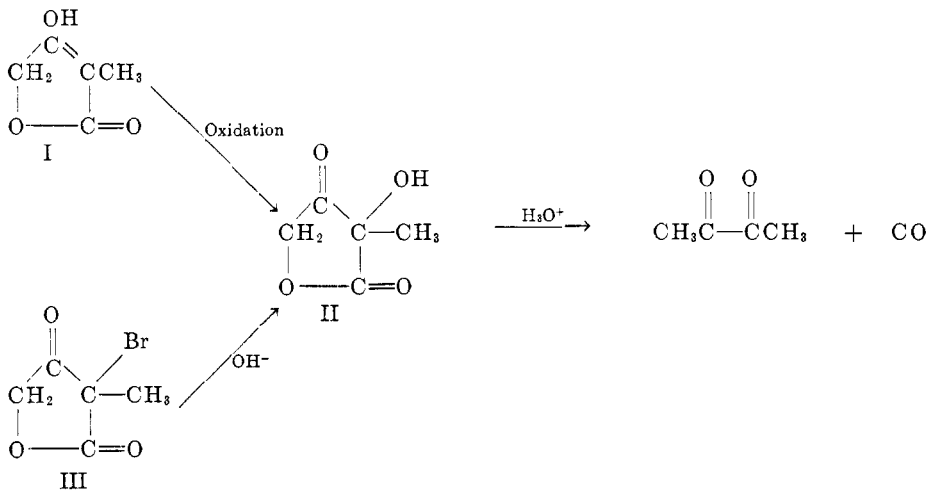

FIGURE 1. OXIDATION OF 3-METHYLTETRONIC ACID

did not produce 2,3-pentanedione. Similarly, no 2,3-butanedione was formed on oxidation of the hydrolysis product of 5-methyltetronic acid. Yet in both instances, traces of the respective α-diketones were formed during the hydrolysis. The oxidation products were not further studied, but they undoubtedly contained degraded acids because some carbon dioxide was evolved during each oxidation. The possibility that the diketones did actually form but were further oxidized is remote for two reasons. First, the diketones are readily produced from the parent tetronic acids under the same experimental conditions. Second, carbon dioxide should not result from the oxidation of either 2,3-pentanedione or 2-3-butanedione. It may be that isomerization to primary ketols is the explanation for the formation of carbon dioxide,[4] but in any event, this does not affect the main argument.

The oxidation of tetronic acids, then, is attended with some hydrolysis. The

[4] This point is under investigation in these laboratories.

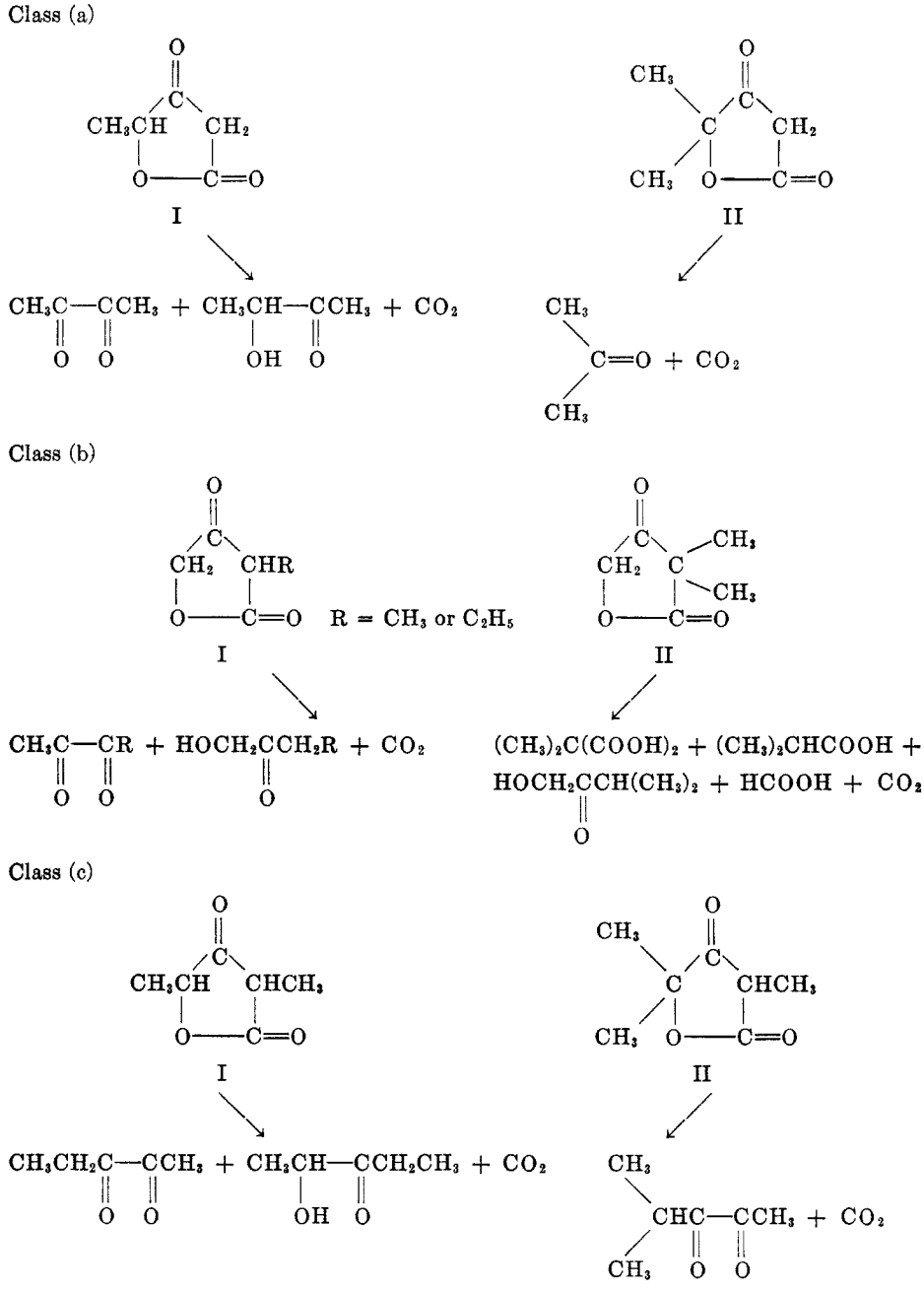

FIGURE 2. TETRONIC ACIDS: COURSE OF OXIDATION BY STRUCTURAL CLASSES

resulting ketols are oxidized, but do not form α-diketones. Thus the route whereby α-diketones are formed must involve oxidation of the tetronic acid *before* hydrolysis of the lactone ring occurs.

The question which next arises concerns the site of oxidation in the tetronic acid molecule. To answer this question we studied 3,3-dimethyltetronic acid[5] [Class (b)(II)], and 5,5-dimethyltetronic acid [Class (a)(II)]. These isomers are unique in that oxidation, before hydrolysis, must attack the 5-position of the former, and the 3-position of the latter. The products obtained from 3,3-dimethyltetronic acid were carbon dioxide, formic acid, isobutyric acid, 1-hydroxy-3-methyl-2-butanone (isolated as the phenylosazone), and dimethylmalonic acid. The formation of dimethylmalonic acid affords clear proof of oxidation at the 5-position. Although α-ketoisovaleraldehyde was anticipated, none was isolated. If any did form, it must have been further oxidized, presumably to formic and isobutyric acids. On the other hand, the *only* products isolated from the oxidation of 5,5-dimethyltetronic acid were carbon dioxide and acetone. This deep degradation of 5,5-dimethyltetronic acid is the more remarkable in view of the fact that 3,5,5-trimethyltetronic acid [Class (c)(II)], which must also undergo initial oxidation at the 3-position, readily forms carbon dioxide and 4-methyl-2,3-pentanedione. A further apparent exception is found in 5-methyltetronic acid [Class (a)(I)], and its isomer, 3-methyltetronic acid [Class (b)(I)], which was studied by Wolff (1). Both of these, on oxidation, yield carbon dioxide and 2,3-butanedione, but it may be noted that either or both of these isomers can be oxidized at the 3- or the 5-position. Similar considerations apply to the last pair of isomers, 3-ethyltetronic acid [Class (b)(I)], and 3,5-dimethyltetronic acid [Class (c)(I)], both of which, on oxidation, furnish carbon dioxide and 2,3-pentanedione.

There is thus a striking difference in oxidation behavior between tetronic acids substituted on the 3-position and those which are free of this substitution. This difference is not readily explained on the basis of classical organic structures, but it becomes comprehensible when the resonance possibilities of these molecules are considered. Determination of the dissociation constants (6), dipole moments (7), and Raman spectra (8) of tetronic acid, 3-hydroxytetronic acid, ascorbic acid, and other monosubstituted tetronic acids, show that these substances are abnormally strong acids due to greater resonance energy in their anionic forms. Moreover, in its undissociated state tetronic acid is represented by IV, with some contribution from the higher energy dipolar forms V and VI (7, 8).

Resonance between similar dipolar forms will likewise contribute to the stability of *enolic* 3-hydroxytetronic acids, *viz.*, IX, X, XI (where R is alkyl or hydrogen). Of the six acids studied only 5,5-dimethyltetronic acid [Class (a)(II)], and 5-methyltetronic acid [Class (a)(I)] are capable of being oxidized to this type of enolic resonating system, *i.e.* after C_3 is hydroxylated, and in the case of 5-methyltetronic acid this will be true only if the 3-position is attacked first. These stabilized structures would be expected to undergo further oxidation *before* decarboxylation occurs, and this must lead to deep degradation. Again, however, 5-methyltetronic acid can be oxidized at the 5-carbon, and this

[5] The substance is not acidic, and should be named α,α-dimethyl-β-ketobutyrolactone. To conform with the older literature it is here called a tetronic acid.

would certainly result in the formation of carbon dioxide and 2,3-butanedione.[6] The fact that 2,3-butanedione is obtained from 5-methyltetronic acid strongly points to some oxidation of the 5-carbon.

Different structural features apply in the cases of 3-ethyltetronic acid [Class (b)(I)], 3,5-dimethyltetronic [Class (c)(I)], and 3,5,5-trimethyltetronic acid [Class (c)(II)]. In their undissociated forms, these acids will be represented by VII (where R′ is alkyl and R is alkyl or hydrogen), with some resonance between dipolar forms analogous to V and VI. However oxidation of these three acids at the 3-position must lead to VIII which is incapable of enolization and dipolar resonance. The stability of VIII will therefore be much less than that of VII,

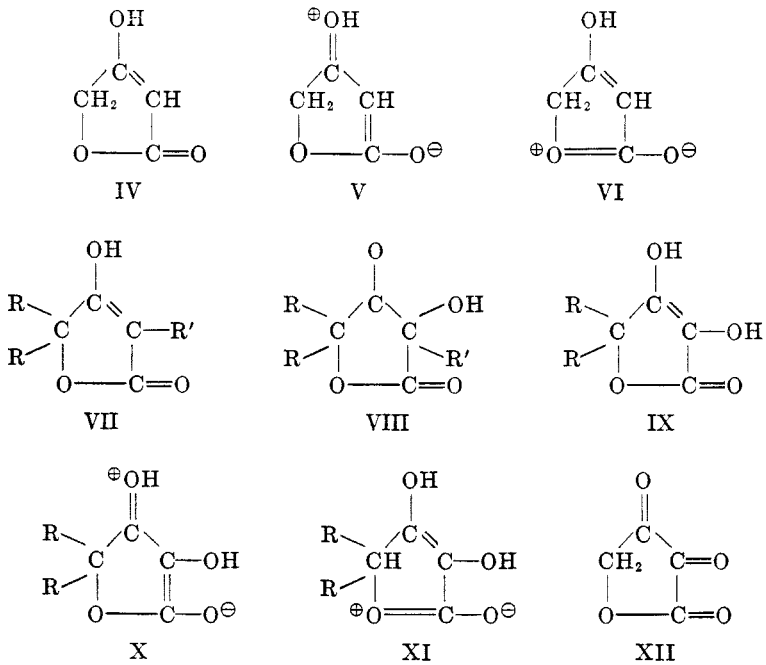

FIGURE 3. TETRONIC ACIDS: RESONANCE STRUCTURES

and decarboxylation will readily occur (compare Fig. 1) and, in fact, occurs in such a way that α-diketones are produced in accordance with the rule which was earlier described.

A somewhat similar situation appears to obtain in the case of 3-ketotetronic acid (XII) which has been prepared (9) by gentle oxidation of 3-hydroxytetronic acid (IX, where R is hydrogen). The ketotetronic acid is unstable and in aqueous solution decarboxylates to form pyruvic acid (9).[7]

[6] Compare the synthesis of α-ketoisovaleraldehyde in the experimental part.

[7] In the absence of any evidence to the contrary, the isolation of pyruvic acid instead of the expected β-hydroxypyruvic aldehyde, seems to us to be yet another example of the peculiar oxidation rule discussed earlier.

The original question as to how α-ketones are formed from 3-alkyl-3-hydroxytetronic acids has thus been accentuated rather than solved by this work. In carrying out the oxidations, however, it was apparent that the production of α-diketones was not a smooth process. As each drop of oxidant engaged the acidic solution of the tetronic acid, a vigorous surge of carbon dioxide occurred, *accompanied* by small amounts of the volatile diketone. Although measurements failed to establish a quantitative relationship between the yield of diketone and the amount of carbon dioxide evolved, obviously because of simultaneous ketol oxidation, however, the complete dependence of diketone formation upon carbon dioxide elimination strongly suggests an intimate relationship. This relationship will form the subject of a second communication.

EXPERIMENTAL

3-Ethyltetronic acid [*Class* (*b*)(*I*)]. Ethyl α-ethylacetoacetate was brominated in ice-water by the method of Conrad and Schmidt (10). The product, obtained in 73% yield, had b.p. 62–66° at 2 mm. It has been shown (11) that a mixture of α-and γ-bromoesters is always obtained under such conditions. Cyclization was accomplished by heating the ester,[8] to which one drop of concentrated hydrobromic acid had been added, at 100° for 12 hours. Cooling caused the dark liquid to solidify to a gray mass. This was broken up and collected; yield 51%. It was recrystallized from water; m.p. 127–128°. Reported m.p. 126.5° (12). The ferric chloride (enol) test was strong.

3,3-Dimethyltetronic acid. [*Class* (*b*) (*II*)]. Ethyl α,α-dimethyl-γ-acetoxyacetoacetate was prepared by the method of Conrad and Gast (13). In agreement with these authors and contrary to Koelsch (14), some cyclization occurred spontaneously over a two-month period, but it was difficult to separate the liquid tetronic acid thus formed from the acetoxyester. It was therefore treated as follows. The acetoxyester (100 g., 0.46 mole) was added dropwise to 400 g. of rapidly stirred concentrated sulfuric acid. The temperature was maintained below 8° during the addition. After being kept in a closed container at refrigerator temperature for 48 hours, the solution was poured onto 1 kg. of chopped ice, and the whole allowed to reach room temperature. After standing for a further two hours, the mixture was exhaustively extracted with chloroform. The chloroform solution was washed free of sulfuric acid with water, and without drying, the solvent was distilled through a short column. Yield, 89.4%, b.p. 207–212° at 760 mm. Conrad and Gast (13) report b.p. 208–212°. The enol test (ferric chloride) was negative. The *oxime* had m.p. 132–134°; reported value (13), 134°.

Anal. Calc'd for $C_6H_9NO_3$: N, 9.79. Found: N, 9.62, 9.96.

3,5-Dimethyltetronic acid [*Class* (*c*) (*I*)]. Ethyl α-propionylpropionate was prepared by the method of McElvain (15). After bromination (10), it was dried and distilled. Yield of bromoester, 56%, b.p. 52.5–62° at 0.5–1.0 mm. Previous work by Hantzsch and Wohlbruck (16) had shown that this bromoester, on heating[9] above 100°, formed *either* α-propionylacrylic acid or 3,5-dimethyltetronic acid. We therefore carried out this thermal reaction in such a way that the by-products could be isolated. The brominated ethyl α-propionylpropionate was heated in a small distillation flask whose side-arm led to the bottom of a test tube containing 5 ml. of water. This test tube was connected in series to two other test tubes which were placed in ice-salt mixture. At 110° (internal temperature), the bromoester began to boil, and at 122° globules of liquid, immiscible with water, collected in

[8] 3-Ethyltetronic acid forms spontaneously from the bromoester on keeping for about three years.

[9] 3,5-Dimethyltetronic acid forms spontaneously from the bromoester on keeping for about one year.

the first test tube. When the internal temperature reached 160° the reaction was complete. The dark brown residue in the distillation flask was poured into ice-water, and the resultant semisolid mass was collected. The yield of dry solid was 76%. The liquid from the first test tube was separated from the water and dried. It had b.p. 37.5–39° and was shown to be ethyl bromide. No other products were obtained. The reaction, then, is a typical cyclization to a tetronic acid, and this view is substantiated by the strongly enolic nature (ferric chloride test) of the solid product.

Recrystallization of the solid product from water furnished fine white crystals, m.p. 121–122.5°. Hantzsch and Wohlbruck (16) reported m.p. 106–108°, while Emmerling and Kristeller (17) gave m.p. 124°.

Methyltetronic acid [*Class* (*a*) (*I*)]. This was prepared according to the directions of Benary (18), and had the reported m.p. 117–119°.

5,5-Dimethyltetronic acid [*Class* (*a*) (*II*)]. The procedure of Benary (19) was used, and after recrystallization of the solid product from benzene it had m.p. 144–146° instead of the reported (19) m.p. 142–143°. Zeisel determination showed the absence of ethoxyl groups,[10] and the enol (ferric chloride) test was strong.

Anal.[11] Calc'd for $C_6H_8O_3$: C, 56.2; H, 6.25.

Found: C, 56.3; H, 6.20.

It was found that the yield of product could be augmented to 50% by distilling the oily mother-liquor under nitrogen at 4 mm. pressure. The lower fraction, boiling at 67–84°, consisted mostly of ethyl malonate, but the fraction boiling at 84–150° contained some 5,5-dimethyltetronic acid which separated on chilling.

3,5,5-Trimethyltetronic acid [*Class* (*c*) (*II*)]. Ethyl isobutyrylacetate was prepared by the procedure of Kroeker and McElvain (20) and alkylated with methyl iodide and sodium ethoxide by the modification of Schroeter (21). Ethyl α-isobutyrylpropionate was obtained in 91.5% yield; b.p. 92° at 16 mm. Bromination was accomplished by the dropwise addition of bromine (1 mole) in an equal volume of carbon tetrachloride to a rapidly stirred solution of the ester (1 mole) in two volumes of carbon tetrachloride, with the internal temperature maintained below 5°. To complete the rearrangement to the γ-bromoester, the bromination mixture was allowed to stand overnight in the cold-room (22). The mixture was then washed with ice-water and dried. After removal of the solvent the residual brown oil was distilled under nitrogen. Yield, 95%; b.p. 88–90° at 4 mm.; a pale straw-colored[12] oil.

Anal. Calc'd for $C_9H_{15}BrO_3$: Br, 31.84. Found: Br, 31.75.

It was *cyclized* according to the following procedure. The bromoester (1 mole) was slowly added to an aqueous solution of barium hydroxide (1.5 formula-weights), and the mixture was shaken for one hour to effect a clear solution. It was then allowed to stand at room temperature for seven days, during which a small amount of flocculent material separated. The mixture was then concentrated under a vacuum to about one-third of its original volume, with the internal temperature maintained below 40°. On cooling to 0° crystals formed. Addition of cold, dilute hydrochloric acid (1:3) dissolved the crystals at *p*H 6. The *p*H was slowly taken to about 1, during which much powdery white material separated. This was collected and the filtrate was extracted with ether. After removal of the ether an oil remained which slowly solidified. This was added to the main batch and the whole was recrystallized from water. Stout needles, some reaching two inches in length, were obtained in 58% yield; m.p. 135–139°. Recrystallization from benzene formed short white needles, m.p. 137–139°. The enol test (ferric chloride) was strong.

Anal.[13] Calc'd for $C_7H_{10}O_3$: C, 59.12; H, 7.09.

Found: C, 58.93; H, 7.01.

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[10] We wish to thank Mr. B. E. Harrell for this determination.

[11] We wish to thank Mr. John F. Yost for this microanalysis.

[12] At temperatures much above 100° the product darkens with elimination of hydrogen bromide.

[13] We wish to thank Mr. T. E. Gompf for this microanalysis.

α-Ketoisovaleraldehyde. The original method of Conrad and Gast (13) involved: (a) bromination of 3,3-dimethyltetronic acid to form 5-bromo-3,3-dimethyltetronic acid, (b) cold hydrolysis of the bromo compound to give 5-hydroxy-3,3-dimethyltetronic acid, and (c) thermal decarboxylation of the hydroxytetronic acid and sublimation of the resultant 3-methyl-2-ketobutyraldehyde. In the present study it was found advantageous to prepare the ketoaldehyde directly by steam-distillation of 5-bromo-3,3-dimethyltetronic acid. Delicate long white needles, relatively insoluble in cold water, were obtained in 22% yield (based on the 3,3-dimethyltetronic acid); m.p. 95–96°, without recrystallization. Conrad and Gast (13) reported 95°, and Dakin and Dudley (23), who prepared the compound by a totally different route, give 95–96°. The reported (13) m.p. of the *phenylosazone* is 115°. When treated with excess phenylhydrazine in acetic acid, our product formed the orange-colored derivative, m.p. 113–114°.

1-Hydroxy-2-pentanone. The general method of Bunnett and Cason (24) was used for the preparation of 1-chloro-2-pentanone from di-*n*-propylcadmium and chloroacetyl chloride. The chloroketone, obtained in 20% yield, had b.p. 47° at 5 mm. Fourneau and Maréchal (25) report 59° at 17 mm. Alcoholysis of the chloroketone was accomplished by Nef's method (26), the ketol being isolated after refluxing the chloroketone in an absolute methanol-sodium formate mixture for 41 hours. The product, obtained in 15% yield, had b.p. 152° at 760 mm. It formed the known (27) 2,4-dinitrophenylosazone when treated with excess reagent. After recrystallization from toluene the orange-red osazone had m.p. 234° with decomposition.

Oxidation and hydrolysis experiments. In the oxidation and hydrolysis experiments in which the evolved carbon dioxide was determined, the following apparatus was used. A three-necked 100-ml. reaction flask was equipped with a condenser for downward distillation, a dropping-funnel, and an inlet tube that reached to the bottom of the flask. The condenser led to a receiver which was connected to a trap cooled in Dry Ice. The trap, in turn, was connected to a sulfuric-acid bubbler. The bubbler was necessary to remove the last traces of the volatile diketones. Attached to the bubbler was a drying-tube filled with Anhydrone, and to this was attached an Ascarite tube. A weighed sample of the tetronic acid was placed in the reaction flask together with dilute sulfuric acid and nitrogen or air (freed from carbon dioxide), was passed through the system until the Ascarite tube maintained a constant weight. The contents of the flask were then brought to the boiling point, and a solution of chromic oxide in water was added dropwise. This method permitted the diketones to distill as formed, and minimized further oxidation. The Ascarite tube was weighed periodically, and when the carbon dioxide evolution became negligible, the reactions were considered complete. For the hydrolysis experiments a vertical condenser was used instead of the downward one, but the rest of the apparatus remained unchanged.

Hydrolysis of 3-ethyltetronic acid. The acid, 12.56 g. (0.098 mole), was boiled in *N* sulfuric acid under nitrogen for 35 hours. By this time the yield of carbon dioxide was 97%. The vertical condenser was replaced by one for downward distillation, and the colorless ketol was distilled from the brown hydrolysis residue. The distillate was exhaustively extracted with ether and the extract was dried over sodium sulfate. Evaporation of the ether left a colorless oil which strongly reduced Fehling's solution in the cold and which, when treated with excess 2,4-dinitrophenylhydrazine reagent, yielded the same osazone that was obtained from synthetic 1-hydroxy-2-pentanone; m.p. and mixture m.p. 234° with decomposition.

The pale yellow *monophenylhydrazone* was prepared from the hydrolysis product and from the synthetic ketol. After recrystallization from aqueous ethanol the m.p. and mixture m.p. was 70°. This derivative is relatively unstable, and in impure condition it rapidly changes to tar.

Anal. Calc'd for $C_{11}H_{16}N_{20}$: N, 14.50. Found: N, 14.40.

Oxidation of 1-hydroxy-2-pentanone. At 0° an aqueous solution of 15.4 g. (0.154 mole) of chromic oxide was added dropwise and under nitrogen to 7.8 g. (0.072 mole) of the ketol dissolved in 200 ml. of water and 22.5 g. (0.23 mole) of sulfuric acid. After the addition, which required two hours, the reactants were allowed to remain at room temperature for

nine hours. At this time the yield of carbon dioxide was 65%. The volatile products were distilled from the reaction mixture. The total yield of carbon dioxide was 68.5%, and some unoxidized ketol was recovered from the Dry-Ice trap. The acidic distillate was made basic with solid sodium bicarbonate, and distilled. The distillate from this operation was strongly reducing, and the preparation of derivatives showed it to contain 1-hydroxy-2-pentanone.

The basic residue, after concentration to small bulk, was acidified with hydrochloric acid and exhaustively extracted with ether. The ether extract was dried over calcium chloride, and distilled. Two fractions were obtained, one boiling about 100° and the other from 140–159°. The higher-boiling fraction was shown to be butyric acid, since its *p*-toluide had m.p. 72°, either alone or admixed with the *p*-toluide of butyric acid. The lower-boiling acid strongly reduced mercuric ion and potassium permanganate solution. It was proved to be formic acid by preparing its *p*-bromophenacyl derivative which had m.p. 139° (28).

Oxidation of 3,5-dimethyltetronic acid. An aqueous solution of 9.6 g. (0.096 mole) of chromic oxide was added dropwise to a boiling solution of 8.0 g. (0.063 mole) of 3,5-dimethyltetronic acid in 64 g. of dilute (1:3) sulfuric acid. Carbon dioxide elimination was vigorous and the yellow diketone slowly distilled from the reaction mixture. The yield of carbon dioxide was not determined in this experiment. Isolation of the diketone was accomplished by the tedious method of von Pechmann (29). The yield of 2,3-pentanedione was 28.4%; b.p. 105–111° [reported b.p. 104–111° (29)]. Treatment with excess hydroxylamine reagent formed the known (30) dioxime, m.p. 172–172.5°. It has been shown (30) that α-diketones form only disemicarbazones; the one from 2,3-pentanedione has m.p. 251–252° (30). Our product had m.p. 254–255°.

Hydrolysis of 3,5-dimethyltetronic acid. Under nitrogen, 1.20 g. (0.0094 mole) of the acid was boiled in 15 ml. of dilute (1:3) sulfuric acid for 100 hours. The yield of carbon dioxide was 90%. A trace of yellow oil resembling 2,3-pentanedione in its color and odor, was found in the Dry-Ice trap. The colorless distillate strongly reduced Fehling's solution, and with excess phenylhydrazine reagent formed an orange derivative, m.p. 163° [the phenylosazone of 2,3-pentanedione has m.p. 166–167° (4)]. After acidification with sulfuric acid, the distillate was oxidized. The yield of carbon dioxide was 10%, but no yellow diketone was obtained.

A similar hydrolysis, but carried out under purified air, formed carbon dioxide in 100% yield after boiling for about 35 hours. More diketone was obtained during this hydrolysis than in the previous one. Oxidation of the distillate failed to form any diketone, but carbon dioxide was obtained in 54% yield on boiling the oxidation mixture for 17 hours.

Oxidation of 3-ethyltetronic acid. The acid (8.8 g., 0.063 mole) was oxidized with 10.6 g. (0.106 mole) of chromic oxide and 60 ml. of dilute (1:3) sulfuric acid. Carbon dioxide was obtained in 64% yield. The yellow diketone was separated from the strongly reducing distillate, and transformed into the dioxime which did not depress the m.p. of the dioxime of 2,3-pentanedione. Based on the weight of dioxime obtained, the yield of diketone was 43%. In several oxidations it was shown that no quantitative relationship existed between the amount of carbon dioxide evolved and the yield of diketone.

Oxidation of 5-methyltetronic acid. The acid, 3.36 g. (0.03 mole), was treated with excess oxidant and it yielded 78% carbon dioxide. The distillate was yellow, neutral to bicarbonate solution, and it strongly reduced Fehling's solution. It gave a positive iodoform test. The yellow oil was separated and when treated with excess 2,4-dinitrophenylhydrazine reagent it formed an orange derivative, m.p. 317°. The 2,4-dinitrophenylosazone of 2,3-butanedione is reported (31) to melt at 314–315°. The disemicarbazone (30) has m.p. 278–279°; our product had m.p. 277°.

Hydrolysis of 5-methyltetronic acid. A 66.5% yield of carbon dioxide was obtained on boiling 2.7 g. (0.024 mole) of this acid in dilute sulfuric acid under nitrogen for 40 hours. Some yellow diketone had also formed. The water-white distillate was separated from the traces of yellow oil, acidified and treated with excess oxidant. On boiling for several hours, the yield of carbon dioxide was 21%, but no diketone was obtained.

Oxidation of 5,5-dimethyltetronic acid. A 3.03-g. sample (0.024 mole) was treated with excess oxidant. A colorless distillate was obtained, and the yield of carbon dioxide was 90%. The distillate was neutral to bicarbonate solution, and it failed to reduce either Fehling's solution or Tollens' reagent. It gave a positive iodoform test, and when treated with 2,4-dinitrophenylhydrazine it formed the known 2,4-dinitrophenylhydrazone of acetone, m.p. alone or admixed with authentic material, 126° (28). A recovery of 0.1 g. of unoxidized tetronic acid was obtained by extracting the oxidation residue with ether.

Oxidation of 3,5,5-trimethyltetronic acid. Oxidation of 4.02 g. (0.028 mole), with excess oxidant produced carbon dioxide in 90% yield. The distillate contained 1.5 ml. of a deep yellow oil; yield of diketone about 50%. The literature (32) gives m.p. 117° for the phenylosazone of 4-methyl-2,3-pentanedione, and m.p. 155° (33) for its dioxime. With excess phenylhydrazine our product formed a derivative, m.p. 114°, and with excess hydroxylamine solution, a compound m.p. 155°. Tetronic acid, 0.2 g., was recovered.

Oxidation of 3,3-dimethyltetronic acid. A 3.28-g. sample (0.027 mole), was oxidized in the usual manner. The yield of carbon dioxide was 140%. The distillate was acidic, colorless, and strongly reduced Fehling's solution. When treated with excess phenylhydrazine in acetic acid, a portion of the distillate yielded an orange-colored derivative, m.p. 115°. When mixed with the phenylosazone of α-ketoisobutyraldehyde (m.p. 113–114°) the mixture m.p. was 113–114°. Since α-ketoisovaleraldehyde is a white solid, volatile with steam and relatively insoluble in water, the distillate must have contained 1-hydroxy-3-methyl-2-butanone.

The distillate was made basic with solid sodium bicarbonate and evaporated to dryness. The residual salt reduced both acidic and basic potassium permanganate solution, showing the presence of formate ion. Ether extraction of a portion of the acidified residual salt furnished a few drops of liquid possessing the characteristic odor of isobutyric acid. A further portion of salt was refluxed with thionyl chloride and then treated with *p*-toluidine. The derivative that formed had m.p. 103° in accord with the reported m.p. (28) of the *p*-toliude of isobutyric acid.

Ether extraction of the oxidation residue furnished a small amount of crystalline material. After recrystallization from ether-ligroin it was obtained as long white needles, m.p. 193–194°, with vigorous decomposition. The substance was acidic and, as its analysis showed, was dimethylmalonic acid (34).

Anal.[14] Calc'd for $C_5H_8O_4$: C, 45.45; H, 6.06.
Found: C, 45.40, 45.32; H, 6.21, 6.08.

SUMMARY

Oxidation studies have been carried out on six tetronic acids, and structural criteria for the production of α-diketones have been established. It has been shown that the diketones result from oxidation of appropriate tetronic acids before hydrolysis of the lactone ring occurs. Those tetronic acids that are not oxidized to α-diketones have been discussed, and an explanation for their behavior has been advanced.

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CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE JOHNS HOPKINS UNIVERSITY]

THE SYNTHESIS OF 2,6-DIAMINOBENZOIC ACID

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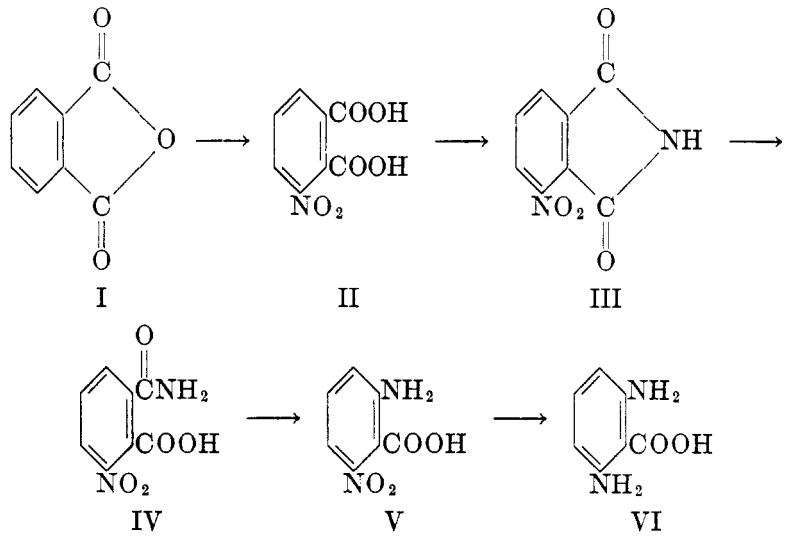
Of the unsubstituted diaminobenzoic acids, the 2,3- (1), 2,4- (2), 2,5- (3)' 3,4- (1), and 3,5- (4) have been prepared. There is not, however, any reference in the literature to the preparation of 2,6-diaminobenzoic acid (VI). In connection with another problem this compound was needed, and this manuscript describes the results obtained in the investigation of a method for the synthesis of [this acid.

The first appr ach to be tried envisaged the utilization of 2,6-dinitrotoluene as an intermediate. Holleman and Boeseken (5) have reported the preparation of this compound from 2,4,6-trinitrotoluene by way of reduction to 4-amino-2,6-dinitrotoluene with the use of ammonium sulfide. These authors reported a yield of 20% for this reduction, but in our hands the yield was never above 10%; the isolation of this quantity was so tedious that this approach was abandoned.

6-Nitroanthranilic acid (V) seemed to be an attractive starting material for the desired acid. This compound has been prepared in various ways; the most widely used is as follows:



I II III

IV V VI

This method was developed by Kahn (6) and improved by Bogert and co-workers (7) some years ago; there does not appear to have been any further investigation on this series of reactions since then. Since a fairly large quantity of V was desired, each of the steps was carefully reinvestigated to ascertain if any improvement in yield or simplification of procedure could be effected.

The nitration of phthalic anhydride with a nitrating mixture of concentrated

nitric acid and concentrated sulfuric acid proceeds very satisfactorily; it is not necessary to use fuming nitric acid as suggested by some workers (8). The nitration of phthalic anhydride with concentrated nitric acid has been carried out by Littmann (9), and the yield of crude product was reported to be 85–90%. Littmann's somewhat involved procedure was considerably simplified and very pure 3-nitrophthalic acid (II) was readily obtained in 26% yield.

The transformation of the acid II to the imide III was carried out according to the procedure of Bogert and Seil (7b). Attempts to transform the imide III directly to the acid V according to the procedure of Seidel and Bittner (10) resulted in a very impure product that could not be readily purified. This observation is in agreement with the report of Bogert and Chambers.

Hydrolysis of the imide to the amido acid IV was carried out by Kahn (6) on a very small scale. When fairly large quantities of the imide were hydrolyzed, it was found that the concentration of imide should not exceed about 5%; otherwise, the product obtained was a mixture from which only the acid II could be isolated on crystallization from water.

With the use of pure IV the acid V could be obtained readily in a high state of purity following the procedure of Bogert and Chambers (7a). If the amido acid was not quite pure, however, an inferior grade of the acid V was obtained; this product could not be readily purified by crystallization.

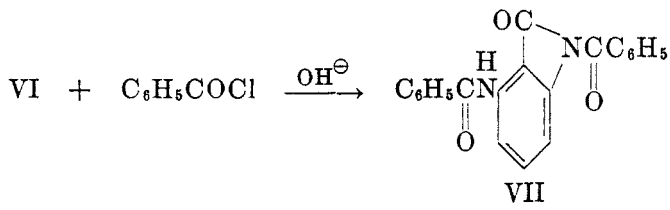
The reduction of the nitro acid V to the diamino acid VI with the usual metal and mineral acid combination seemed unpromising, for the nitro acid readily loses carbon dioxide in the presence of small amounts of mineral acid. For example, attempts to esterify the nitro acid with the use of hydrogen chloride or sulfuric acid as catalyst result in the formation of *m*-nitroaniline (6).

Reduction of the nitro acid with Adams' catalyst took place in methanol or ethanol, but no crystalline material could be isolated from the reaction mixture. The reduction was satisfactorily accomplished in methanol with the use of Raney nickel catalyst at three atmospheres pressure. The crude acid was obtained in 40% yield.

The diamino acid is not very stable. The pure acid crystallizes from anhydrous ethyl ace ate and hexane in the form of white needles, m.p. 104° (uncorr.). In the course of two days the material has nearly completely decomposed to a green tar. If the acid is dissolved in solvents that contain some water, the solution turns green-black in color, and the acid cannot be isolated again. One sample of the acid was carefully dried under vacuum and, if kept under vacuum, seemed to be stable for about one week. In the usual Dumas apparatus for the determination of nitrogen, micro-bubbles could not be obtained with this acid, apparently indicating rather rapid decomposition.[1]

On benzoylation of this amino acid only the benzamidobenzoyl anthranil (VII) could be isolated in a pure state from the complex reaction mixture. The benzoylation of an anthranilic acid derivative frequently results in a mixture of the benzoyl anthranil and benzamido acid (11).

[1] Observation of Mrs. June Long.



VII

A hydrochloride of the amino acid could be obtained, but it was too unstable for a satisfactory analysis.

If this diamino acid could be successfully diazotized, a convenient route to the synthesis of several 2,6-disubstituted benzoic acids would be available. Unfortunately, several attempts to prepare the diazonium salt in the usual manner yielded only intractable tars. It is possible that diazotization under anhydrous conditions might proceed satisfactorily.

Acknowledgement. We are indebted to Mrs. Marjorie Melville for experimental assistance during part of this work.

EXPERIMENTAL[2]

3-Nitrophthalic acid (II). To a mixture of 175 g. of phthalic anhydride and 175 cc. of concentrated nitric acid in a 3-l. round-bottom flask there was slowly added with shaking 175 cc. of concentrated sulfuric acid. The mixture was heated for three hours on the steam-bath, after which it was cooled and poured with constant stirring into 500 cc. of cold water. An additional 60 cc. of water was used to rinse the flask. The suspension was cooled to 10°, filtered, and pressed as dry as possible with the aid of a rubber dam. The filter cake was thoroughly stirred for a few minutes with 200 cc. of ice-water and the precipitate was crystallized from 200 cc. of glacial acetic acid. The solution was allowed to stand at room temperature for 24 hours to ensure complete precipitation. The yield of small, hard prisms, m.p. 216–218° (vac.) [reported (8) 217° (vac.)], was 70 g. (26%).

3-Nitrophthalamic acid (IV). The imide III (96 g.) was shaken with a solution of 56 g. of potassium hydroxide in 2 l. of water until solution had taken place (*ca.* two hours). The solution was cooled and carefully acidified. The precipitate was washed with a small amount of cold water, and dried. The yield of amido acid, m.p. 153–155° with resolidification and remelting 212–213° [reported (6) 152–155° with resolidification and remelting 212°] was 84 g. (80%). If the above reaction was repeated using only 1 l. of water as solvent, the product melted over a wide range, 124–160°. Crystallization from warm water afforded only 3-nitrophthalic acid, m.p. 216–218° (vac.).

2,6-Diaminobenzoic acid (VI). 6-Nitroanthranilic acid (1 g.) was dissolved in 10 cc. of absolute methanol and *ca.* 1 g. of Raney nickel catalyst was added. The reduction was carried out in the Parr apparatus for one hour; the uptake of hydrogen corresponded to 80% of the calculated. The solution was rapidly filtered with suction, and the nickel was washed with a few cc. of methanol. The yellow solution was evaporated to dryness *in vacuo* (best below 20°). The residue remaining after evaporation ranged in color from yellow to greenish-black depending on the temperature of evaporation. Enough warm ethyl acetate was added to dissolve all soluble material, and the product was obtained on the addition of hexane. The yield was 330 mg. (40%). The pure acid, m.p. 103.5–104° (dec.) was obtained as short needles after several recrystallizations from a mixture of ethyl acetate and hexane.

Anal. Calc'd for $C_7H_8N_2O_2$: C, 55.24; H, 5.29.
Found: C, 55.73; H, 5.20.

[2] Melting points are uncorrected.

Treatment of this acid with benzoyl chloride and dilute alkali in the cold yielded the anthranil VII as the alkali-insoluble product. The compound crystallized from ethyl acetate as long, faintly-yellow needles, m.p. 205–205.5°.

Anal.[3] Calc'd for $C_{21}H_{14}N_2O_3$: N, 8.18. Found: N, 8.48.

No definite product could be isolated from the alkali-soluble material.

A *hydrochloride*, m.p. 160–160.5° (dec.) could be obtained, but it decomposed too rapidly to permit analysis.

The amino acid did not form an oxalate.

SUMMARY

1. The synthesis of 2,6-diaminobenzoic acid by the reduction of 6-nitroanthranilic acid has been reported.

2. The synthesis of 6-nitroanthranilic acid from phthalic anhydride has been reinvestigated.

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[3] Analysis by Mrs. June Long.

[CONTRIBUTION FROM THE CHEMICAL DEPARTMENT OF THE GENERAL ELECTRIC COMPANY]

DERIVATIVES OF *o*- AND *p*-(α-PHENYLETHYL)PHENOL

K. C. FRISCH

Received November 14, 1949

Due to the availability and the low cost of the raw materials, the α-phenylethylphenols and their derivatives seem to offer a wide field of applications.

The reaction between phenol and styrene in acid medium was investigated by Koenigs (1, 2), as early as 1890–1891. He reported the preparation and the structure proof of the reaction products of phenol and styrene, which consisted of a mixture of *o*- and *p*-(α-phenylethyl)phenol. Niederl and co-workers (3, 4, 5), brought forward considerable evidence for the mechanism of this reaction. The reaction presumably proceeds through addition of the acid, usually sulfuric acid, to the ethylenic double bond. The addition compound then reacts with the phenol to form the phenyl ether which on rearrangement yields the phenylethylphenol.

Recently (6, 7, 8, 9), several patents appeared, describing methods for the preparation of α-phenylethylphenols as well as variations in the nature of the phenol and the unsaturated hydrocarbon. However, very little is known of the derivatives of *o*- and *p*-(α-phenylethyl)phenol.

The esters of *o*- and *p*-(α-phenylethyl)phenol, with exception of the acetates, were prepared by extending the method of Cherry (10), using acetic anhydride as a dehydrating agent. The acetates were prepared by refluxing the α-phenylethylphenols with acetic anhydride in the presence of a small amount of anhydrous sodium carbonate.

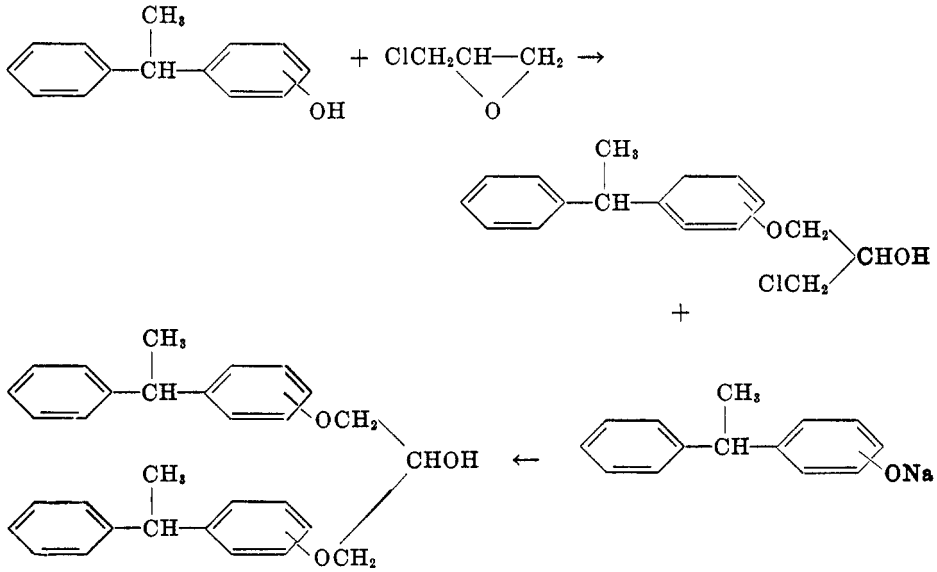
Alkylation of the α-phenylethylphenols was effected by reacting them with the corresponding alkyl bromides in the presence of anhydrous potassium carbonate and acetone as solvent.

The reaction of the α-phenylethylphenols with epichlorohydrin lent itself conveniently to the preparation of the 1,3-substituted glycerol ethers. Using two moles of α-phenylethylphenol to one mole of epichlorohydrin and working in an alkaline medium, the formation of the glycid ether was partly suppressed in favor of the 1,3-substituted glycerol ether. Based on the analogy of the reaction of phenol with epichlorohydrin (11), the reaction presumably proceeds in the following steps, see page 588.

The β-ethanol ethers were prepared by using ethylene oxide in the presence of sodium hydroxide as catalyst.

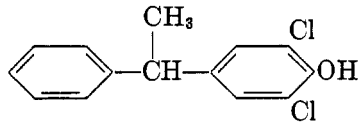
The phenoxyacetic acids were made using the method described by Pokorny (12). These substances appear to be of interest due to their relationship to well-known plant growth substances.

In view of the ever increasing use of chlorinated phenol derivatives as fungicides, growth substances, etc., it was found of interest to prepare the chlorinated *o*- and *p*-(α-phenylethyl)phenols and some of their derivatives. The chlorination

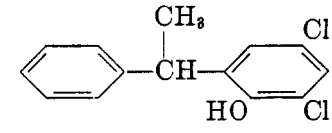


was carried out in carbon tetrachloride as solvent and led to the di-substitution products as could be expected under the conditions of the experiments.

The *p*-(α-phenylethyl)phenol yielded 2,6-dichloro-4-(α-phenylethyl)phenol (I) and the *o*-(α-phenylethyl)phenol gave 2,4-dichloro-6-(α-phenylethyl)phenol (II).



(I)



(II)

Esters and ethers of these chlorinated products were made in an analogous fashion to that of the unsubstituted α-phenylethyl phenols.

EXPERIMENTAL

The *o- and p-(α-phenylethyl)phenols* used were prepared in this laboratory by the following procedure. Phenol and styrene were reacted in a mole ratio of 4:1 in the presence of sulfuric acid (0.74% of total weight). The styrene was added dropwise to the phenol with stirring in order to avoid polymerization. The mixture was refluxed for four hours. The acid was then neutralized with sodium carbonate solution. The precipitate, consisting of sodium sulfate and sodium carbonate, was filtered off and the water and excess phenol were distilled off. The residual mixture of the *o*- and *p*-(α-phenylethyl)phenol was separated by distillation in a Stedman column. The *o*-isomer distilled at 300–302° at 742.2 mm. and the *p*-isomer at 315–316° at 742.2 mm. The total yield was 75–85%, the *p*-isomer constituting 59–60% and the *o*-isomer 40–41%.

Procedure for esterification of o- and p-(α-phenylethyl)phenol. A round-bottom flask was fitted with a six-ball Snyder column, at the top of which was mounted a still-head with a side-arm fitted with a stopcock. The still-head was connected to a reflux condenser and thermometer, and the side-arm to a downward condenser, provided with an adapter and receiving flask at its end. In the reaction flask was placed: 1 mole of *o*- or *p*-(α-phenyl-

ethyl)phenol, 1 mole of a monocarboxylic acid (½ mol for dicarboxylic acids), and 1 mole of acetic anhydride. The mixture was refluxed for a period of time ranging from ½–2 hours (the latter being the case for dicarboxylic acids). The stopcock on the side-arm of the still-head was then opened and the acetic acid distilled off. The residual material was washed with dilute sodium hydroxide to remove any starting materials and was extracted with ether. The ether extract was dried over sodium sulfate. The solvent was removed and the residual product purified either by recrystallization or by a vacuum-distillation.

The *acetates* of *o*- and *p*-(α-phenylethyl)phenol were prepared in the following way: In a 500-cc. round-bottom flask was placed: 100 g. of *o*- or *p*-(α-phenylethyl)phenol, 300 cc. of acetic anhydride, and 10 g. of anhydrous sodium carbonate. The mixture was refluxed for a period of time ranging from 1½ to 5½ hours. The excess acetic anhydride and the acetic acid were distilled off and residual liquid vacuum-distilled.

p-(α-Phenylethyl)phenyl acetate. Colorless liquid, distilling at 186–189° at 6 mm. Yield: 88%.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.65.
Found: C, 79.87; H, 6.43.

o-(α-Phenylethyl)phenyl acetate. Colorless liquid, distilling at 148° at 2.2 mm. Yield: 82%.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.65.
Found: C, 80.08; H, 6.64.

p-(α-Phenylethyl)phenyl propionate. Colorless liquid, distilling at 198–204° at 7 mm. Yield: 93%.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.08.
Found: C, 80.43; H, 6.99.

o-(α-Phenylethyl)phenyl propionate. Colorless liquid, distilling at 136–139° at 1.2 mm. Yield: 88%.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.08.
Found: C, 80.44; H, 6.80.

p-(α-Phenylethyl)phenyl butyrate. Colorless liquid, distilling at 159° at 1.1 mm. Yield: 91%.

Anal. Calc'd for $C_{16}H_{20}O_2$: C, 80.6; H, 7.4.
Found: C, 80.49; H, 7.54.

o-(α-Phenylethyl)phenyl butyrate. Colorless liquid, distilling at 140° at 0.6 mm. Yield: 88%.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.4.
Found: C, 80.95; H, 6.9.

p-(α-Phenylethyl)phenyl crotonate. Colorless liquid, distilling at 185–188° at 1.8 mm. Yield: 67%.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.2; H, 6.77.
Found: C, 80.6; H, 6.62.

o-(α-Phenylethyl)phenol crotonate. Colorless liquid, distilling at 142–146° at 1.4 mm. Yield: 63%.

Anal. Calc'd for $C_{18}H_{18}O_2$: C, 81.20; H, 6.77.
Found: C, 81.48; H, 7.02.

Bis-o-(α-phenylethyl)phenyl adipate. Colorless liquid, distilling at 128° at 1.3 mm. Yield: 30%.

Anal. Calc'd for $C_{34}H_{34}O_4$: C, 80.6; H, 6.7.
Found: C, 80.2; H, 6.7.

Bis-p-(α-phenylethyl)phenyl adipate. Colorless liquid, distilling at 165° at 3.0 mm. Yield: 29%.

Anal. Calc'd for $C_{34}H_{34}O_4$: C, 80.6; H, 6.7.
Found: C, 81.0; H, 6.9.

Bis-p-(α-phenylethyl)phenyl sebacate. Colorless liquid, distilling at 150–154° at 1.3 mm. Yield: 36%.

Anal. Calc'd for $C_{38}H_{42}O_4$: C, 81.1; H, 7.4.
Found: C, 81.4; H, 6.8.

Bis-o-(α-phenylethyl)phenyl sebacate. Colorless liquid, distilling at 125–127° at 0.7–0.8 mm. Yield: 32%.

Anal. Calc'd for $C_{38}H_{42}O_4$: C, 81.1; H, 7.4.
Found: C, 81.23; H, 6.7.

Procedure for the preparation of alkyl ethers of o- and p-(α-phenylethyl)phenol. In a round-bottom flask was placed: 1 mole of *o*- or *p*-(α-phenylethyl)phenol, 1 mole of alkyl bromide, 1 mole of anhydrous potassium carbonate, and 5 moles of acetone. The mixture was refluxed for 3½ hours. The white precipitate, consisting of potassium bromide, was filtered off. The filtrate was freed from solvent and washed with dilute sodium hydroxide solution and water to remove any starting materials. It was then extracted with ether and the ether extract dried over sodium sulfate. The solvent was distilled off and the product purified by a vacuum-distillation.

p-(α-Phenylethyl)phenyl n-propyl ether. Colorless liquid, distilling at 189–190° at 6 mm. Yield: 45%.

Anal. Calc'd for $C_{17}H_{20}O$: C, 85.0; H, 8.3.
Found: C, 84.85; H, 8.49.

o-(α-Phenylethyl)phenyl n-propyl ether. Colorless liquid, distilling at 157–160° at 4 mm. Yield: 30%.

Anal. Calc'd for $C_{17}H_{20}O$: C, 85.0; H, 8.3.
Found: C, 85.06; H, 8.03.

p-(α-Phenylethyl)phenyl n-butyl ether. Colorless liquid, distilling at 192–197° at 6 mm. Yield: 45%.

Anal. Calc'd for $C_{18}H_{22}O$: C, 85.0; H, 8.65.
Found: C, 84.87; H, 8.41.

o-(α-Phenylethyl)phenyl n-butyl ether. Colorless liquid, distilling at 160° at 3 mm. Yield: 30%.

Anal. Calc'd for $C_{18}H_{22}O$: C, 85.0; H, 8.65.
Found: C, 85.05; H, 8.80.

Procedure for the preparation of the glycerol diethers of o- and p-(α-phenylethyl)phenol. In a 500-cc. round-bottom flask was placed: 50 g. of *o*- or *p*-(α-phenylethyl)phenol, 10.6 g. of sodium hydroxide in 100 cc. of water, and 11.7 g. of epichlorohydrin. The mixture was refluxed for five hours. Afterwards it was washed with a dilute sodium hydroxide solution and extracted with ether. The ether extract was dried over sodium sulfate. After filtering the solvent was removed and the product was distilled *in vacuo*.

1,3-Bis-[p-(α-phenylethyl)phenoxy]propanol-2. Light yellow oil, distilling at 164–166° at 3 mm. Yield: 20%.

Anal. Calc'd for $C_{31}H_{32}O_3$: C, 84.16; H, 7.23.
Found: C, 84.06; H, 7.14.

1,3-Bis[o-(α-phenylethyl)phenoxy]propanol-2. Light yellow oil, distilling at 142–144° at 2.6 mm. Yield: 20%.

Anal. Calc'd for $C_{31}H_{32}O_3$: C, 84.16; H, 7.23.
Found: C, 83.74; H, 7.21.

Procedure for the preparation of β-ethanol ethers of o- and p-(α-phenylethyl)phenol. In a pressure-bottle was placed: 0.1 mole of *o*- or *p*-(α-phenylethyl)phenol, 0.025 mole of sodium hydroxide, 25 cc. of water, and 0.1 mole of ethylene oxide. The bottle was placed in a thermostatically-controlled water-bath overnight at 40°. A shaking device provided agitation. Two layers formed. The organic layer was separated and fractionally distilled.

2-(α-Phenylethyl)phenoxyethanol-2. Colorless cubes from ligroin, m.p. 83° (uncorr.); b.p. 175° at 0.3 mm. Yield: 66%.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.45.
Found: C, 79.1; H, 7.50.

4-(α-Phenylethyl)phenoxyethanol-2. Colorless liquid, distilling at 175° at 0.6 mm. Yield: 64%.

Anal. Calc'd for $C_{16}H_{18}O_2$: C, 79.3; H, 7.45.
Found: C, 79.1; H, 7.50.

Procedure for the preparation of o- and p-(α-phenylethyl)phenoxyacetic acids. In a beaker was placed: 0.2 mole of *o*- or *p*-(α-phenylethyl)phenol, 0.2 mole of monochloroacetic acid, 0.21 mole of sodium hydroxide, and 75 cc. of water. The mixture was concentrated on the steam-bath. It was then dissolved in 400 cc. of hot water. After cooling it was made acid to litmus and extracted with ether. The ether extract was dried over sodium sulfate, the solvent was evaporated, and the residual liquid fractionally-distilled.

2-(α-Phenylethyl)phenoxyacetic acid. Colorless prisms from benzene, m.p. 135° (uncorr.). Yield: 48%.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 75.2; H, 6.4.

4-(α-Phenylethyl)phenoxyacetic acid. Colorless plates from ligroin, m.p. 100° (uncorr.). Yield: 51%.

Anal. Calc'd for $C_{16}H_{16}O_3$: C, 75.0; H, 6.3.
Found: C, 75.1; H, 6.4.

Procedure for the chlorination of o- and p-(α-phenylethyl)phenol. In a 3-l. three-necked flask, equipped with stirrer, gas inlet tube, and outlet tube, was placed 100 g. of *o*- or *p*-(α-phenylethyl)phenol and 500 cc. of carbon tetrachloride. The reaction flask was immersed in a cold-water bath. A stream of chlorine gas was passed through the solution at a fairly rapid rate for three hours. The solvent was then evaporated and the residual liquid distilled *in vacuo*.

2,6-Dichloro-4-(α-phenylethyl)phenol. Light yellow oil, distilling at 196–202° at 6 mm. Yield: 50%.

Anal. Calc'd for $C_{14}H_{12}Cl_2O$: Cl, 26.59. Found: Cl, 26.53.

2,4-Dichloro-6-(α-phenylethyl)phenol. Light yellow oil, distilling at 174–175° at 3.2 mm. Yield: 53%.

Anal. Calc'd for $C_{14}H_{12}Cl_2O$: Cl, 26.59. Found: Cl, 26.28.

2,4-Dichloro-6-(α-phenylethyl)phenyl allyl ether was prepared in the following way: In a 500-cc. three-necked flask, equipped with stirrer, reflux condenser, and dropping-funnel, was placed 27.4 g. of 2,4-dichloro-6-(α-phenylethyl)phenol together with a solution of 4.6 g. of sodium hydroxide in 50 cc. of water and 50 cc. of methanol. Then 13.7 g. of allyl bromide was added gradually through the dropping-funnel. The reaction mixture was stirred for 40 minutes more. The oily product was washed with a dilute sodium hydroxide solution, extracted with ether, and the extract was dried over sodium sulfate. The solvent was removed and the remainder of the liquid was distilled *in vacuo*. Rejecting the forerun, the product distilled at 158–162° at 1.2 mm. as a light yellow liquid. Yield: 50%.

Anal. Calc'd for $C_{17}H_{16}Cl_2O$: C, 66.45; H, 5.2.
Found: C, 66.71; H, 5.33.

The esters of the chlorinated o- and p-(α-phenylethyl)phenols were prepared in the same manner as described for the unsubstituted phenylethylphenols.

2,6-Dichloro-4-(α-phenylethyl)phenyl acetate. Light yellow liquid, distilling at 140–144° at 1.6 mm. Yield: 51%.

Anal. Calc'd for $C_{16}H_{15}Cl_2O_2$: Cl, 22.75. Found: Cl, 22.63.

2,4-Dichloro-6-(α-phenylethyl)phenyl acetate. Colorless prisms from alcohol, m.p. 74.5–75.5° (uncorr.). Yield: 60%.

Anal. Calc'd for $C_{16}H_{15}Cl_2O_2$: C, 62.1; H, 4.52.
Found: C, 61.96; H, 4.35.

2,4-Dichloro-6-(α-phenylethyl)phenyl propionate. Colorless oil, distilling at 180–182° at 1.7 mm. Yield: 40%.

Anal. Calc'd for $C_{17}H_{16}Cl_2O_2$: C, 63.4; H, 4.65.
Found: C, 63.80; H, 4.65.

Acknowledgment. The author wishes to express his appreciation to Miss J. Tolman and Mr. W. Steuer who performed the analyses.

SUMMARY

1. A series of new aliphatic esters, ethers, alcohol-ethers, and oxyacetic acids of *o*- and *p*-(α-phenylethyl)phenol was prepared and characterized.

2. The glycerol diethers of *o*- and *p*-(α-phenylethyl)phenol were prepared conveniently by the reaction with epichlorohydrin.

3. The chlorination of *o*- and *p*-(α-phenylethyl)phenol in carbon tetrachloride as solvent, yielded the corresponding dichloro compounds.

4. Esters and ethers of these dichloro compounds were prepared.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, STATE UNIVERSITY OF IOWA]

THE PREPARATION OF THYROXINE ANALOGS

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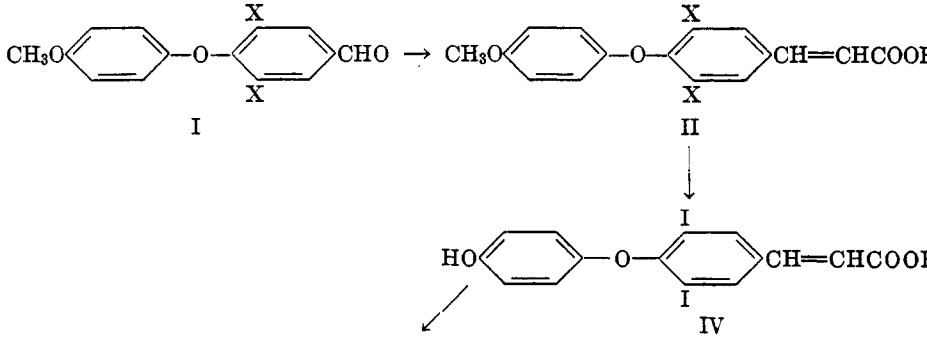
Variation of the side chain in tryptophan as exemplified by indoleacrylic acid produces a compound which interferes with the growth-stimulating action of tryptophan (1). In order to determine whether such a variation in structure among amino acids is general in producing antagonistic effects, β-substituted acrylic acids which have the same diphenyl ether nucleus as thyroxine have been synthesized for testing as possible antithyroid agents.

3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) and 3,5-dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br) were prepared by condensing 3,5-diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I) and 3,5-dibromo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = Br) (2) with malonic acid in the presence of pyridine and piperidine.



[1] Abstracted in part from the Ph.D. thesis (1949) of S. C. Wang and the M.S. thesis (1947) of Priscilla Lyons.

Halogenation of the two cinnamic acids to the corresponding tetrahalogenated compound could not be accomplished directly. Bromination of the bromocinnamic acid (II, X = Br) gave the hexabromo compound (III). Proof for this structure was the liberation of iodine from a solution of sodium iodide in acetone by III with the formation of sodium bromide. Iodination of the corresponding iodocinnamic acid (II, X = I) failed even under drastic conditions such as treatment with an excess of iodine in methanolic potassium hydroxide for 48 hours. Iodination could be accomplished, however, to the tetraiodo compound (V) if the demethylated product (IV) was used. Evidence for the *ortho* substitution of the iodine atoms is the intense red color produced by this compound (V) when warmed in alcohol with nitrous acid and then treated with ammonia. This color test is in general characteristic of *ortho*-diiodophenols (3).

The treatment with hydriodic acid apparently does not affect the double bond, since the presence of unsaturation in the tetraiodo compound (V) and also in the demethylated diiodocinnamic acid (IV) was demonstrated by absorption spectra measurements and polarographic studies. The substituted propionic acid (VI) necessary for this comparison was prepared from 3,5-diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) by treatment with hydriodic acid and red phosphorus in acetic anhydride.

All the compounds with the exception of 3,5-dibromo-4-(4′-methoxyphenxoy) cinnamic acid showed a thyroxine-like action. The results will be reported elsewhere.

EXPERIMENTAL[2]

3,5-Dibromo-4-(4′-methoxyphenoxy)benzaldehyde (I, X=Br). This aldehyde was prepared according to the directions of Schuegraf (2) with a slight modification. The intermediate nitrile was purified by distillation at reduced pressure; b.p. 205°/1 mm.

3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br). A mixture of 3,5-dibromo-4-(4′-methoxyphenoxy)benzaldehyde (4.9 g.) and malonic acid (2.33 g.) in pyridine (8.1 ml.) containing three drops of piperidine was refluxed for three hours on the steam-bath. The resulting light tan solution was filtered into a mixture of conc'd hydrochloric acid (7.5 ml.) and 13 g. of ice with stirring. The white solid formed was filtered and washed, first with 10% hydrochloric acid, and then with water. The product (4 g., 87%) when recrystallized from ethyl acetate melted at 228–230°.

Anal. Calc'd for $C_{16}H_{12}Br_2O_4$: C, 44.89; H, 2.83.
Found: C, 45.25; H, 2.86.

β-[3,5-Dibromo-4-(4′-methoxyphenoxy)phenyl]-α,β-dibromopropionic acid (III). 3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = Br) (2 g.) was kept in contact with bromine vapor in a desiccator until its weight increased by 1.5 g. (about 4–5 hours). The red color in the product was removed by dissolving the compound in alcohol and reprecipitating it by the addition of water. The product, recrystallized from benzene, melted at 210–215° with decomposition.

Anal. Calc'd for $C_{16}H_{10}Br_6O_4$: C, 25.77; H, 1.35.
Found: C, 26.00; H, 1.52.

Bromination of the dibromocinnamic acid (II, X = Br) in acetic acid gave a non-homogeneous product.

The hexabromo derivative when dissolved in acetone containing sodium iodide liberated iodine with the formation of sodium bromide. Upon pouring into water and filtering 3,5-

[2] Melting points are not corrected.

dibromo-4-(3′,5′-dibromo-4′-methoxyphenoxy)cinnamic acid was obtained. Recrystallization from ethanol or dilute acetone gave a crystalline product which melted at 273–275° d. (block)

Anal. Calc'd for $C_{16}H_{10}Br_4O_4$: C, 32.80; H, 1.72.

Found: 32.39; H, 1.91.

3,5-Diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I). This aldehyde (I, X = I) was prepared according to the directions of Harington and Barger (3).

3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I). 3,5-Diiodo-4-(4′-methoxyphenoxy)benzaldehyde (I, X = I) (4.8 g.) and malonic acid (2 g.) in pyridine (10 ml.) containing three drops of piperidine were treated in a similar fashion to that used with the corresponding dibromo compound. The product (5.2 g.), when recrystallized from benzene, melted at 250–251°.

Anal. Calc'd for $C_{16}H_{12}I_2O_4$: C, 36.81; H, 2.32.

Found: C, 37.31; H, 2.58.

The diiodocinnamic acid (II, X = I) was resistant to iodination with iodine in either ammonium hydroxide, alcoholic ammonium hydroxide, saturated sodium bicarbonate solution or benzene in the presence of mercuric oxide. No iodination was observed upon treating the compound in methanolic 2 *N* potassium hydroxide with ten times the theoretical amount of iodine for 48 hours with vigorous stirring.

3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV). 3,5-Diiodo-4-(4′-methoxyphenoxy) cinnamic acid (II, X = I) (0.5 g.) was refluxed with hydriodic acid (*d*, 1.70) (5 ml.) in glacial acetic acid (5 ml.) for one hour. The reaction mixture was poured into water and the crude solid (0.46 g.) was recrystallized from dilute alcohol, m.p. 262° with decomposition.

Anal. Calc'd for $C_{15}H_{10}I_2O_4$: C, 35.46; H, 1.28.

Found: C, 35.52; H, 2.31.

The *benzoate* of this compound prepared by treating the acid with benzoyl chloride in 10% sodium hydroxide, upon recrystallization from dilute ethanol, melted at 244–246°.

Anal. Calc'd for $C_{22}H_{14}I_2O_5$: C, 43.16; H, 2.30.

Found: C, 43.50; H, 2.22.

3,5-Diiodo-4-(3′,5′-diiodo-4′-hydroxyphenoxy)cinnamic acid(V).3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV, 0.4 g.) dissolved in *N* sodium hydroxide (40 ml.) was treated with stirring with 8 ml. of *N* potassium triiodide. After two hours the solution was saturated with sulfur dioxide and the gummy pink product, yield, 0.58 g., was purified by dissolving in 1% sodium hydroxide in 70% ethanol and reprecipitating with glacial acetic acid three times followed by recrystallization from a mixture of ethyl alcohol and acetic acid. The colorless powder obtained did not have a definite melting point. It started to darken at 180° and gradually turned into a dark viscous liquid above 200°.

Anal. Calc'd for $C_{15}H_{10}I_4O_4$: C, 23.71; H, 1.06.

Found: C, 24.35; H, 1.61.

This product gave an intense orange color when warmed in alcohol with nitrous acid and turned red when treated with ammonia (3).

β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI). A mixture of 3,5-diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II, X = I) (0.33 g.), red phosphorus (0.24 g.), and hydriodic acid (*d*, 1.70) (2 ml.) in acetic anhydride (2 ml.) was refluxed for 75 minutes and filtered into 200 ml. of water. The solid (0.15 g.) was recrystallized from dilute alcohol; m.p. 235–238°. Additional product (0.1 g.) could be obtained by extracting the precipitate upon the filter with hot ethanol (10 ml.) and pouring into cold water (50 ml.).

Anal. Calc'd for $C_{15}H_{12}I_2O_4$: C, 35.32; H, 2.37.

Found: C, 35.29; H, 2.34.

The *benzoate* of this compound, prepared by treating the acid in 10% sodium hydroxide with benzoyl chloride, melted at 232–234° when recrystallized from dilute alcohol.

Anal. Calc'd for $C_{22}H_{16}I_2O_5$: C, 43.01; H, 2.63.

Found: C, 42.36; H, 2.90.

2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy)benzal]-5-oxazolone. This azalactone was prepared according to the directions of Harington and Barger (3).

Absorption spectra. All spectra were determined with a Beckman Quartz Spectropho-

tometer Model DU in silica cells with a path length of 1 cm. The solutions used were prepared with a concentration of 10 mg. of the sample in a liter of 95% ethanol. Measurements of the optical densities were made regularly at 2 mμ intervals within the range 220–300 mμ and at 5 mμ intervals above 300 mμ except in the neighborhood of maxima where the interval was reduced to 1 mμ.

The spectra obtained for these compounds are given in Figures 1 and 2; the wave-length and molar extinction coefficients for the maxima in the spectrum of each compound are listed in Table I.

An examination of Table I indicates that in general these compounds exhibit two maxima. Similar to other benzene derivatives with unsaturated side chains the fine structure is absent. This apparent simplicity in the absorption band structure indicates that in all three substituted cinnamic acids the whole molecule acts as a single resonator. The maximum in the 275 mμ region is characteristic of the halogenated cinnamic acids and occurs at

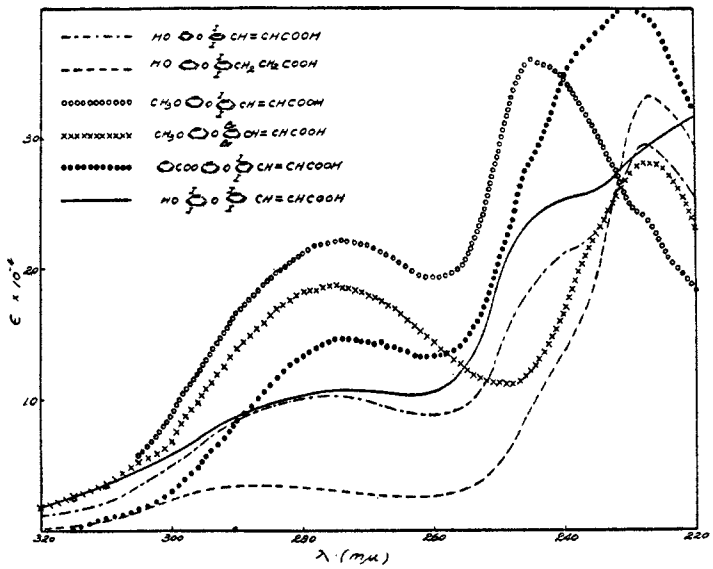


FIG. 1. ABSORPTION SPECTRA OF HALOGENATED 4-PHENOXYCINNAMIC ACIDS AND β-[3,5 DIIODO-4-(4′-HYDROXYPHENOXY)PHENYL]PROPIONIC ACID IN ETHANOL

a slightly greater wave length than that of cinnamic acid (4). The absence of this band for β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid verifies the structure of this compound.

Polarographic behavior. The polarographic measurements were made with a Sargent Model XII Polarograph at 25°. The electrolysis cell consisted of a cylindrical vessel provided with side-arms for the admission of nitrogen and for connection to the mercury pool.

The compounds were studied in a 0.001 *M* concentration in a 75% dioxane-water mixture with 0.175 *M* tetrabutylammonium iodide as a supporting electrolyte and 0.001% Methyl Red as a maximum suppressor. To eliminate the hydrogen wave one ml. of 0.0416 *N* tetramethylammonium hydroxide was included in each 25 ml. of solution for compounds with a carboxyl group and 2 ml. of the base for compounds with a free phenolic group and a carboxyl group.

The anode potential, measured against a saturated calomel electrode with a sintered-glass salt bridge of the type described by Laitinen (5), was −0.4534 volts.

The dropping-mercury electrode had the following characteristics. At a pressure of 65.6 cm. of mercury the drop time in the solution used was 3.87 seconds (open current).

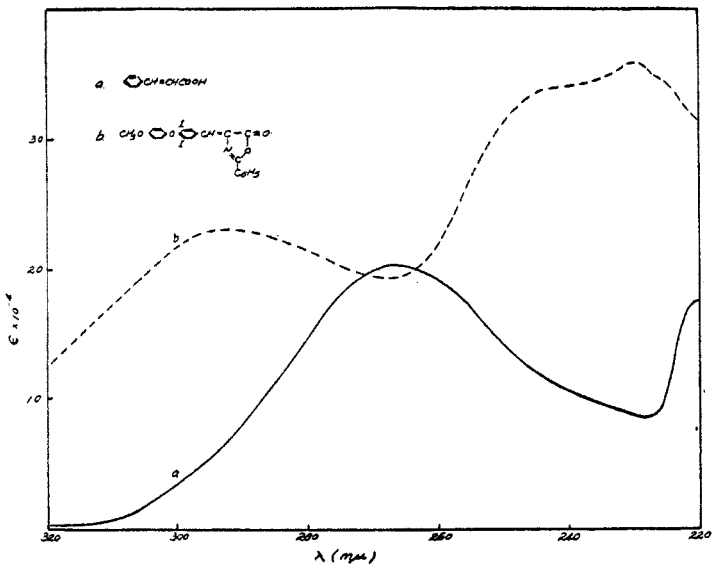


FIG. 2. ABSORPTION SPECTRA OF CINNAMIC ACID AND 2-PHENYL-4-[3,5-DIIODO-4-(4′-METHOXYPHENOXY)BENZAL]-5-OXAZOLONE IN ETHANOL

TABLE I

ULTRAVIOLET ABSORPTION MAXIMA FOR HALOGENATED CINNAMIC ACIDS AND RELATED COMPOUNDS IN ETHANOL

COMPOUND	MAXIMA		MAXIMA	
	mμ	ε × 10⁻⁴	mμ	ε × 10⁻⁴
Cinnamic acid	220	1.75	267	2.02
3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II)	227	2.80	275	1.87
3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II)	245	3.60	274	2.22
3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV)	227	2.94	276	1.02
3,5-Diiodo-4-(4′-benzoyloxyphenoxy)cinnamic acid	229	4.06	274	1.46
3,5-Diiodo-4-(4′-hydroxy-3′,5′-diiodophenoxy) cinnamic acid (V)	220	3.12	273	1.07
β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI)	227	3.32	289	0.35
2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy) benzal]-5-oxazolone	230	3.60	292	2.31

The value of m was 1.44 mg. sec.$^{-1}$ with a calculated value of $m^{2/3} t^{1/6}$ of 1.598 mg.$^{2/3}$ sec$^{-1/2}$.

The half-wave potentials and diffusion current constants are given in Table II. Three polarograms corrected for residual current are shown in Figure 3.

An examination of the half-wave potentials in Table II indicates that all the compounds with the exception of β-[3,5-diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid give a wave at −2.05 volts. This value therefore represents reduction of the α,β-double bond.

TABLE II

HALF-WAVE POTENTIALS AND DIFFUSION CURRENT CONSTANT OF SUBSTITUTED CINNAMIC ACIDS AND RELATED COMPOUNDS IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE-75% DIOXANE SOLUTION

COMPOUND	$E_{1/2}$ *vs* S.C.E. volts	$I_d/Cm^{2/3}t^{1/6}$
Cinnamic Acid	−2.03	1.99
3,5-Dibromo-4-(4′-methoxyphenoxy)cinnamic acid (II)	−1.66	1.25
	−1.91	1.09
	−2.06	0.99
3,5-Diiodo-4-(4′-methoxyphenoxy)cinnamic acid (II)	−1.22	1.58
	−1.53	1.40
	−2.07	1.34
3,5-Diiodo-4-(4′-hydroxyphenoxy)cinnamic acid (IV)	−1.34	1.53
	−1.68	1.12
	−2.05	0.87
3,5-Diiodo-4-(4′-hydroxy-3′,5-diiodophenoxy)cinnamic acid (V)	−1.26	1.71
	−1.58	0.87
	−1.84	1.15
	−2.03	0.81
β-[3,5-Diiodo-4-(4′-hydroxyphenoxy)phenyl]propionic acid (VI)	−1.36	1.43
	−1.72	1.18
2-Phenyl-4-[3,5-diiodo-4-(4′-methoxyphenoxy)benzal]-5-oxazolone	−0.93	0.81
	−1.37	1.99
	−1.67	0.93
	−2.08	0.44

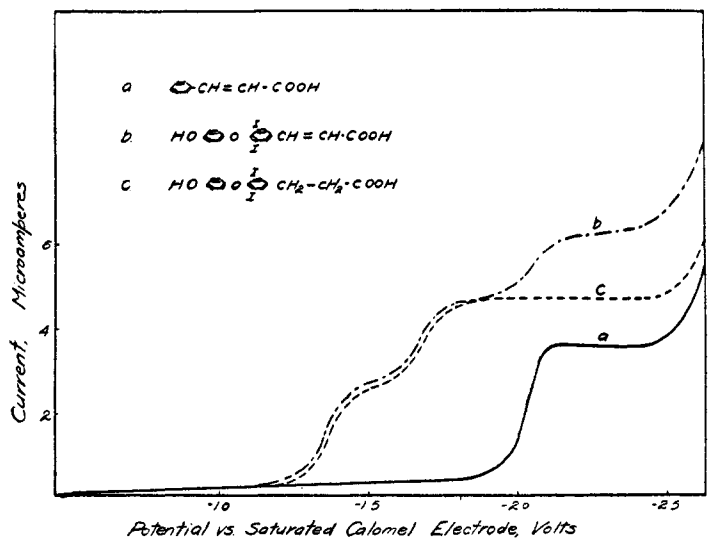


FIG. 3. POLAROGRAMS OF CINNAMIC ACID, 3,5-DIIODO-4-(4′-HYDROXYPHENOXY)CINNAMIC ACID AND β-[3,5-DIIODO-4-(4′-HYDROXYPHENOXY)PHENYL]PROPIONIC ACID IN 0.175 *M* TETRABUTYLAMMONIUM IODIDE, 75% DIOXANE

(Corrected for residual current)

Comparison of the diffusion current constant for cinnamic acid with that of the ψ-methyl ester of phthalaldehyde acid (6) points to a two-electron reduction and the formation of dihydrocinnamic acid. A similar behavior must take place with the halogenated derivatives.

The earlier waves represent the reduction of the halogens on the aromatic ring since the values for the iodo compounds are more positive than those for the bromo compounds. The half-wave potentials at −1.26 v., −1.58 v., and −1.84 v. observed for 3,5-diiodo-4-(4′-hydroxy-3′,5′-diiodophenoxy)cinnamic acid are more negative than the three waves reported for thyroxine at −1.20 v., −1.42 v., and −1.70 v. (7) due to the presence of the cinnamic acid derivative as the phenoxide ion.

SUMMARY

1. 3,5-Diiodo-4-[4′-hydroxy-3′,5′-diiodophenoxy]cinnamic acid and related compounds have been prepared for testing as possible antithyroid agents.

2. Ultraviolet absorption data and polarographic data are presented as proof for the unsaturation in this compound.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF INDIANA UNIVERSITY]

THIOCARBONYLS. V. N-METHYL-4-THIOQUINOLONE DERIVATIVES

E. CAMPAIGNE, RICHARD E. CLINE[1], AND C. E. KASLOW

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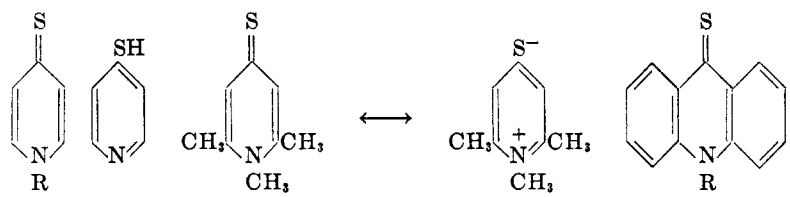
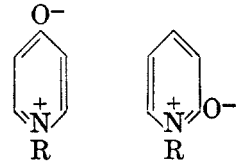
Efforts to synthesize nitrogen heterocyclic thiones usually lead to the formation of mercaptans unless the nitrogen atom is substituted. King and Ware (1) treated 4-pyridone with phosphorus pentasulfide and obtained a yellow, water-soluble, high-melting, salt-like substance which they regarded as 4-thiopyridone (I, R = H). I reacted with methyl iodide to yield 4-methylmercaptopyridine hydriodide. The properties of I indicate that it exists entirely as 4-mercaptopyridine (Ia). Gleu and Schaarschmidt (2) found similarly that thioacridones gave exclusively the S-alkyl derivatives upon alkylation and concluded that they exist principally in the thiol form. Surrey (3) points out that although 4-amino- and 4-hydroxy-quinoline form 1-quinolineacetic acids with chloroacetic acid, 4-mercaptoquinoline yields 4-quinolylmercaptoacetic acid under the same conditions. This reaction indicates a greater degree of aromatic resonance in 4-mercaptoquinoline than in 4-hydroxyquinoline. Renfrew (4) suggests that the darker color and greater degree of solubility in organic solvents exhibited by 4-mercaptoquinolines indicate a greater shift toward the thione form than is found in the 2-mercaptoquinolines.

Several N-substituted nitrogen heterocyclic thiones have been synthesized, however. Kendall (5) prepared N-methyl-4-thiopyridone (I, R=CH_3) from 4-methylmercaptopyridine by heating the quaternary methyl tosylate in pyridine. Michaelis and Holken (6) synthesized N-methyl-4-thiolutidone (II) by treating 4-chlorolutidine methiodide with two equivalents of potassium bisulfide. Gleu and Schaarschmidt (2) obtained almost quantitative yields of N-substituted thioacridones (III, R=CH_3, C_2H_5, C_6H_5) when the appropriate N-substituted-9-chloroacridinium dichlorophosphate was treated with sodium bisulfide or sodium thiosulfate in water solution.



[1] From a thesis submitted by Richard E. Cline to the Graduate School of Indiana University in partial fulfillment of the requirements for the degree, Master of Arts in Chemistry. For the fourth paper in this series, see *J. Org. Chem.*, **12**, 807 (1947).

It is probable that even the N-substituted thiones exist primarily in the aromatic ionic form. Bergstrom (7) points out that the ultraviolet absorption spectra of N-alkylpyridones indicate that the aromatic ring is still present, and suggests that these compounds are best illustrated by formulas such as IV and V.

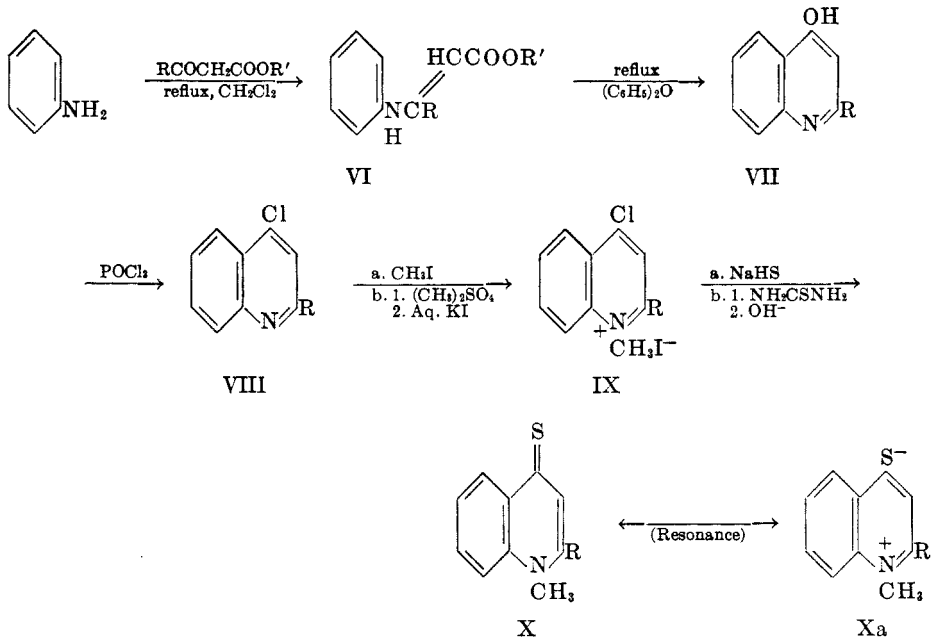


IV V

In view of the decreased tendency of sulfur to form double bonds, and the greater acidity of mercaptans, one would expect even more of the ionic aromatic structure in thiopyridones than in pyridones. Michaelis and Holken (6) suggest that N-methyl-4-thiolutidone exists in a salt form (IIa), since it reacts with methyl iodide to produce 4-methylmercaptolutidine methiodide, rather than N,N-dimethyl-4-thiolutidone iodide.

Although both 4-thiopyridones and thioacridones have been prepared, no N-alkyl-4-thioquinolones have been reported in the literature. Recent interest in sulfur-containing quinolines (3, 4, 8) and our concern with thiocarbonyl derivatives (9) led us to prepare N-methyl-4-thioquinolone (X, R=H), N-methyl-4-thioquinaldone (X, R=CH_3), N-methyl-2-phenyl-4-thioquinolone (X, R=C_6H_5), and N-methyl-2-carbethoxy-4-thioquinolone (X, R = $COOC_2H_5$). Methods of synthesizing N-heterocyclic thiones have been reviewed (9). It was apparent that the most promising methods of synthesizing the 4-thioquinolone derivatives involved treating a 4-haloquinolinium salt with a sulfurizing agent such as bisulfide, thiosulfate, or thiourea.

The 4-chloroquinolines involved in the preparation of the 4-thioquinolones were obtained through well-known methods of synthesis. 4-Chloroquinaldine was produced in an over-all yield of 65% through the Conrad-Limpach procedure (10) for the preparation of 4-hydroxyquinaldine, and was then treated with phosphoryl trichloride. Both 4-chloroquinoline and 2-carbethoxy-4-chloroquinoline were obtained from 2-carbethoxy-4-hydroxyquinoline; the latter substance was prepared through the Lisk and Stacy (11) method of condensing aniline and oxalacetic ester and ring closure of the ethyl β-anilino-β-carbethoxyacrylate in boiling phenyl ether. 2-Carbethoxy-4-hydroxyquinoline was saponified and the 4-hydroxyquinaldic acid decarboxylated in boiling phenyl ether to give a 57% over-all yield of 4-hydroxyquinoline. The condensation of aniline and ethyl benzoylacetate in boiling chloroform and ring-closure of the ethyl β-anilino-β-phenylacrylate in boiling phenyl ether gave 2-phenyl-4-hydroxyquinoline which was converted to 2-phenyl-4-chloroquinoline in an over-all yield of 48%.



The character of the group in the 2-position has a definite influence, both on the synthesis and the properties of the thiones. The groups used in this study were either electron-attracting or electron-releasing, the order of electron-attraction being:

$$COOC_2H_5 > C_6H_5 > H > CH_3$$

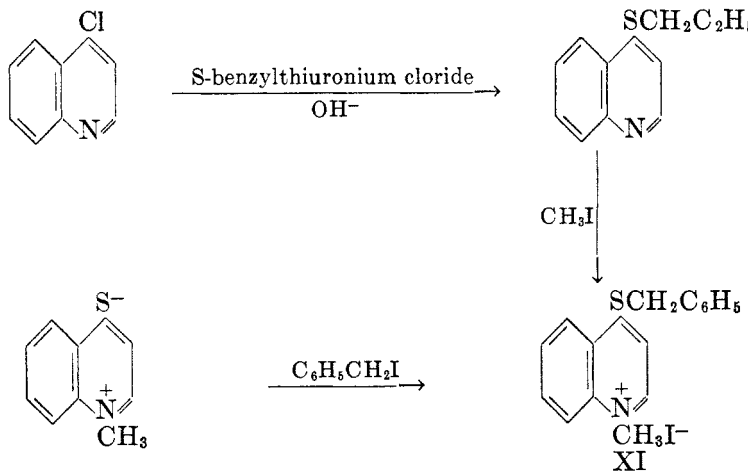
This gradation in influence is apparent in the formation of the quinolinium salts. Thus 4-chloroquinaldine methiodide and 4-chloroquinoline methiodide were obtained in nearly quantitative yield by allowing the respective quinoline derivatives to react with methyl iodide for several days at room temperature. The 2-phenyl- and 2-carbethoxy-4-chloroquinolines did not react under these conditions. 2-Phenyl-4-chloroquinoline methiodide was prepared by heating 2-phenyl-4-chloroquinoline with methyl sulfate and treating the impure methosulfate salt with aqueous potassium iodide. All attempts to isolate a pure quinolinium salt of 2-carbethoxy-4-chloroquinoline failed.

The thiones were readily prepared by treating the 4-chloroquinolinium salts in alcohol solution with either sodium or potassium bisulfide, or thiourea. In the first experiments potassium hydrosulfide was prepared by passing hydrogen sulfide into an alcoholic solution of potassium ethoxide, but later it was found that a commercial grade of solid sodium hydrosulfide gave equally satisfactory results.

The reaction with sodium hydrosulfide was found to give the best and most consistent results, except with 2-carbethoxy-4-chloroquinoline. In this case

apparently the alkaline reagent hydrolyzed the ester linkage, and no product was isolated. When the quinolinium salt (either methiodide or methosulfate) was treated with thiourea in alcohol, a precipitate was obtained, which is probably a thiuronium salt. The thiuronium salt obtained from 2-carbethoxy-4-chloroquinolinemethosulfate hydrolyzed at once when added to water, to form the thioquinolone, but the thiuronium salts from 4-chloroquinoline methiodide and 4-chloroquinaldine methiodide required dilute alkali for hydrolysis.

The properties of the 4-thioquinolones bear out the observation that even in the N-alkylheterocyclic thiones the aromatic resonance form (Xa) is a major contribution to the structure. The influence of this contribution is decreased, however, by electron-attracting groups in the 2-position. Thus the melting points decrease as R varies in electron-releasing character from $CH_3 > H > C_6H_5 > COOC_2H_5$, indicating a decrease of the ionic form of the compound (Xa). The colors change from bright yellow through yellow, orange, and red-orange in the same way, indicating a greater contribution of the chromophoric thione structure (X). All of the thioquinolones form white hydrochlorides when benzene solutions are treated with dry hydrogen chloride. However, only the N-methyl-4-thioquinaldone hydrochloride could be filtered out. The other white hydrochlorides evolved hydrogen chloride and reverted to the yellow free bases in air. The solubility of the free bases in dilute hydrochloric acid decreased as R varied from methyl to carbethoxyl, N-methyl-2-carbethoxy-4-thioquinolone being completely insoluble. The product formed when benzyl iodide was allowed to react with N-methyl-4-thioquinolone was 4-benzylmercaptoquinoline methiodide (XI). This was demonstrated by synthesizing XI in an unequivocal manner from 4-chloroquinoline through 4-benzylmercaptoquinoline, as shown.



XI

The ultraviolet absorption curves (Fig. 1) of the four compounds, taken in methanol on a Model DU Beckman specrophotometer, show a definite, though small, shift toward the visible range as the substituent varies from methyl to

carbethoxyl. This would be the expected effect. The important maxima and minima are tabulated in Table I.

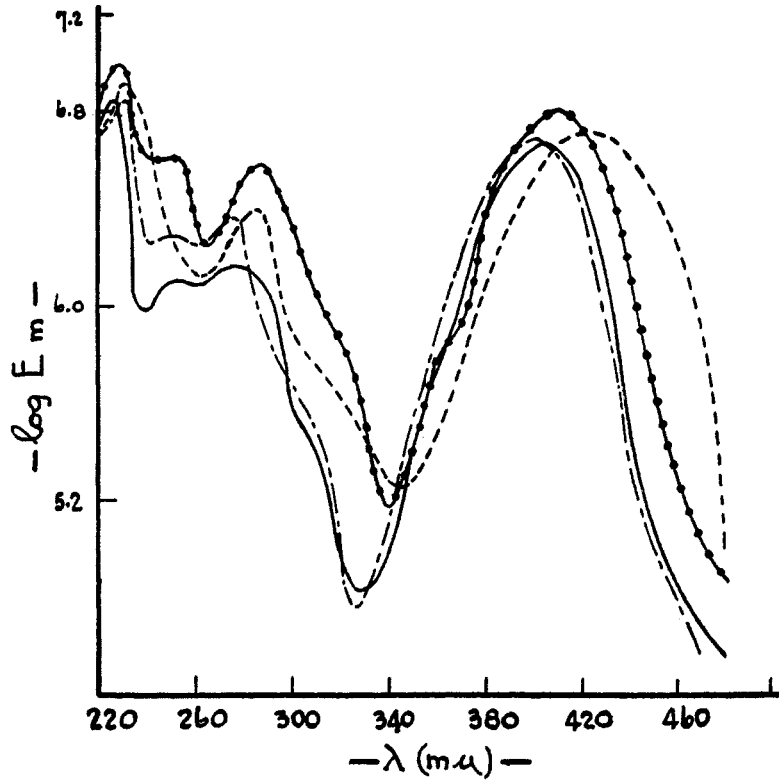


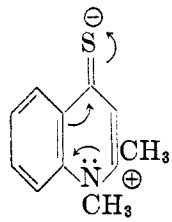
FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in methanol solution) of 2-substituted-N-methyl-4-thioquinolones (X). — - — - R = methyl; ——— R = hydrogen; —·—·— R = phenyl; -------- R = carbethoxyl.

TABLE I

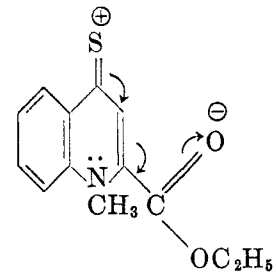
ABSORPTION MAXIMA AND MINIMA OF 2-SUBSTITUTED-N-METHYL-4-THIOQUINOLONES IN MILLIMICRONS

2-SUBSTITUENT	1ST MAXIMUM	MINIMUM	2ND MAXIMUM
Methyl	275	326	401
Hydrogen	275	330	404
Phenyl	286	340	410
Carbethoxyl	286	346	424

The inductive effect of electron-attracting and electron-releasing groups may be pictured as in XII and XIII.



XII



XIII

It can be readily seen that structure XII augments the aromatic resonance contribution, increases ionic character, and provides a center of reactivity on the sulfur atom, whereas structure XIII counteracts the aromatic resonance, and would tend to decrease the negative ionic charge of the sulfur atom. These are the effects observed.

EXPERIMENTAL

4-Chloroquinaldine methiodide (IX, R = CH_3). In an ice-cooled flask 10 g. (0.056 mole) of 4-chloroquinaldine (12) was mixed with 6.2 ml. (8.4 g., 0.066 mole) of dimethyl sulfate. A white precipitate formed at once, but the mixture was heated for a few minutes on a steam-bath to insure completeness of the reaction. Then 20 g. (0.12 mole) of potassium iodide dissolved in 26 ml. of water was added, and a brownish-yellow solid precipitated. After recrystallization from glacial acetic acid, bright yellow needles m.p. 223–224°, and weighing 13.5 g. (0.042 mole, 75%) were obtained. Alekseeva (13) found m.p. 222–223°. The same product was obtained if 4-chloroquinaldine was allowed to stand in excess methyl iodide for 24 hours.

N-Methyl-4-thioquinaldone (X, R = CH_3). A mixture of 4 g. (0.012 mole) of IX (R = CH_3), and 3 g. (0.038 mole) of sodium hydrosulfide[2] in 400 ml. of absolute ethanol was refluxed for 12 hours. Upon cooling, reddish-yellow needles were deposited. These were washed with water, and recrystallized from ethanol, giving 1.96 g. (0.010 mole, 83%) of yellow needles m.p. 224–225° with decomposition. A mixed melting point with IX (R = CH_3) was depressed.

Anal. Calc'd for $C_{11}H_{11}NS$: N, 7.4; S, 16.93.

Found: N, 7.7; S, 17.51.

A solution of X (R = CH_3) in benzene was treated with dry hydrogen chloride until no further precipitation occurred. The white crystalline product, 4-mercaptoquinaldine methochloride, melted at 203–205°.

Anal. Calc'd for $C_{11}H_{12}ClNS$: Cl, 16.35; N, 6.20.

Found: Cl, 16.62; N, 6.05.

4-Chloroquinoline methiodide (IX, R = H). This compound was prepared by adding 47 g. (0.29 mole) of 4-chloroquinoline (14) in 5-ml. portions at 24-hour intervals to 80 ml. of methyl iodide. The methyl iodide solution was cooled before each addition, and then allowed to stand at room temperature. The excess methyl iodide was then removed by evaporation, and the product washed with ether; 79.7 g. (0.26 mole, 90%) of yellow crystals, m.p. 208–210° with decomposition, was obtained. Hamer (14) reported a 62% yield of product melting at 208° by a similar procedure.

N-methyl-4-thioquinolone (X, R = H). A mixture of 4 g. (0.051 mole) of commercial so-

[2] Kindly supplied by the Hooker Electrochemical Company. It contained 28% water of crystallization.

dium hydrosulfide and 5 g. (0.0162 mole) of IX (R = H) in 200 ml. of ethanol was refluxed for 6 hours. Upon cooling, yellow needles of N-methyl-4-thioquinolone were deposited. These were washed with water, yielding 2.75 g. (0.0157 mole, 97%); m.p. 209–210°. A mixed melting point with IX (R = H) was 180–185°.

Anal. Calc'd for $C_{10}H_9NS$: N, 8.0; S, 18.28.

Found: N, 8.01; S, 18.88.

The same compound was obtained when 5 g. (0.016 mole) of IX (R = H) was refluxed in 200 ml. of ethanol with 3 g. (0.04 mole) of thiourea for 5 minutes, and the dark red precipitate (thiuronium salt) filtered, dissolved in 200 ml. of water, and treated with 20 ml. of 10% NaOH. The orange precipitate was recrystallized from ethanol as yellow needles, 1.43 g. (81%); m.p. 208–209°. A mixed melting point with the compound prepared from sodium hydrosulfide was 208–209°.

4-Benzylmercaptoquinoline methiodide (XI). A small amount of X (R = H) was added to excess benzyl iodide and allowed to stand for several days. The yellow precipitate was recrystallized from methanol; m.p. 210–212° with decomposition. This compound gave a positive halogen test with aqueous silver nitrate, and a mixed melting range with N-methyl-4-thioquinolone of 168–210°.

Anal. Calc'd for $C_{17}H_{16}INS$: N, 3.56. Found: N, 3.44.

The same product was obtained when 4-benzylmercaptoquinoline was treated with methyl iodide for several days. 4-Benzylmercaptoquinoline was synthesized from 4-chloroquinoline by the method of Baker, Dodson, and Riegel (8). Refluxing 1.1 g. (0.0067 mole) of 4-chloroquinoline with 1.1 g. (0.0055 mole) of S-benzylthiuronium chloride and 1 g. of KOH in 10 ml. of ethanol for 1½ hours gave, after washing with water and recrystallizing, 1.3 g. (0.0052 mole, 77%) of white crystals of *4-benzylmercaptoquinoline*, m.p. 135–136°.

Anal. Calc'd for $C_{16}H_{13}NS$: S, 12.80. Found: S, 12.54.

N-Methyl-2-phenyl-4-thioquinolone (X, R = C_6H_5). Crude 2-phenyl-4-chloroquinoline methiodide was prepared by heating 3.3 g. of 2-phenyl-4-chloroquinoline (15) and 2 ml. of dimethyl sulfate for four hours at 100–120°. When cooled, the transparent glassy solid was boiled with 6 g. of potassium iodide in 9 ml. of water for several hours, and the oily layer allowed to crystallize. A mixture of 2 g. of the yellow needles so obtained, 3 g. of commercial sodium hydrosulfide, and 225 ml. of absolute alcohol was refluxed for 12 hours. The N-Methyl-2-phenyl-4-thioquinolone crystallized from the cooled reaction mixture, and after washing with water, was recrystallized from methanol in yellow-orange needles, m.p. 175–176°; weight 0.74 g. (0.0028 mole, 56%).

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.6; S, 12.74.

Found: N, 5.4; S, 12.96.

The same product was obtained in 30% yield when the crude 4-chloro-2-phenylquinoline methosulfate was treated with alcoholic potassium bisulfide.

2-Carbethoxy-4-chloroquinoline (VIII, R = $CO_2C_2H_5$). Four grams (0.018 mole) of 2-carbethoxy-4-hydroxyquinoline (16) was mixed with 8.4 g. (0.055 mole) of phosphoryl trichloride and allowed to stand at room temperature until the reaction ceased. Before pouring the reaction mixture into ice-water, the gummy material was dissolved by the addition of 10 ml. of absolute ethanol. After neutralization, the solid was recrystallized from dilute acetone as white needles. The yield of 2-carbethoxy-4-chloroquinoline was 3.2 g. (74%), m.p. 85–86°.

Anal. Calc'd for $C_{12}H_{10}ClNO_2$: N, 5.94. Found: N, 6.03.

N-Methyl-2-carbethoxy-4-thioquinolone (X, R = $COOC_2H_5$). Since a crystalline methiodide could not be isolated, the crude methosulfate was reacted directly with thiourea. A mixture of 3 ml. (0.03 mole) of dimethyl sufate and 2.7 g. (0.0096 mole) of 2-carbethoxy-4-chloroquinoline was heated at 110–120° for 15 minutes. The dark brown oil was added to 50 ml. of ethanol containing a large excess of thiourea. After refluxing about ten minutes, it was poured into 200 ml. of water and the crystals recrystallized from ethanol as red-orange needles, weighing 0.9 g. (0.0036 mole, 37%); m.p. 140–141°.

Anal. Calc'd for $C_{13}H_{13}NO_2S$: N, 5.67; S, 12.95.

Found: N, 5.84; S, 12.59.

SUMMARY

N-methyl-4-thioquinolone, and its analogs containing the methyl, phenyl, and carbethoxyl groups in the 2-position have been synthesized.

The properties of these compounds are those of the ionic aromatic structure, but electron-attracting groups in the 2-position decrease this resonance contribution. An electronic interpretation is discussed.

BLOOMINGTON, INDIANA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

PREPARATION OF 1,8-NAPHTHALIDE AND 8-METHYL-1-NAPHTHOIC ACID[1]

JAMES CASON AND J. D. WORDIE[2]

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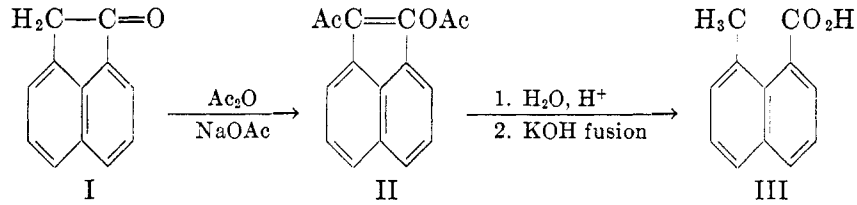
For use in the syntheses described in the following paper, a quantity of 8-methyl-1-naphthoic acid was required. This acid has been reported by Errera and Ajon (1) as melting at 130–131°, but their method of synthesis by way of naphthalonic acid appeared quite unpromising, especially since their melting point was considerably below the value of 152–153° reported by Ghigi (2). The latter investigator prepared the acid by the sequence represented in formulas I–III. The structure assigned to II, the product obtained on heating acenaphthenone (I) with acetic anhydride and sodium acetate, is due to Ghigi and is not neces-



sarily endorsed by the present authors, but there was obtained by us a product of the reported melting point. Hydrolysis of the enol acetate (II), followed by potassium hydroxide fusion, did yield the desired 8-methyl-1-naphthoic acid (III), m.p. 150.2–151°, but unfortunately the yield in the best of several runs was only 3%. Since this sample of acid was identical with that prepared by the method described below, the acid obtained by Ghigi is definitely identified, and the melting point reported by Errera and Ajon is in considerable error.

The potassium hydroxide fusion of acenaphthenone was also attempted, but the only product obtained was tar.

Ghigi reported that treatment of acenaphthenone with acetic anhydride and pyridine (2, 3) yielded a product described as II plus a molecule of pyridine, and it was reported that hydrolysis gave the same acetylacenaphthenone as obtained by hydrolysis of II. We obtained a product of the melting point reported by Ghigi, for the reaction in pyridine, but we were not able to hydrolyze it to the product obtained from II, and the structure assigned to the product obtained in pyridine seems to us in doubt.

Another attempted synthesis of 8-methyl-1-naphthoic acid utilized 1,8-naphthaldehydic acid (IV) as starting material. The reduction of the aldehyde group was attempted by high pressure hydrogenation of the sodium salt, Clemmensen reduction, and modified Wolff-Kishner reduction (4), but no 8-methyl-1-naph-

[1] The authors are indebted to the Cancer Research Fund of the University of California for a grant in support of part of this research.

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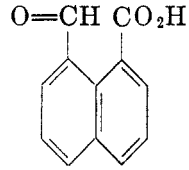
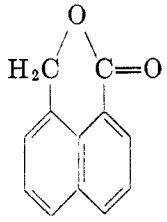
thoic acid was obtained. Since the completion of this work, Fuson and Munn (5) have reported isolation of about an 8% yield of 8-methyl-1-naphthoic acid from the Clemmensen reduction, and the melting point was in agreement with that reported by Ghigi (2) and also obtained by us. Fuson and Munn also reported



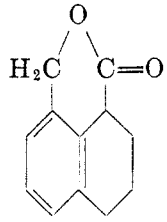
IV

an excellent yield of 1,8-naphthalide (V) by a cross-Cannizzaro reaction on 1,8-naphthaldehydic acid. Our best preparation of 8-methyl-1-naphthoic acid utilizes 1,8-naphthalide, but it was prepared by another method on account of the difficult accessibility of 1,8-naphthaldehydic acid. The latter compound is prepared by cleavage of acenaphthenequinone (6) with aqueous potassium hydroxide according to Graebe and Gfeller (7). These authors reported an "almost quantitative" yield, but Zink (8) reported an 82% yield and formation of some 1,8-naphthalic acid, while Fuson and Munn (5) reported a yield of 68–73% and did not report removal of naphthalic acid from their product. In our hands, no naphthaldehydic acid was obtained when the procedure of Graebe and Gfeller was followed rigorously, the chief product being 1,8-naphthalic acid. Under milder conditions, we were able to obtain naphthaldehydic acid, but separation of naphthalic acid was always necessary. In some runs the yields were of the order reported by Fuson and Munn; however, even under carefully controlled conditions, working in an atmosphere of nitrogen, the average yield was about 50%. This investigation was finally abandoned in favor of the one-step preparation of naphthalide described below.

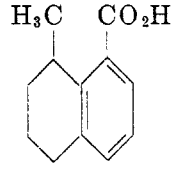
The catalytic hydrogenation of phthalic anhydride to phthalide, using benzene solution and copper chromite catalyst, has been reported by Lazier and coworkers (9). The hydrogenation of 1,8-naphthalic anhydride with copper chromite catalyst in benzene solution has been found to yield a considerable variety of products, and the compounds represented by formulas V–VIII have been isolated from the mixture, although the structures represented by formulas VI



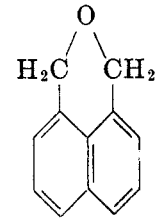
V



VI



VII



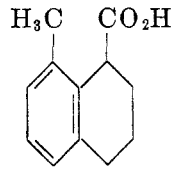
VIII

and VIII have not been established unequivocally. The ether (VIII) was obtained only as an impure liquid and the structure was assigned on the basis of its

stability to hot alkali and formation of a solid picrate whose analysis indicates only one atom of oxygen in the naphthalene derivative. The structure of the tetrahydronaphthalide (VI) seems established except for the position of the aromatic ring. The indicated position was assigned on the basis of the instability of the compound, which would indicate a methylene activated by the aromatic ring. This compound was not separated from the isomeric tetrahydronaphthalide, in the mixture obtained from hydrogenation of naphthalic anhydride, and the pure isomer was actually isolated from a reduction of naphthalide in alkali.

The position of the aromatic ring in 5,6,7,8-tetrahydro-8-methyl-1-naphthoic acid (VII) was established unequivocally by its ultraviolet absorption spectrum,[3] which is shown in Figures 1 and 2. In Figure 1, it is seen that the curve for VII is much more similar to that for benzoic acid than to that for phenylacetic acid. In Figure 2, it is apparent that the curve for VII is nearly identical with that for 5,6,7,8-tetrahydro-1-naphthoic acid, but bears no resemblance to the curve for 1,2,3,4-tetrahydro-1-naphthoic acid.

Fuson and Munn (5) hydrogenated naphthalic anhydride with copper chromite catalyst at 260°, but the only compound reported as isolated from this reaction was a tetrahydro-8-methyl-1-naphthoic acid, m.p. 150°, which was the same



IX

as the acid obtained on reduction of 1,8-naphthalide with Raney nickel-aluminum alloy. Although not mentioned by Fuson and Munn, this acid was also obtained by Willstätter and Jaquet (10) by reduction of naphthalic anhydride with a platinum catalyst. Since the structure of our acid (VII) of m.p. 118.9–119.6° has been established, it follows that the acid of m.p. 150° reported by the other investigators has the structure shown in formula IX.

The composition of the mixture obtained on hydrogenation of naphthalic anhydride was found to be quite sensitive to temperature and amount of hydrogen absorbed. For maximum production of 1,8-naphthalide (V), it was found best to hydrogenate at 220° until about three mole-equivalents of hydrogen had been absorbed, then work up the mixture and rehydrogenate the material (mostly unreacted naphthalic anhydride) insoluble in benzene. In this manner, a 35% yield of naphthalide could be obtained. Separation of naphthalide (V) from the tetrahydronaphthalides proved exceedingly difficult until it was discovered that if the aqueous alkaline solution obtained by saponification of the mixed naphthalides is adjusted to *p*H about 10, the desired substance (V) crystallizes quanti-

[3] We are indebted to Mr. Joe Lavigne for these spectra, which were obtained on a Cary spectrophotometer. The tetrahydro-1-naphthoic acids were kindly supplied by Dr. W. G. Dauben.

tatively from the solution while the tetrahydronaphthalides remain in solution. Finally, acidification precipitates the tetrahydronaphthalides mixed with a little naphthalic acid.

The reduction of naphthalimide with zinc and alkali, according to the procedure of Gardner and Naylor (11) for preparation of phthalide, was attempted

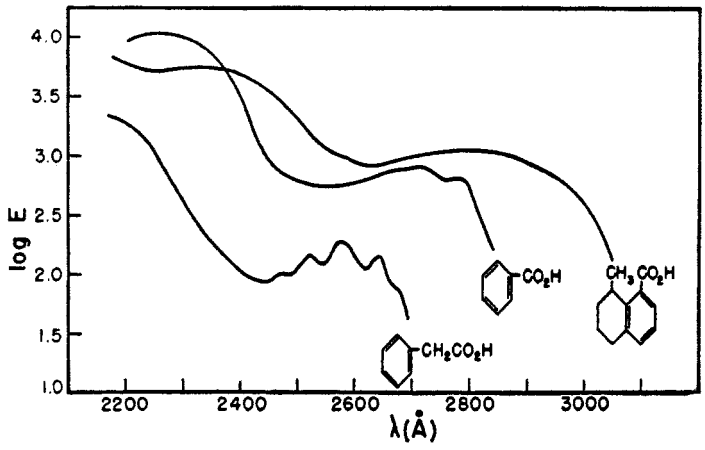


FIGURE 1

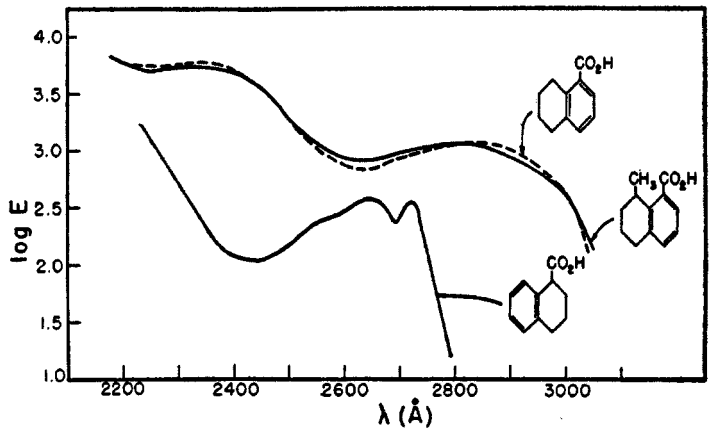


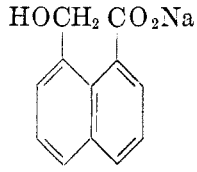
FIGURE 2

FIGURES 1-2. ABSORPTION SPECTRA OF AROMATIC AND HYDROAROMATIC ACIDS

but no naphthalide was isolated. The hydrogenation of naphthalic anhydride with copper chromite catalyst in alcohol solution, or in alcohol containing one equivalent of sodium ethoxide yielded mixtures from which no known product could be isolated. The preparation of the half ester of naphthalic acid is not feasible, for when a solution of the salt obtained from naphthalic anhydride and one equivalent of sodium ethoxide is acidified, the original precipitate rapidly reverts to naphthalic anhydride. In this connection, it is of interest that when 1,8-naph-

thalic acid is heated with ethanol at the boiling point, the acid is rapidly converted to naphthalic anhydride.

Since saponification of naphthalide gives the sodium salt of the hydroxy acid



X

(X), the hydrogenation to 8-methyl-1-naphthoic acid is readily accomplished with copper chromite catalyst. In a similar reduction (12) of a keto acid in aqueous alkali, hydrogenation proceeded at 200°, but the present hydrogenation was best carried out at 250° and a pressure of 300 atmospheres or more. It was also found that at least 1.3 equivalents of alkali are necessary for an optimum yield. With 1.05 equivalents of alkali, the yield of 8-methyl-1-naphthoic acid was only 11%.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses are by the Microanalytical Division of the Department of Chemistry of the University of California.

8-Acetyl-7-acenaphthenone. It was found most convenient not to isolate the acetyl derivative, II. The procedure of Ghigi (2) was modified as follows. A mixture of 7.7 g. of acenaphthenone (13), 1.0 g. of anhydrous sodium acetate, and 70 ml. of acetic anhydride was heated under reflux for ten hours (a shorter heating period leads to recovery of acenaphthenone). After cautious addition of 50 ml. of water to the hot solution there was added a mixture of 5 ml. of glacial acetic acid and 5 ml. of concentrated sulfuric acid; then refluxing was continued for one hour. Dilution of the reaction mixture with 750 ml. of water precipitated 7.5 g. of brown solid which was dissolved in 200 ml. of 1% aqueous sodium hydroxide. The insoluble material was extracted with an additional 100 ml. of water, only a trace of black tar remaining insoluble. Acidification of the deep red aqueous solution precipitated 5.4 g. (56%) of 8-acetyl-7-acenaphthenone as a yellow powder, m.p. 114.1–119.1°, re-m.p. 117.7°. Crystallization from hexane gave yellow needles, m.p. 116.7–120.6°. Ghigi (2) reported m.p. 117°.

Potassium hydroxide fusion of 8-acetyl-7-acenaphthenone. To 20 g. of potassium hydroxide in a nickel crucible heated in a bath at 265° there was added during ten minutes, with mixing, 2.0 g. of 8-acetyl-7-acenaphthenone. Heating and stirring at the same temperature was continued for an additional ten minutes, then the mixture was cooled and extracted with 250 ml. of boiling water. After filtration of 1.4 g. of insoluble material, the clear yellow alkaline solution was acidified to give a precipitate of 0.7 g. of crystals and gummy material. Sublimation at a bath temperature of 150–200° and 1 mm. pressure, followed by crystallization of the sublimate, gave 0.2 g. of yellow powder, m.p. 115–125°. After removal of 0.1 g. of carbonate-insoluble material and crystallization from acetone-hexane (1:5), there was obtained 0.06 g. of 8-methyl-1-naphthoic acid as colorless plates, m.p. 150.2–151.0°, no depression in m.p. on mixing with a sample of this acid prepared as described below.

1,8-Naphthaldehydic acid[4] (IV). Results in this preparation were variable, but the following represents average results obtained in the best procedure. A mixture of 5.0 g. of

[4] Preliminary work on this compound was carried out by Dr. Lloyd Beck in 1941 while he was a Senior at DePauw University, Greencastle, Indiana.

acenaphthenequinone (6) and 30 ml. of 30% aqueous potassium hydroxide was heated in a steam-bath, with stirring, in an atmosphere of nitrogen for 12 minutes (time elapsing from placing the cold mixture in the steam-bath until its removal). The color changed from yellow through green to red-purple. The reaction mixture was diluted with 300 ml. of water, a small precipitate was filtered, and the filtrate was acidified to yield a mixture of naphthalic acid and naphthaldehydic acid. The precipitate was heated under reflux in ethanol solution for 15 minutes to precipitate naphthalic acid as the insoluble anhydride (8). After treatment with charcoal and concentration of the filtrate to about 15 ml., 10 ml. of benzene was added. There crystallized 2.9 g. (53%) of brown naphthaldehydic acid, m.p. 155–162° (dec.). The decomposition point varies with rate of heating. The best sample, obtained after four crystallizations from benzene-ethanol, melted at 169–171° (dec.) when the bath was heated at the rate of 3° per minute. Previous investigators (5, 7, 8) have reported the m.p. 167°.

A heating time of 10 minutes at 150°, for the alkaline cleavage, has been previously reported (5). Since 30% aqueous potassium hydroxide was used, this temperature must have been that of the bath, so the internal temperature is unknown but it was obviously below 100° for much of the 10-minute period. For only 30 ml. of stirred aqueous alkali, we found that the internal temperature was only 87° after six minutes in a steam-bath.

1,8-Naphthalide (V). Commercial naphthalic anhydride could not be hydrogenated until after purification. Most of the material used in this investigation was the light-colored material commercially available in 1936. One recrystallization of this material from methyl benzoate (100 g. of anhydride per liter of solvent) gave colorless needles, m.p. 273–275°, suitable for hydrogenation. Samples of naphthalic anhydride currently available are of very poor quality and could be hydrogenated only after treatment with charcoal in alkaline solution followed by at least two crystallizations from methyl benzoate.

Hydrogenation of 1,8-naphthalic anhydride at 260° with copper chromite, according to the method reported for phthalic anhydride (9), gives over-hydrogenation, as will be described below in connection with the ether, VIII. Essentially no hydrogenation occurs below 190°, and best yields of naphthalide were obtained in the range 210–220°.

In the best procedure for preparation of 1,8-naphthalide, a steel pressure bomb was charged with 90 g. of purified naphthalic anhydride, 300 ml. of thiophene-free benzene, and 18 g. of copper chromite catalyst (14). For hydrogenation, the initial pressure at 20° was 2500 p.s.i., and the maximum pressure reached at 220° was 4250 p.s.i. When the pressure at 220° had dropped (10 hrs.) to a value corresponding to the consumption of 2.9 mole-equivalents of hydrogen, the hydrogenation was interrupted, and the cooled contents of the bomb were extracted with benzene. The benzene-insoluble material, containing the catalyst and unreacted naphthalic anhydride was re-hydrogenated similarly in 90 ml. of benzene. The separation of various fractions is most easily followed by a Flow Sheet, as indicated. The benzene extracts from the first and second hydrogenations may be most conveniently worked up together, but in the Flow Sheet the amounts isolated from the first and second hydrogenations are indicated in that order. The naphthalide crystallizing at the thymolphthalein end-point was white, m.p. 152–155°. This material was suitable for conversion to 8-methyl-1-naphthoic acid, but a purified sample was obtained by reprecipitation from alkaline solution at the thymolphthalein end-point and two crystallizations from ethanol. The constant m.p. of 156.6–157.2° was obtained [literature, m.p. 159–160° (1); 156–157° (5)]. The saponification equivalent could be determined by rapid titration in a solution containing more than 50% ethanol.

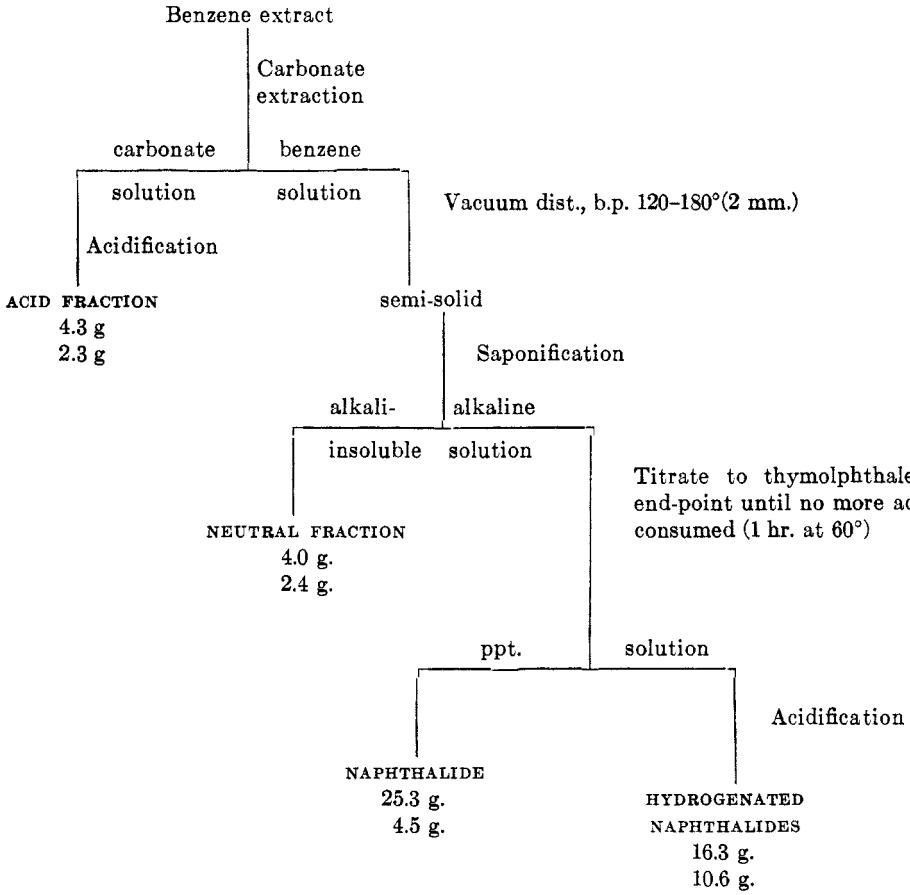
Anal. Calc'd for $C_{12}H_8O_2$: C, 78.25; H, 4.38; Eq. wt., 184.2.
Found: C, 78.01; H, 4.23; Eq. wt., 182.0.

Naphthalide and naphthalic anhydride appear to form a mixed crystal melting considerably above naphthalide, and samples of naphthalide not purified by precipitation at *p*H 10 always melted considerably above the purified material. Presence of naphthalic anhydride was first discovered by its isolation as follows. A 0.5-g. sample of impure naphthalide of m.p. 181–192° was dissolved in 80 ml. of hot ethanol containing 2.5 g. of picric acid. On cooling, there crystallized 0.05 g. of needles, which on crystallization from ethanol weighed

0.02 g. and melted at 271–273°, no depression on mixing with naphthalic anhydride. This anhydride was not formed by picric acid oxidation of naphthalide, for boiling of the filtrate caused no further crystallization of anhydride. Picric acid was removed with ammonium hydroxide, and naphthalide was recovered by solution in sodium hydroxide, acidification, and crystallization from ethanol. The recovered material melted at 155.8–158°. Addition of about 25% naphthalic anhydride to this material raised the m.p. to 200–250°.

FLOW SHEET

SEPARATION OF PRODUCTS FROM HYDROGENATION OF NAPHTHALIC ANHYDRIDE



Tetrahydronaphthalide (probably VI). The fraction designated hydrogenated naphthalides in the Flow Sheet was crystallized from ethanol-water (1:1) to give material of m.p. 76–150°. The analysis of this fraction gave: C, 76.50; H, 5.80 (calc'd for tetrahydronaphthalide: C, 76.57; H, 6.43). A pure sample of tetrahydronaphthalide was isolated from the hydrogenation of naphthalide in the presence of 1.1 equivalents of aqueous alkali with copper chromite catalyst at 250°. For details of a similar hydrogenation, refer to the preparation of 8-methyl-1-naphthoic acid. From 5.5 g. of naphthalide was obtained a lactone fraction consisting of 2.5 g. of yellow and white material. Mechanical separation of the white material, followed by crystallization from acetone-hexane (1:10) yielded 0.4 g. of colorless plates, m.p. 88.9–89.5°.

Anal. Calc'd for $C_{12}H_{12}O_2$: C, 76.57; H, 6.43.
Found: C, 76.35; H, 6.56.

After storage of the analytical sample for six months in the dark, it had changed to an orange semi-solid material.

8-Methyl-5,6,7,8-tetrahydro-1-naphthoic acid. When hydrogenation was carried out as described for preparation of 1,8-naphthalide, but with a larger ratio of catalyst, a smaller ratio of benzene, and highly purified naphthalic anhydride, a much larger acid fraction was obtained. The relative importance of these variables has not been established. In a typical run, a steel bomb was charged with 280 g. of naphthalic anhydride, 80 g. of copper chromite catalyst, and 320 ml. of benzene. The initial pressure at 25° was 2500 p.s.i. After 4½ hours at 200°, 2.5 mole-equivalents of hydrogen had been absorbed, and the mixture was worked up. The total material insoluble in benzene was 250 g. (catalyst and naphthalic anhydride). The benzene solution was worked up as outlined on the Flow Sheet to yield 42.0 g. of an acid fraction, 8.0 g. of a neutral fraction, 16.9 g. of naphthalide, and 21.6 g. of hydrogenated naphthalides. The acid fraction was distilled, b.p. 190–200° (4 mm.), and crystallized from acetone hexane (1:3) to yield a first crop of 5.8 g., m.p. 118.5–119.5°, and a second crop of 9.8 g., m.p. 97–103°. Recrystallization of the first crop yielded colorless needles, m.p. 118.9–119.6°.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.41; Eq. wt. 190.
Found: C, 75.88; H, 7.32; Eq. wt. 187.

Picrate of peri-naphthopyran (VIII). On hydrogenation of 10 g. of naphthalic anhydride at 260° as described by Lazier (9), about half of the product (2.5 g.) was a yellow oil collected at 85–135° (5 mm.) on distillation in a Claisen flask. This oil was insoluble in boiling 1 *N* sodium hydroxide and yielded a picrate which, after three crystallizations from ethanol, melted at 173.5–175°.

Anal. Calc'd for $C_{18}H_{13}N_3O_8$: C, 54.14; H, 3.28.
Found: C, 53.69; H, 3.43.

No other products were isolated from this hydrogenation.

8-Methyl-1-naphthoic acid. A steel bomb was charged with 9.8 g. of naphthalide, 37.4 ml. of 1.85 *N* sodium hydroxide, 18.5 ml. of water, and 1.95 g. of copper chromite catalyst. Initial pressure at 20° was 2500 p.s.i. and maximum pressure at 250° was 4800 p.s.i. Hydrogenation was continued at 250° until the pressure became constant (about 3 hrs.); then the cooled bomb was washed out with water. Filtration and acidification of the clear yellow filtrate gave a precipitate which yielded 8.7 g. of carbonate-soluble product. Sublimation at a bath temperature of 130–190° (2 mm.) yielded 5.4 g. (55%) of nearly white 8-methyl-1-naphthoic acid, m.p. 147.2–151.0°. This material was suitable for use in synthesis. The best sample obtained by crystallization from acetone-hexane (1:5) melted at 152.2–153.2°.

A similar hydrogenation in which the maximum pressure at 250° was only 3900 p.s.i. gave a yield of only 40%. At the lower pressure, with only 1.2 equivalents of alkali the yield was 33%, and with 1.05 equivalents the yield was 11%.

SUMMARY

There is described a method for obtaining 1,8-naphthalide by hydrogenation of 1,8-naphthalic anhydride. Certain other products obtained from this hydrogenation have been characterized. 8-Methyl-1-naphthoic acid has been prepared by hydrogenation of naphthalide in aqueous alkali.

BERKELEY, CALIFORNIA

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

SYNTHESES IN THE *PERI*-SUBSTITUTED NAPHTHALENE SERIES[1]

JAMES CASON AND J. D. WORDIE[2]

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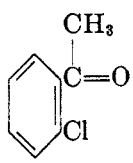
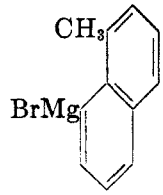
The initial objective of these investigations was synthesis of 1′,9-dimethyl-1,2-benzanthracene. The desirability of obtaining this compound, in order to permit its testing for possible carcinogenic activity, has already been discussed by Fieser and Seligman (1), and these investigators attempted unsuccessfully (1, 2) to accomplish its synthesis. There seems little doubt that the difficulties encountered in these syntheses are associated with the very pronounced steric hindrance between the two methyl groups, and it has become of considerable interest to learn whether the synthesis of the molecule is at all possible. The possibility of such a synthesis is strongly indicated by the work of Newman and collaborators, who have synthesized 4,5-dimethylphenanthrene derivatives. For example, 4,5,8-trimethyl-1-phenanthrylacetic acid was obtained by Newman and Hussey (3), and resolved into an optically active form. This shows that the methyl groups are forced out of the plane of the ring and overlap each other, thus creating an asymmetric molecule. It may be stated, at the outset, that the present work has not resulted in synthesis of the desired 1′,9-dimethyl-1,2-benzanthracene, but a number of the previously encountered difficulties have been overcome, and a study has been made of several highly hindered *peri*-substituted naphthalene derivatives.

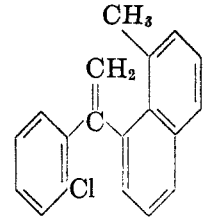
In one of the previous approaches (2) to the above-mentioned synthesis, an attempt was made to obtain the chloroalkene III by way of reaction of *o*-chloroacetophenone (I) with 8-methyl-1-naphthylmagnesium bromide (II) or the analogous lithium reagent. Addition of the Grignard reagent to the carbonyl group, followed by dehydration of the resulting carbinol, would give compound III, but no identifiable product was obtained from this reaction. In view of recent work



I



II



III

on Grignard reactions involving hindered molecules, especially that of Arnold and co-workers (4), it seems probable that ketone I would react entirely as the

[1] The authors are indebted to the Cancer Research Fund of the University of California for a grant in support of part of this research.

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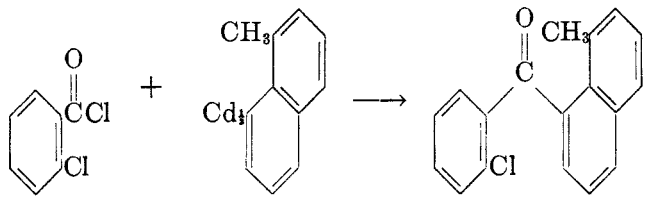
enol with the Grignard reagent II, although *para*-substitution of the 8-methyl-1-naphthyl group might be encountered (5). In the present work, a reaction between *o*-chlorophenylmagnesium bromide and 1-acetylnaphthalene resulted in very little addition to the carbonyl group, and most of the 1-acetylnaphthalene was recovered.

In order to avoid difficulty with the enolization reaction, we proposed to prepare the chloroalkene III by way of reaction of a methyl Grignard or lithium reagent with ketone IV, which has no *alpha* hydrogens. The simplest approach to this ketone appeared to be reaction of *o*-chlorobenzoyl chloride with the 8-



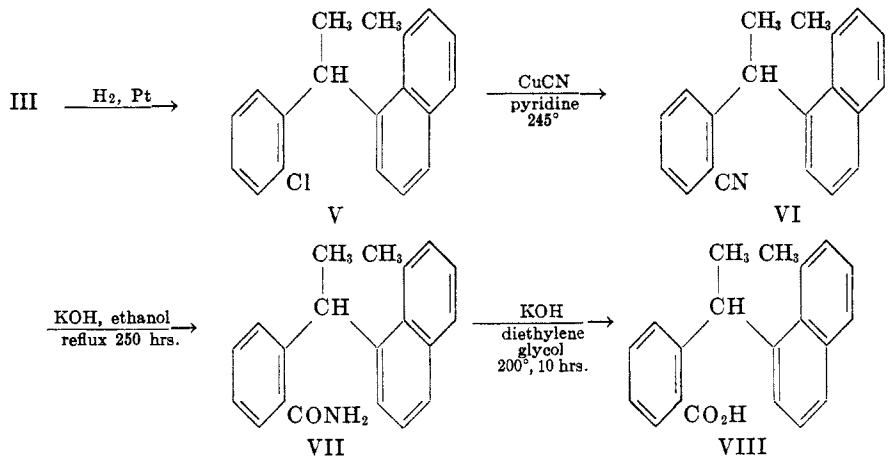
IV

methyl-1-naphthyl cadmium reagent. Since 1-chloro-8-methylnaphthalene seemed less inaccessible than the 1-bromo compound, the chloro compound was used for preparation of the cadmium reagent. This chloronaphthalene was prepared by the previously-described procedure (2), proceeding from 1-nitronaphthalene by way of 1-chloro-8-nitronaphthalene, 1-chloro-8-aminonaphthalene, and 1-chloro-8-bromonaphthalene to the desired 1-chloro-8-methylnaphthalene. Difficulty was experienced with the second step of this sequence, but a reproducible procedure was worked out.

1-Chloro-8-methylnaphthalene was converted to the cadmium reagent by way of the lithium reagent. The chloronaphthalene in dilute ether solution reacted with freshly cut lithium very sluggishly, if at all, but when the solution was concentrated a vigorous reaction set in and proceeded with no further difficulty. Reaction of the cadmium reagent with *o*-chlorobenzoyl chloride proceeded exothermally, but the ketone obtained from the reaction melted at 74.5–105°, and no pure compound could be isolated. Apparently, migration from the hindered 1-position had occurred at some stage of the preparation, presumably during formation or reaction of the lithium reagent. When 1-(*o*-chlorobenzoyl)naphthalene was prepared from *o*-chlorobenzoyl chloride and di-1-naphthylcadmium obtained from 1-chloronaphthalene *via* the lithium reagent, a small amount of migration appears to have occurred. The ketone was not readily purified sufficiently to give the melting point observed when the preparation was from 1-naphthoyl chloride and bis-(*o*-chlorophenyl)cadmium. It seems probable that this migration would not occur, even with the hindered naphthalene derivative, if the Grignard reagent were used, but the preparation of 1-bromo-8-methylnaphthalene appears so tedious that a different approach was adopted. The lithium reagent may be avoided if the carboxyl is shifted to the naphthalene ring and the cadmium reagent prepared from *o*-chlorophenylmagnesium bromide. The prepa-

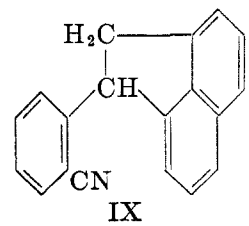
ration of 8-methyl-1-naphthoic acid, required for this alternative synthesis, has been described in the preceding paper (6).

The reaction of 8-methyl-1-naphthoyl chloride with bis-(*o*-chlorophenyl)cadmium gave a 76% yield of distilled ketone IV free from isomers, and crystallization readily yielded material melting at 73.8–74.4°. Although the methyl Grignard reagent reacted very slowly and unsatisfactorily with this ketone, lithiummethyl reacted as rapidly as it was added, and there appeared to be no tendency for a competing reaction with the chlorine. Dehydration of the resultant carbinol and fractionation of the product through a column gave a 69% yield of the chloroalkene, III. Conversion of this chloroalkene to 1-(*o*-carboxyphenyl)-1-(8-methyl-1-naphthyl)ethane (VIII), the acid desired for cyclization experiments, was accomplished by the indicated sequence of reactions.



The first two steps, to yield V and VI, were accomplished without difficulty, following the procedures used previously (7) for a similar compound, except that in the hydrogenation step there was some attack on chlorine. Removal of the chlorine-free by-product was accomplished by fractional distillation.

As indicated in the chart, heating under reflux with alcoholic potassium hydroxide for 250 hours hydrolyzed the nitrile only as far as the amide. None of acid VIII was isolated at this stage. Since it has previously been reported (7) that hydrolysis of *o*-7-(acenaphthyl)benzonitrile (IX) under identical conditions



IX

gives a 69% yield of the corresponding acid, it is apparent that VI is far more hindered than IX. A study of models indicates that this is entirely reasonable.

The presence of the methylene bridge in IX holds all the carbons in one plane except for the benzene portion of the molecule. The phenyl grouping is free to swing into a plane at approximately right angles to the plane of the remainder of the molecule, and this somewhat relieves the crowding around the nitrile grouping. On the other hand, in VI the naphthyl group is free to rotate, and interference between the methyls forces the naphthalene ring into a position of serious interference with the nitrile grouping.

We were unable to convert the amide, VII, to the acid with nitrite, following the improved procedure recently published (8), but high-temperature saponification gave a nearly quantitative conversion to the acid. The latter procedure appears to be the favored method for conversion of highly hindered amides to the acids, in instances where the molecule can withstand alkali at the required temperatures. The course of the reaction is easily followed by titration of the ammonia evolved.

In the low-temperature hydrolysis yielding the amide VII, there was also obtained about 7% yield of an acid which was isomeric, but not identical, with acid VIII. Shorter periods of hydrolysis did not decrease the yield of this acid, and it seems certain that the substance is the isomer of VIII having the carboxyl group in the unhindered *para* position. This isomer would arise from a small amount of *p*-bromochlorobenzene present in the *o*-bromochlorobenzene used as starting material and prepared from technical *o*-chloroaniline. Although intermediates III, IV, and V were crystallized to a constant melting point for analysis, distilled samples were used for subsequent steps in the synthesis. This is no disadvantage since the *p*-isomer is easily removed if the two-stage hydrolysis is used.

All efforts to cyclize acid VIII were unsuccessful, although there were utilized what appear to be the most powerful methods of cyclization known at present. These were anhydrous hydrogen fluoride, zinc chloride and acetic anhydride (9), and the inverse Friedel and Crafts procedure (10). In the first and last procedures, the crude reaction products from the cyclization were reduced with zinc and alkali (11), in hopes that the hydrocarbon would be more easily isolated than the anthrone, but no compound with the properties expected for the desired hydrocarbon could be obtained. The principal products in all instances were insoluble, high molecular weight materials.

A study of models suggests that failure of acid VIII to cyclize is due to the fact that interference between the methyl groups prevents the two aromatic systems from approaching the same plane, thus preventing the carboxyl from coming sufficiently near for reaction with the 2-position in the naphthalene ring system. It is further suggested by a study of models that if 8-methyl-5,6,7,8-tetrahydro-1-naphthoic acid (6) were used as starting material for synthesis of an acid analogous to VIII but containing the tetralin ring system, cyclization should be possible, for the methyl in the angular ring would then be out of the plane of the rest of the molecule. The final step introducing the strain would then be dehydrogenation, and this appears hopeful, for no new carbon-carbon bonds would be established. This latter procedure will be explored in this laboratory as soon as

there has been developed a procedure suitable for supplying 8-methyl-5,6,7,8-tetrahydro-1-naphthoic acid in sufficient quantity.

Before 8-methyl-1-naphthoic acid was used in the preparations just described, model experiments were carried out starting with 1-naphthoic acid. In this work there were prepared the chloroketone, chloroalkene, and chloroalkane differing from III, IV, and V by lacking the methyl group in the 8-position in the naphthalene ring. There was also prepared 1-acetyl-8-methylnaphthalene by reaction between 8-methyl-1-naphthoyl chloride and dimethylcadmium.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses are by the Microanalytical Division of the Department of Chemistry of the University of California.

1-Chloro-8-nitronaphthalene.[3] 1-Nitronaphthalene was chlorinated as has been previously described (2), but direct crystallization of the product separating from the chlorination mixture gave the reported yield (36%) of 1-chloro-8-nitronaphthalene only after prolonged systematic crystallization. If the precipitate was first fractionated through a 65-cm. Vigreux column and the fraction boiling above 170° (1–2 mm.) used for recrystallization, a yield of 25–30% was readily obtained. Material melting at 91° or higher was used for reduction. For the best sample, m.p. 94.0–94.6°.

1-Chloro-8-aminonaphthalene.[3] The previously-reported procedure (12) for the preparation of this compound seems not sufficiently detailed to permit reproducible results. The following procedure consistently gave very little recovered starting material or reductive removal of chlorine.

A mixture of 60 g. of 1-chloro-8-nitronaphthalene, 48.4 g. of iron powder reduced with hydrogen, and 80 ml. of water was stirred vigorously with a Hershberg stirrer and heated under reflux for eight hours, the flask being immersed in a steam-bath or boiling-water bath. At the beginning of the reduction 4 ml. of concentrated hydrochloric acid was added, and during the reduction an additional 8 ml. of acid was added in 2-ml. portions. The cooled reaction mixture was treated with 20 ml. of concentrated aqueous ammonium hydroxide, then the total precipitate was extracted with portions of boiling ethanol until dilution of the extract with water gave no precipitate. The ethanol filtrates were concentrated and diluted with water, and the precipitated amine was dissolved in a boiling mixture of 290 ml. of 1 *N* hydrochloric acid and 900 ml. of water. After removal of a small amount of insoluble oil (unreduced nitro compound), addition of ammonium hydroxide precipitated 44.0 g. of amine, m.p. 74–80°. Systematic crystallization from ethanol yielded 33 g. (64%) of amine melting at 92° or above, and suitable for use in the next step. The best sample melted at 93.5–94.7°. This yield of purified amine is below previous reports (2, 12).

1-Chloro-8-bromonaphthalene.[3]. A hot mixture of 69.0 g. of 1-chloro-8-aminonaphthalene and 140 ml. of 48% hydrobromic acid was rapidly chilled to 0° with stirring and diazotized at this temperature by the addition of a cold solution of 30 g. of sodium nitrite in 175 ml. of water. After addition was complete the mixture was stirred 40 minutes at the same temperature, then 48 g. of urea was added and stirring continued for 20 minutes. The diazonium solution was added in one portion to 67 g. of cuprous bromide dissolved in 640 ml. of 48% hydrobromic acid cooled to 0°. After stirring for 15 minutes at 0° and an additional 15 minutes after removal of the cooling-bath, the mixture was heated on a steam-bath. The reaction mixture was diluted with 500 ml. of water, the precipitate removed by filtration, and the aqueous solution extracted with benzene. The precipitate was added to the benzene

[3] In this preparation, the authors were assisted by Mr. Charles F. Allen.

extract, and after filtration of a little insoluble material, the benzene solution was washed with sodium carbonate solution, water, concentrated sulfuric acid, water, and sodium bicarbonate solution. Removal of solvent and distillation from a Claisen flask yielded 70.3 g. (75%) of a light yellow product, b.p. 150–160° (5–6 mm.). Crystallization from 300 ml. of ethanol yielded 57.8 g. (62%) of colorless plates, m.p. 93.0–95.0°. Only small amounts of satisfactory material could be obtained by systematic working of material obtained from the filtrate. The best sample of 1-chloro-8-bromonaphthalene melted at 94.6–96.6° [literature: 96.5–97° (2), 94–95° (13)].

The somewhat different procedure previously used (2) for this preparation gave only a 49% yield of distilled product.

1-Chloro-8-methylnaphthalene was prepared by reaction of 8-chloro-1-naphthylmagnesium bromide with methyl sulfate essentially as has been described (2), except that the product was distilled through a 65-cm. Podbielniak type column to give 52% yield of a product of b.p. 134–136° (10 mm.), m.p. 67.2–70.3°, and suitable for use in the subsequent synthesis. Fieser and Seligman (2) reported a 60% yield of distilled product, which melted at 68–69° after recrystallization.

Reaction of bis-(8-methyl-1-naphthyl)cadmium with o-chlorobenzoyl chloride was carried out essentially as described below for the preparation of 1-(*o*-chlorobenzoyl)naphthalene, procedure B. Distillation of the products through a 65-cm. Podbielniak type column yielded 8.7 g. of an oil, b.p. 102–140° (10.5 mm.), 0.8 g. of intermediate, and 4.4 g. (32%) of a viscous oil, b.p. 195–205° (2 mm.). The latter fraction solidified slowly on standing, and crystallization from hexane gave 1.5 g. of fine needles, m.p. 74.5–105°. This material was not further investigated.

1-(o-Chlorobenzoyl)-8-methylnaphthalene (IV). A Grignard reagent was prepared from 0.12 mole of *o*-bromochlorobenzene and 0.12 mole of magnesium in 60 ml. of ether, and this was converted to the cadmium reagent with 0.066 mole of anhydrous cadmium chloride in the usual manner (14). After distillation of ether and addition of 100 ml. of benzene, there was added during 10 minutes, in 50 ml. of benzene, the acid chloride prepared from 0.04 mole of 8-methyl-1-naphthoic acid (6) and 2 mole-equivalents of thionyl chloride. During the addition, the temperature of the reaction mixture rose from 28 to 45°. The mixture was stirred for 4 hours at 40–45°, then worked up in the usual manner (14), and the product was distilled from a Claisen flask to yield 8.2 g. (76%) of ketone IV, b.p. 165–195° (2 mm.).

This material was used for further synthesis, but a crystalline sample could not be obtained until a sample was distilled through the 65-cm. Podbielniak type column. From 8.2 g. obtained as above there resulted 6.5 g. of material, b.p. 195–200° (3 mm.), which slowly crystallized on standing. One crystallization from hexane yielded material of m.p. 73.8–74.4°, not altered by further crystallization.

Anal. Calc'd for $C_{18}H_{13}ClO$: C, 77.01; H, 4.67; Cl, 12.63.

Found: C, 76.90; H, 4.79; Cl, 12.85.

1-(o-Chlorophenyl)-1-(8-methyl-1-naphthyl)ethene (III). To a solution of 11.1 g. (0.04 mole) of ketone IV in 50 ml. of ether, in an atmosphere of nitrogen, there was added, with stirring during 15 minutes, 40 ml. of approximately 0.9 *N* methyllithium in ether. The reaction caused gentle refluxing, and after stirring 15 minutes the Gilman test was negative. After addition of an additional 20 ml. of the methyllithium solution and continued stirring under reflux, the Gilman test was positive after 20 minutes. The reaction mixture was decomposed by the addition of 10 ml. of saturated aqueous ammonium chloride. Removal of ether left a red oil which was heated under reflux for one hour with 70 ml. of glacial acetic acid, to effect dehydration of the carbinol which is the reaction product. The acetic acid solution was diluted with water, the product was extracted with benzene, and after removal of benzene the ethylene III was distilled from a Claisen flask, b.p. 180–195° (2.5 mm.), wt. 10.2 g. Since this material could not be hydrogenated, it was distilled through the 65-cm. Podbielniak type column to yield 7.1 g. (69%) of a pale yellow oil, b.p. 187–192° (2 mm.), which soon began to crystallize. This material was hydrogenated at once as described below.

For analysis, a sample was crystallized from acetic acid and obtained as small, colorless cubes, m.p. 81.0–81.6°.

Anal. Calc'd for $C_{19}H_{15}Cl$: C, 81.86; H, 5.42.
Found: C, 81.85; H, 5.51.

1-(o-Chlorophenyl)-1-(8-methyl-1-naphthyl)ethane (V). A solution of 7.1 g. of freshly distilled ethylene III in 85 ml. of glacial acetic acid and 15 ml. of anhydrous ether was hydrogenated at room temperature and atmospheric pressure in the presence of 0.2 g. of commercial platinum oxide catalyst. After absorption of one mole-equivalent of hydrogen (10 hours) the reaction was interrupted, and after filtration and distillation of solvent the residual oil was fractionated through the 65-cm. Podbielniak type column. There was a forerun of 1.5 g., distilling principally at 160–170° (2 mm.), and the product (V) was collected at 185–190° (2 mm.), wt. 5.4 g. (75%). This distilled sample was used for the next step, but for analysis a sample was crystallized twice from methanol to yield colorless blades of m.p. 63.4–65.0°.

Anal. Calc'd for $C_{19}H_{17}Cl$: C, 81.27; H, 6.10.
Found: C, 81.29; H, 5.71.

1-(o-Cyanophenyl)-1-(8-methyl-1-naphthyl)ethane (VI). A mixture of 4.7 g. of ethane V, 1.5 g. of cuprous cyanide (dried in a vacuum at 100°), 0.4 ml. of acetonitrile (distilled from phosphorus pentoxide), and 4 ml. of pyridine (distilled from barium oxide) was heated in a sealed tube at 242–246° for 28 hours. The reaction mixture was shaken out with benzene and a 3% aqueous solution of sodium cyanide, some insoluble tar being removed by suction filtration. The benzene layer was washed with dilute hydrochloric acid, sodium bicarbonate solution, and water, then distilled from a Claisen flask to yield 3.1 g. (68%) of a yellow oil, b.p. 180–200° (2.5 mm.). Since this product was not obtained crystalline, it was not further characterized except by conversion to the amide, VII.

1-(o-Amidophenyl)-1-(8-methyl-1-naphthyl)ethane (VII). The distilled nitrile VI (3.1 g.) was hydrolyzed by heating under reflux in a steel flask for 250 hours with a solution of 18.2 g. of potassium hydroxide in 120 ml. of ethanol and 70 ml. of water. Solid present in the reaction mixture was filtered, and the filtrate was diluted with water and extracted with benzene. The solid and residue from distillation of most of the benzene was crystallized (charcoal) from hexane to yield 0.91 g. (28%) of colorless needles, m.p. 197–199°. The yield of amide under different hydrolytic conditions was not improved, and the low yield is ascribed in part to the accumulation of impurities in the distilled samples of III and V used for the synthesis.

For analysis there was used a sample of m.p. 203.5–203.9°, obtained by one additional crystallization.

Anal. Calc'd for $C_{20}H_{19}NO$: C, 83.01; H, 6.62.
Found: C, 83.36; H, 6.43.

The alkaline solution remaining after extraction of the above amide was acidified to yield 0.33 g. of acidic material. After two crystallizations (charcoal) from benzene-hexane (1:2), there was obtained 0.14 g. of nearly colorless needles, m.p. 183.4–185.6°. Since the composition of this acid is the same as that of VIII, but a mixture of the two gives a depressed m.p., this acid is *1-(p-carboxyphenyl)-1-(8-methyl-1-naphtyhl)ethane.*

Anal. Calc'd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25.
Found: C, 82.56; H, 6.25.

1-(o-Carboxyphenyl)-1-(8-methyl-1-naphthyl)ethane (VIII). In a steel vessel there was heated under reflux at a bath temperature of 190–200° a mixture of 393 mg. of amide VII, 3.0 g. of potassium hydroxide, and 20 ml. of diethylene glycol. The vessel was swept out with a slow stream of nitrogen which was bubbled through boric acid solution, and evolution of ammonia was followed by titration as has been previously described (15). After 80% of the theoretical amount of ammonia had been evolved (usually 8–10 hours), the cooled reaction mixture was diluted with 150 ml. of water and 52 mg. of unsaponified amide was filtered. Acidification of the clear alkaline filtrate precipitated 320 mg., (94%, based on amide consumed) of acid VIII, m.p. 179.0–181.4°. This m.p. was not altered by recrystallization from benzene-hexane, and a sample immersed in a bath at 180.5° melted completely; thus polymorphism is indicated.

Anal. Calc'd for $C_{20}H_{18}O_2$: C, 82.73; H, 6.25.
Found: C, 82.38; H, 6.37.

Attempts at cyclization of acid VIII. A. With acetic anhydride and zinc chloride. Following the method of Fieser and Hershberg (9), a mixture of 50 mg. of VIII, 0.3 ml. of glacial acetic acid, 0.25 ml. of acetic anhydride, and a trace of anhydrous zinc chloride was heated under reflux for two hours, then diluted with water. The sticky precipitate was dissolved in ether, and extracted with aqueous carbonate but no acidic material was recovered. No crystalline material could be isolated from this substance, so it was reduced with zinc and alkali according to Martin (11), a procedure frequently used (7) for reduction of an anthrone to an anthracene.

No acidic material was recovered after the reduction. On chromatography on activated alumina, the tower retained a narrow red band and a broad yellow band, while a substance giving a blue fluorescence in ultraviolet light passed rapidly through the tower. The green-yellow oil remaining after evaporation of the eluate was insoluble in 15 ml. of hot ethanol, and gave no sublimate at 2 mm. pressure and a bath temperature of 200°. Apparently, cyclization to higher molecular weight substances had occurred.

B. With anhydrous hydrogen fluoride (16). A mixture of 88 mg. of acid VIII and 5 ml. of anhydrous hydrogen fluoride was allowed to stand for 2.5 hours, then poured on ice. The crude reaction product, which contained no carbonate-soluble material, was reduced with zinc and alkali, and the product was worked up as described above. The yellow band was washed out of the column to yield 11 mg. of non-fluorescent material, while the fluorescent eluate yielded 40 mg. of oil. The latter fraction did not sublime at 200° and 2 mm., and the sublimate collected at 220° and 1.5 mm. was an insoluble, noncrystalline material.

C. Inverse Friedel and Crafts procedure. A 185-mg. sample of acid was cyclized according to the procedure of Johnson and Glenn (10), and the crude cyclization product was reduced with zinc and alkali. After chromatography, the fluorescent eluate yielded 45 mg. of material similar to that encountered in the other procedures, and elution of the large yellow zone yielded 165 mg. of orange oil. The latter fraction, at 170° and 1.5 mm., gave 145 mg. of sublimate which after precipitation from alcohol melted at 45–50° and gave an analysis indicating the presence of oxygen in the molecule. The behavior and weight of material recovered indicates reaction with the benzene solvent although this was never observed by Johnson and Glenn.

1-Acetyl-8-methylnaphthalene. A cadmium reaction was carried out as described for preparation of IV, starting with 0.02 mole of 8-methyl-1-naphthoic acid and the methylmagnesium bromide prepared from 0.025 mole of magnesium. The reaction product was saponified with alcoholic potassium hydroxide in order to remove any methyl 8-methyl-1-naphthoate formed as a by-product in the cadmium reaction (14), but no acidic material was recovered. Distillation of the neutral product from a Claisen flask yielded 2.8 g. (76%) of a yellow oil which slowly crystallized, m.p. 40.0–43.0°. Crystallization from methanol-water (5:2) gave small colorless plates, m.p. 47.9–48.9°.

Anal. Calc'd for $C_{13}H_{12}O$: C, 84.75; H, 6.57.
Found: C, 84.69; H, 6.59.

The *picrate* crystallized from ethanol as yellow needles, m.p. 84.0–84.4°.

Anal. Calc'd for $C_{19}H_{15}N_3O_8$: C, 55.21; H, 3.66.
Found: C, 55.02; H, 3.62.

1-(o-Chlorobenzoyl)naphthalene. A. A cadmium reaction was carried out as described for preparation of IV, starting with 0.33 mole of 1-naphthoic acid and the Grignard reagent from 1 mole of magnesium and 1.1 mole of *o*-bromochlorobenzene. Distillation from a Claisen flask yielded 57.4 g. (65%) of a yellow oil, b.p. 195–203° (1.5 mm.). After standing several days, crystallization set in, and a sample crystallized three times from hexane melted at 83.4–83.9°.

Anal. Calc'd for $C_{17}H_{11}ClO$: Cl, 13.30. Found: Cl, 13.58.

B. A total of 8.1 g. (0.05 mole) of 1-chloronaphthalene (b.p. 115.2–115.8° at 10 mm.) was converted to the lithium derivative with 0.8 g. (0.11 mole) of lithium cut from lithium

wire into very small pieces, in an atmosphere of nitrogen. Initially, a mixture of 50 ml. of ether, 0.2 g. of lithium, and 5 ml. of a 10% solution of 1-chloronaphthalene in ether was heated under reflux for 30 minutes, without any evidence of reaction. Since Vesely and Stursa (17) had prepared this lithium derivative in rather concentrated ether solution, ether was distilled until a volume of about 25 ml. remained, whereupon a reaction set in immediately as evidenced by red spots on the lithium and a deep red solution. Addition of 25 ml. of ether stopped reaction essentially completely, and reduction of volume again gave a vigorous reaction. The remainder of the chloronaphthalene, diluted with an equal volume of ether, was added during about three hours, the lithium was added in 0.2-g. lots at one-hour intervals, and finally the mixture was stirred under reflux for an additional two hours. To the cooled reaction mixture, containing a small amount of lithium, was added 5.1 g. (0.028 mole) of anhydrous cadmium chloride. After heating under reflux for 25 minutes the Gilman test was positive, so an additional 1.0 g. of cadmium chloride was added, but the Gilman test was positive after heating for an additional 90 minutes. After adding 100 ml. of ether and 1.0 g. of additional cadmium chloride, followed by 90 minutes heating, the Gilman test was negative. Such a procedure seems necessary to obtain a negative Gilman test; initial addition of 7 g. of cadmium chloride is no advantage.

Ether solvent was replaced with benzene, and reaction with *o*-chlorobenzoyl chloride was carried out essentially as described for the preparation of IV. Distillation of the product through the 65-cm. Podbielniak type column gave 7.4 g. (55%) of product, b.p. 198–205° (2.5 mm.). After one crystallization from hexane, the m.p. was 75.5–77.5°, and the mixture with a sample of m.p. 80.4–82.4°, obtained by Procedure A after one crystallization, melted at 77.5–80.5°.

1-(o-Chlorophenyl)-1-(1-naphthyl)ethene. In the manner described for the preparation of ethylene III, a reaction was carried out between methyllithium and 1-(*o*-chlorobenzoyl)naphthalene, and the resultant carbinol was dehydrated by heating with acetic acid. Distillation of the alkene through the 65-cm. Podbielniak type column gave a 55% yield of a viscous, pale yellow oil, b.p. 168–170° (1.5 mm.). This substance was not obtained in a crystalline condition.

Anal. Calc'd for $C_{18}H_{13}Cl$: C, 81.66; H, 4.95; Cl, 13.39.
Found: C, 81.82; H, 5.03; Cl, 13.11.

1-(o-Chlorophenyl)-1-(1-naphthyl)ethane. A solution of 7.3 g. of freshly distilled alkene (described above) in 45 ml. of glacial acetic acid was hydrogenated at atmospheric pressure and room temperature in the presence of 0.2 g. of commercial platinum oxide catalyst. After absorption of 0.67 mole-equivalent of hydrogen in 23 hours hydrogenation had ceased, and was completed in an additional 2 hours after an additional 0.2 g. of catalyst was added. Distillation of the product through the 65-cm. Podbielniak type column gave 6.6 g. (89%) of a colorless oil, b.p. 167–169° (1.7 mm.). This oil had become only partly crystalline after standing several months.

Anal. Calc'd for $C_{18}H_{15}Cl$: Cl, 13.29. Found: Cl, 13.32.

SUMMARY

In the course of syntheses leading to the preparation of 1-(*o*-carboxyphenyl)-1-(8-methyl-1-naphthyl)ethane, several hindered *peri*-substituted naphthalene derivatives have been prepared. All attempts to convert the above acid to 1′,9-dimethyl-1,2-benzanthracene were unsuccessful.

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[CONTRIBUTION FROM CHEMISTRY DEPARTMENT, OREGON STATE COLLEGE]

THE INFLUENCE OF MOLYBDATES ON THE HYDROGEN PEROXIDE OXIDATION OF NAPHTHALENE AND β-NAPHTHOL[1]

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Molybdates, as well as oxides and salts of other so called "peracid formers" such as tungsten, vanadium, titanium, zirconium, and tantalum, in the presence of hydrogen peroxide are known to be very specific oxidants for certain inorganic reactions of hydrogen peroxide (1). Furthermore, organic acids such as formic and acetic which are capable of forming peracids have behaved in the same manner as the metallic peracids in several instances.

The use of peracetic and perbenzoic acids as oxidizing agents in organic chemistry is well known, but only in a few cases have molybdates been used with hydrogen peroxide in the oxidation of organic compounds. Toennies and Kolb (2) oxidized methionine to methionine sulfone with hydrogen peroxide and a mixture of perchloric acid and ammonium molybdate; Larsson (3) found that the oxidation of thioacetic acid and β,β′-thiodipropionic acids to the corresponding sulfoxides and sulfones by hydrogen peroxide proceeded rapidly in the presence of molybdic acid. In both cases, however, the amount of molybdate used seemed excessive and its use as a catalyst in hydrogen peroxide oxidations, by no means recognized. One of the few examples where molybdate was used catalytically is the oxidation of acetaldehyde to acetic acid by hydrogen peroxide in the presence of molybdenum trioxide or vanadium pentoxide, described by Takigawa (4) in an analytical volumetric procedure for the determination of acetaldehyde. Milas and co-workers (5) in their work on the hydroxylation of the unsaturated substances have recognized the possibilities of the peracids as selective catalysts and have extended their studies to a number of these compounds.

Since the metallic peracids are such selective oxidants for inorganic reactions, a preliminary study of the use of molybdate as a catalyst for the hydrogen peroxide oxidation of organic compounds was made in this laboratory. β-Naphthol was selected for comparative purposes as the reductant for the initial experiments, inasmuch as considerable information regarding its behavior during peracetic acid oxidations has been published.

Boeseken and Koenigsfeldt (6) reported that a good yield of *o*-carboxycinnamic acid, together with a small amount of an unknown substance $C_{20}H_{14}O_4$, was obtained by the slow oxidation of β-naphthol using peracetic acid in glacial acetic acid. Greenspan (7) improved this procedure by using a concentrated instead

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of a dilute solution of peracetic acid, which resulted in an almost immediate deposition of crystals of *o*-carboxycinnamic acid.

In this laboratory β-naphthol was oxidized with hydrogen peroxide in glacial acetic, (a) with and (b) without molybdate in the reaction mixture. Without molybdate the reaction occurred very slowly, a precipitate forming after several days, but only after an additional amount of hydrogen peroxide had been added. However, in the presence of molybdate, the reaction was completed in a matter of hours.

Both reaction products (with and without molybdate) upon examination were found to be mixtures of at least two acids. These two acids were easily separated, due to insolubility of the second acidic constituent in sodium bicarbonate solution, into *o*-carboxycinnamic acid and an unknown acid melting at 280–281°. This latter acid had the properties of an acid described by Ehrlich (8), which he obtained in small yield in addition to *o*-carboxycinnamic acid during the oxidation of β-naphthol with dilute permanganate, and to which he assigned the empirical formula $C_{20}H_{12}O_4$. According to Ehrlich, the acid melts at 280–281°, is difficultly soluble in alcohol and practically insoluble in other solvents; from the saponification number it appears to be dibasic, but yields only a monosalt and a monoethyl ester.

Later Dischendorfer and Danzigar (9) established the structure of this acid and found it to be 4-(2-carboxyphenyl)-5,6-benzocoumarin. This explains the fact that the compound forms only the monoester and monosalt while it appears to be dibasic on titration. The acid isolated in this laboratory was insoluble in bicarbonate solution and gave a saponification value of half the molecular weight.

It is interesting that Boeseken and Koenigsfeldt reported an uncharacterized by-product ($C_{20}H_{14}O_4$, m.p. 265–267°) obtained during the peracetic acid oxidation of β-naphthol, which these workers concluded was one of the bisdihydroxy naphthalenes on the basis of its insolubility in bicarbonate solution.

When β-naphthol was suspended in very dilute hydrochloric acid solution containing a trace of ammonium molybdate and an excess 30% hydrogen peroxide was added slowly, an exothermic reaction started immediately, but instead of proceeding to *o*-carboxycinnamic acid, the solution turned dark red and a black resin (I) precipitated. From the red solution a small amount of an orange-red substance (II) separated on standing. In the absence of molybdate, the same reaction proceeded at a very slow rate; after thirty hours the solution was red and a red precipitate separated. This was found to be mostly unreacted β-naphthol, mixed with a small amount of a fine red precipitate.

The failure to obtain *o*-carboxycinnamic acid indicates that molybdate-catalyzed hydrogen peroxide in glacial acetic acid and in dilute hydrochloric acid (in which permolybdic acid is probably the responsible oxidizing agent) react in a completely different manner, under the prevailing conditions. This may be due to differences in the oxidant, but may also be due to differences in the solvents. There are many examples in the literature that demonstrate the decisive influence of the solvent on the course of the reaction when hydrogen peroxide or the peracids are used as reagents.

The black resin (I) was found to consist of a mixture of (II) and another un-

identified yellow solid. A study of the properties of (II) was then undertaken; the orange compound was found to be soluble in all ordinary organic solvents, in sodium hydroxide, sodium carbonate, and concentrated sulfuric and acetic acids. It was insoluble in sodium bicarbonate and dilute acids. The red alkaline solution turned readily dark, and compound (II) was not reprecipitated with dilute acids in the original form. Compound (II) gave a dark green color in concentrated sulfuric acid and a red color in glacial acetic. Recrystallization from dilute acetone gave shiny dark red crystals. Molecular weight determinations gave an average value of 313, which indicates that condensation of two naphthol molecules must have taken place.

Due to the interesting properties of (II), a series of experiments was undertaken in order to improve its yield. When the reaction was conducted in a homogeneous medium, such as aqueous alcohol or acetone, more satisfactory results were obtained. Water seems to be necessary for the reaction, since the solution only becomes colored after addition of water to the reaction mixture. This might possibly be due to the solubility of the molybdate in the solvents used. The isolation of the product from the reaction mixture when alcohol or acetone were used as solvents, presented a special problem, since the precipitate obtained by pouring the solution into water was always too fine to be filtered. This difficulty was avoided by pouring the reaction mixture into a large volume of water and salting out the orange precipitate, which was then obtained in excellent yields.

Since earlier studies of peracetic acid oxidations of the naphthols had extended to naphthalene (10), similar experiments were conducted with molybdate-catalyzed hydrogen peroxide. Naphthalene has been reported to have been slowly oxidized to *o*-carboxycinnamic acid (10) by peracetic acid. When naphthalene was treated in a glacial acetic acid medium with hydrogen peroxide in presence of ammonium molybdate the reaction proceeded slowly but when heated it started immediately and gave a phthalide, the lactone of 3-(2-carboxyphenyl)-3-hydroxypropanoic acid, in 69% yield as against a 43% yield in the absence of ammonium molybdate.

EXPERIMENTAL

Oxidation of β-naphthol with hydrogen peroxide in glacial acetic acid in the presence of sodium molybdate. β-Naphthol (20 g., 0.139 mole) and 100–150 mg. of sodium molybdate were dissolved in 120 ml. of glacial acetic acid and 100 ml. of 30% hydrogen peroxide was very slowly added to the stirred material over a period of 4–5 hours. The reaction mixture was stirred an additional twenty hours, cooled in an ice- and salt-bath and then diluted with 200 ml. of cold water to complete the precipitation.

The crude acid product was removed, suspended in a cold saturated solution of sodium bicarbonate, and stirred for one-half hour. The insoluble material was removed, suspended in 50 ml. of cold ethanol to remove soluble impurities, and filtered. The precipitate was decolorized with charcoal and recrystallized from hot ethanol. Yield, 1.2 g. of acid, m.p. 282–283°.

Anal. Calc'd for $C_{20}H_{12}O_4$: C, 75.9; H, 3.83; Sap. equivalent, 158.
Found: C, 76.2; H, 4.06; Sap. equivalent 160.

The bicarbonate solution after acidification gave 14.1 g. of crude *o*-carboxycinnamic acid, m.p. 172–174°. After decolorization with Norit and recrystallization from a water-ethanol mixture, m.p. 188–190°; yield 11.2 g.

Anal. Calc'd for $C_{10}H_8O_4$: C, 62.5; H, 4.20; Neutral equivalent, 96.

Found: C, 62.4; H, 3.86; Neutral equivalent, 96.

Oxidation of β-naphthol with hydrogen peroxide and ammonium molybdate in an aqueous alcohol medium. To a stirred mixture containing 1 g. of β-naphthol, 25 mg. of ammonium molybdate, 5 ml. ethanol, and 2 ml. glacial acetic acid was added dropwise 1.6 ml. of 30% hydrogen peroxide. This mixture was then saturated with water and after 10–15 minutes was placed in a refrigerator for 2–3 hours until the completion of reaction (this time factor is important in order to obtain an uncontaminated product). Alcohol was then added to dissolve the partially precipitated product. This alcoholic solution in turn was poured into 500–700 ml. of stirred water, which upon treatment with salt, yielded 1 g. of an orange product.

The product was dissolved in acetone, the solution filtered, cooled, and water added to induce crystallization. After standing for two hours at room temperature shiny dark red crystals melting at 148° were obtained.

Anal. Calc'd for $C_{20}H_{14}O_4$: C, 75.5; H, 4.43; Mol. wt., 318.

Found: C, 75.1; H, 4.40; Mol. wt., 313.

Oxidation of naphthalene with hydrogen peroxide in the presence of ammonium molybdate. Naphthalene (10 grams, 0.0782 mole) 0.2 g. of ammonium molybdate, and 250 ml. of glacial acetic acid were placed in a 500-ml., 3-necked flask equipped with a stirrer, reflux condensor, and dropping-funnel. The solution was brought to a gentle reflux and 84.0 g. of 30% hydrogen peroxide was slowly added over a period of four hours. The acetic acid solution was diluted with an equal volume of water, cooled in an ice-bath, and filtered to remove the unreacted naphthalene (2.3 g.). The filtrate was distilled under reduced pressure to remove the solvent and the residue was maintained at 100° for two additional hours to remove the last traces of water and acetic acid.

After several extractions with hot benzene the cooled extractant yielded 8.0 g. of slightly colored solid, m.p. 149–150°; 69% yield (without molybdate, yield 43%). Recrystallization from a *n*-heptane–*n*-amyl alcohol (9:1) mixture gave crystals, m.p. 152°, neutral equivalent 192.5. A mixed melting point of this compound with the sublimate of *o*-carboxycinnamic acid gave no depression.

Greenspan gives m.p. 153° for the lactone of β-hydroxy-β-*o*-carboxyphenylpropanoic acid, neutral equivalent 192.0.

SUMMARY

The catalytic influence of molybdate salts (2) on hydrogen peroxide oxidations of naphthalene and β-naphthol was demonstrated. The effect of the solvent on the molybdate-catalyzed hydrogen peroxide oxidation of β-naphthol was also illustrated. A new method for the preparation of 4-(2-carboxyphenyl)-5,6-benzocoumarin and a new oxidation product of β-naphthol, $C_{20}H_{14}O_4$, are reported.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY, THE JOHNS HOPKINS UNIVERSITY]

THE REACTION OF *m*-METHYLBENZYLMAGNESIUM BROMIDE WITH CARBON DIOXIDE

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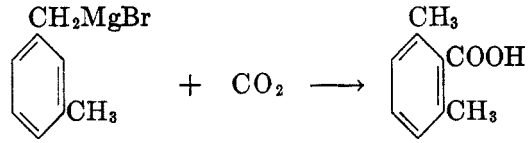
Recently Musseron and Du (1) have carried out an extensive study on the reaction of methyl-substituted benzyl Grignard reagents with several reactants. The carbonation of the Grignard reagent formed from *m*-methylbenzyl bromide was among the reactions studied. The only product that was reported from this



I

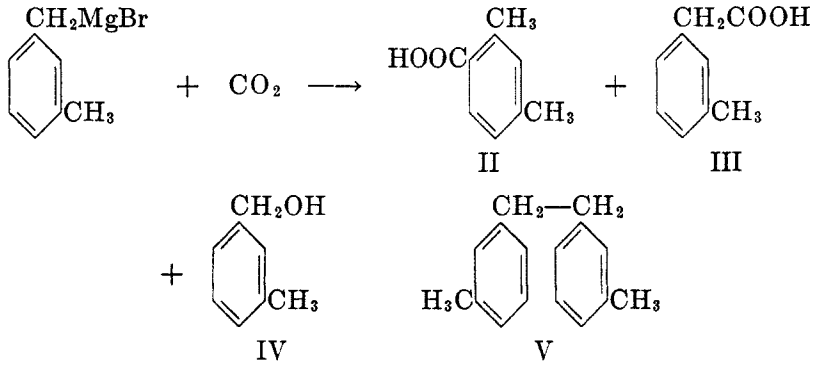
reaction was 2,6-dimethylbenzoic acid (I). The sole criterion for the identity of the product was a melting point, 115–116°, which is in good agreement with the melting point reported by other workers (2) for this acid.

The rearrangement observed in the course of this reaction was first discovered by Tiffeneau and Delange (3), who found that *o*-methylbenzyl alcohol rather than the expected β-phenylethyl alcohol is the product from the reaction of benzylmagnesium chloride and formaldehyde. The rearrangement most often observed is to the *ortho* position. However, in recent years rearrangement to the *para* position seems to have been definitely established. Austin and Johnson (4) have reported that 2,6-dichlorobenzylmagnesium chloride and acetyl chloride yield 3,5-dichloro-4-methylacetophenone, although the experimental details indicate that the reaction product may have been a mixture. More recently Burtle and Shriner (5) have definitely established the presence of about 5% *para* product in the reaction of benzylmagnesium chloride with diethyl sulfate. Musseron and Du (1) report that *o*-methylbenzylmagnesium bromide reacts with ethylene oxide to give 90% of the *para* product and 10% of the *ortho*.

In connection with another problem, we were in need of a quantity of I, and, as this procedure seemed convenient, the preparation of I as described by Musseron and Du was repeated.

The Grignard reagent from *m*-methylbenzyl bromide was prepared according to the usual procedure and also with the use of the "entrainment" procedure of Grignard (6) in which one mole of ethyl bromide is added to a mole of benzyl halide to enhance the formation of the benzyl Grignard reagent. The Grignard reagent was carbonated by bubbling dry carbon dioxide into the ethereal solution, and by pouring the ethereal solution on to Dry Ice. These variations in procedure produced no observable variation in the course of the reaction.

When the reaction mixture was worked up, the products were separated into acidic and neutral fractions. From the acidic fraction a solid acid could be readily



isolated, melting point 113–115° after one crystallization. Further recrystallization, however, raised the melting point to 122–123°. That this acid was not I but was instead 2,4-dimethylbenzoic acid (II) was definitely established by conversion of the acid to the amide. In addition to this acid there was also an oil in the acidic fraction that slowly solidified on standing in a desiccator. This was characterized as *m*-methylphenylacetic acid (III) through the amide. From the neutral fraction *m*-methylbenzyl alcohol (IV) was isolated along with a small quantity of higher-boiling material. This may have been the ditolylethane V, but there was insufficient material for complete characterization.

EXPERIMENTAL[1]

m-Methylbenzyl bromide. The bromination of *m*-xylene was carried out according to the directions of Schramm (7) except that artificial illumination was used. On fractionation of the reaction mixture the following fractions were obtained: (a) recovered *m*-xylene (14%), b.p. 61° (23 mm.); (b) *m*-methylbenzyl bromide, b.p. 74° (4 mm.), $n_D^{27.6°}$ 1.5545, d_{20}^{20} 1.373 (74%); (c) crude solid *m*-xylenyl bromide (11%).

Reaction of m-methylbenzylmagnesium bromide with carbon dioxide. The following is a typical experiment. The *m*-methylbenzyl bromide (50 g.) was dissolved in dry ether (400 ml.) and was slowly dropped with vigorous stirring on to an excess (7.2 g.) of magnesium. The reaction proceeded during the addition of the halide and stopped soon after the last of the halide had been added. The reaction mixture was slowly poured over crushed Dry Ice (*ca.* 100 g.) and then allowed to stand at room temperature overnight. After hydrolysis with dilute hydrochloric acid, the layers were separated, and the aqueous layer was extracted once with ether. The ether solutions were combined and extracted with sodium carbonate solution. The carbonate solution was acidified and extracted with ether. The ether gave 26 g. of crude acid, m.p. 30–85°. Crystallization from dilute ethanol gave white needles, m.p. 113–115°. On further recrystallization material was obtained (6.4 g.) with m.p. 122–123° [reported (8) for 2,4-dimethylbenzoic acid, 125–126°]. A mixed m.p. of this acid with an authentic sample of 2,6-dimethylbenzoic acid (2) was 95–110°. The amide prepared from the acid in the usual manner melted at 182–183° [reported (9) for 2,4-dimethylbenzamide, 179–181°; reported (2) for 2,6-dimethylbenzamide, 138.5–139°]. On evaporation of the mother liquors a yellow oil remained that slowly solidified on standing in a desiccator, m.p. 40–50°. The melting point was not appreciably improved on crystallization. The amide

[1] Melting points are uncorrected.

prepared in the usual manner melted at 142–142.5°, and there was no depression on admixture of an authentic sample (10) of *m*-methylphenylacetamide.

The ethereal solution remaining after removal of the acidic material was dried and the ether evaporated. The residue was distilled and 2.1 g. of a pale yellow oil, b.p. 120–123° (26 mm.) [reported (1) for *m*-methylbenzyl alcohol 215° (740 mm.)] was obtained. Oxidation of this oil with permanganate gave *m*-toluic acid, m.p. 111–112°, undepressed when mixed with an authentic sample. A small quantity of a viscous, red-brown oil remained in the distillation flask. It did not appear to be either an alcohol or ketone. Attempts to oxidize this material did not lead to any recognizable products.

SUMMARY

1. The reaction of *m*-methylbenzylmagnesium bromide with carbon dioxide results in the formation of a mixture of 2,4-dimethylbenzoic acid, *m*-methylphenylacetic acid, and *m*-methylbenzyl alcohol. No 2,6-dimethylbenzoic acid could be isolated from the reaction mixture.

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[CONTRIBUTION FROM THE MEDICAL SCHOOL, DIVISION OF PHARMACOLOGY AND EXPERIMENTAL THERAPEUTICS, AND COLLEGE OF PHARMACY, UNIVERSITY OF CALIFORNIA, AND RADIATION LABORATORY AND DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CALIFORNIA]

THE SYNTHESIS[1] OF CODEINE LABELED IN THE 3-METHOXY GROUP WITH C^{14}

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Of the opium alkaloids closely related to morphine in chemical structure, codeine is probably the most important because it possesses less addiction properties than morphine and is very widely used in clinical work.

In order to investigate the mechanism of analgesic reaction and addiction we have prepared this compound labeled with C^{14} in the 3-methoxyl group. It was felt that for pharmacological experiments labeling the molecule in the methoxyl carbon would be more useful than in the N-methyl group, since biological systems appear able to effect N-methyl exchanges.

A review of the literature (1) reveals that codeine has been prepared from morphine by methylation with a number of reagents such as methyl sulfate, diazomethane, and phenyltrimethylammonium ethoxide. Although some of these methods are practical even for industrial production, they were not readily adapted to the preparation of labeled codeine since the reagents were not available labeled with C^{14} or would result in an insufficient utilization of C^{14}.

The methylation of morphine with methyl iodide (which is available tagged with C^{14}) has been studied independently by Grimaux (2, 3) and by Hesse (4). Both workers reported an extremely small yield of codeine. This is due to the fact that in the morphine molecule there are three reactive groups capable of undergoing the methylation reaction, namely, the phenolic group, the tertiary amino group, and the allylic secondary alcohol group. An active methylation reagent like methyl iodide, when allowed to react with morphine in the presence of alkali, will methylate all three reactive groups, so that the final product may consist of a mixture of codeine, codeine methyl ether, and the methiodides of these alkaloids.

Since the reactive group in the morphine molecule that interferes most with the preparation of codeine is the tertiary amino group rather than the allylic secondary alcoholic group, it was believed that by decreasing the basicity of the tertiary amino group through oxide formation, that is, by using morphine-N-oxide instead of morphine for the methylation, the entering methyl group could be made to go almost exclusively to the phenolic group. The methylation of morphine-N-oxide with methyl sulfate and alkali and the reduction of the resulting codeine-N-oxide to codeine have been patented (5), although the use of methyl iodide in this protective methylation reaction does not seem to have been studied.

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In order to obtain the maximum yield based on methyl iodide, we desired to use pure morphine-N-oxide as the starting material. The direct oxidation of morphine with 30% hydrogen peroxide to the N-oxide by the method described in the literature (6, 7) was studied, and although the crude morphine-N-oxide could be obtained in good yield, the loss of material on recrystallization as the nitrate was excessive.

Therefore, the protective oxidation of Mannich (8) was adopted. Morphine was first converted to the mono-sodium derivative and then allowed to react with chloromethyl ether. The syrupy methoxymethyl ether of morphine thus obtained was oxidized with 30% hydrogen peroxide and the product, the methoxymethyl ether of morphine-N-oxide, was isolated as the crystalline acetone derivative, from which pure morphine-N-oxide was obtained after hydrolysis with dilute sulfuric acid and subsequent alkalinization with ammonia (9).

With this pure morphine-N-oxide as the starting material, methylation was carried out successfully with methyl-C^{14} iodide (10). The codeine-N-oxide thus obtained was immediately reduced by sulfur dioxide to codeine. After purification, the free base was converted to both codeine-C^{14} sulfate and codeine-C^{14} hydrochloride. These salts possess properties identical with the U.S.P. products described in the literature (11).

EXPERIMENTAL

Preparation of the methoxymethyl ether of morphine. The methoxymethyl ether of morphine was prepared by the method of Mannich (8) in a 63% yield of crude material.

Oxidation of the methoxymethyl ether of morphine. Crude methoxymethyl morphine was oxidized with hydrogen peroxide as described by Small (9). The yield of crystalline methoxymethyl morphine-N-oxide acetone compound, m.p. 98°, was 46% based on morphine.

Conversion of the methoxymethyl ether of morphine-N-oxide acetone compound to morphine-N-oxide. Methoxymethyl morphine-N-oxide acetone compound (37 g.) was stirred with 18.5 ml. of cold 25% sulfuric acid and the solution was allowed to stand at room temperature for 2½ hours. Then, 75 ml. of water was added and the acid solution was neutralized with concentrated ammonium hydroxide. White crystals formed readily. The mixture was allowed to stand in an ice-bath for one-half hour and the crystals were filtered off, washed with a little cold water and then with cold acetone, and dried in a desiccator. The yield was 25.3 g. (42.0% based on morphine) m.p. 271°.

Preparation of codeine (1). In a dry box 6.0 g. (20 moles) of pure morphine-N-oxide was dissolved in chilled sodium methoxide prepared from 0.46 g. (20 moles) of metallic sodium and 20 ml. of absolute methyl alcohol. The flask containing the brownish-orange solution was connected to a vacuum (12) manifold through the condenser and a stopcock and the solution was frozen with liquid nitrogen. Then, 2.22 g. (15.6 moles) of methyl iodide containing 5.1 mc. of C^{14} was distilled *in vacuo* into the reaction flask. The flask containing the frozen mixture was moved to a hood and the mixture refluxed on the steam-bath for four hours. After cooling, 5 ml. of water was added and sulfur dioxide was passed into the solution for one hour to reduce the codeine-N-oxide. To the flask containing the codeine, 30 ml. of water was added and the methyl alcohol was vacuum-distilled. Then, 10 ml. of 6 *N* sodium hydroxide was added to dissolve the morphine and the codeine was extracted with two 25-ml. and four 10-ml. protions of chloroform. The chloroform solution was washed with two 10-ml. aliquots of distilled water, dried with potassium carbonate, filtered, and evaporated to dryness.

Purification of codeine. The impure codeine was dissolved in the minimum amount of

benzene and petroleum ether (b.p. 30–60°) was added until no further increase in the yellowish-orange turbidity was observed; then the turbidity was removed by filtration. Excess petroleum ether was added to the filtrate to precipitate the codeine. The yellowish-orange turbidity was treated with benzene and petroleum ether once more. The turbidity appeared to be an impurity and was discarded. The benzene-petroleum ether solution was allowed to stand in an ice-box for complete precipitation. The precipitate was filtered off and the filtrate reworked for a second crop; m.p. of the codeine, 155°.

The codeine was dissolved in the minimum amount of absolute ethyl alcohol and hydrogen chloride gas was passed into the solution to convert the free base to the hydrochloride salt. The alcoholic solution of codeine hydrochloride was evaporated to dryness on a steam-bath and the residue was dissolved in the minimum amount of 95% ethyl alcohol and filtered. The filtrate was allowed to stand in an ice-box for one hour. The crystalline needles of codeine hydrochloride were collected by filtration, washed with cold absolute ethyl alcohol, and dried. The various fractions were thus purified. The combined yield was 3.65 g., which represents a 62.8% yield based on methyl iodide or 49.1% based on radioactive barium carbonate used to begin the synthesis. The specific activity of this material was 0.91 ± 0.02 μc/mg. while the calculated value was 0.88 ± 0.02 μc/mg.

Anal. Calc'd for $C_{18}H_{22}ClNO_3$: C, 64.37; H, 6.60; OCH_3, 9.23.
Found: C, 64.33; H, 6.55; OCH_3, 9.02.

As an additional check, two-dimensional paper chromatograms (13) were made of this product and radioautographs made of the paper. Only one radioactive spot was found, thus indicating the radiopurity of the product.

Acknowledgments. The authors wish to thank Professors Melvin Calvin and Hamilton H. Anderson for their help and encouragement and Mr. Robert Selff for his technical assistance.

SUMMARY

Codeine labeled in the 3-methoxy position with C^{14} has been prepared on a 20-mole scale in a yield of 63% based on methyl-C^{14} iodide.

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[CONTRIBUTION FROM THE CHEMICAL CORPS TECHNICAL COMMAND]

REACTIONS OF DIALKYL PHOSPHITES. SYNTHESIS OF DIALKYL CHLOROPHOSPHATES, TETRAALKYL PYROPHOSPHATES, AND MIXED ORTHOPHOSPHATE ESTERS[1]

GEORGE M. STEINBERG

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Consistent with the interest of the author in the reactions of organic phosphites, it was his purpose to determine the course of the new and interesting reaction discovered by Atherton, Openshaw, and Todd (1) that takes place with considerable vigor when a dialkyl or diaryl phosphite, carbon tetrachloride, and ammonia or a primary or secondary amine are mixed.

1. $$\underset{\underset{\text{I}}{(RO)_2POCl}}{(RO)_2POH} + CCl_4 + 2\,NH_3 \rightarrow \underset{\underset{\text{II}}{(RO)_2POCCl_3}}{(RO)_2PONH_2} + HCCl_3 + NH_4Cl$$

In their paper, they suggested that the reaction probably goes through an intermediate stage involving the formation of either the corresponding dialkyl chlorophosphate (I) or dialkyl trichloromethylphosphonate (II).

It was found in this laboratory that the reaction between diethyl chlorophosphate and ammonia takes place at once with the evolution of much heat and the immediate formation of a copious white precipitate. The vigor of this reaction was of the same magnitude as that observed in the phosphite reaction. On the other hand, with diethyl trichloromethylphosphonate, prepared by the method described by Kosolapoff (2), ammonia gave no apparent reaction even after ten minutes. However, it has been reported (3) that reaction between dialkyl trichloromethyl phosphonates and amines can be made to take place with the resultant formation of dialkyl alkylamino phosphonates.

By replacing the ammonia with a tertiary base it was found possible to isolate the dialkyl chlorophosphate in yields of as high as 85%. The main reaction is accompanied by a side reaction which yields a high-boiling product and the base hydrochloride. These products are probably the result of reaction between the dialkyl phosphite and the dialkyl chlorophosphate in the presence of the base.

2. $$(RO)_2POH + CCl_4 \xrightarrow{R'_3N} (RO)_2POCl + HCCl_3$$

3. $$(RO)_2POH + (RO)_2POCl + R'_3N \rightarrow (RO)_2POP(OR)_2(?) + R'_3N\cdot HCl$$

When diethyl phosphite and diethyl chlorophosphate were reacted in the presence of triethylamine, there were formed triethylamine hydrochloride and a high-boiling liquid, which on the basis of chemical analysis and physical properties appeared to be a mixture of the expected tetraethyl hypophosphate (17%) and

[1] Presented at the Atlantic City meeting of the American Chemical Society, September 1949.

tetraethyl pyrophosphate (83%). Nylen (4) obtained a similar mixture of products from the reaction of sodium diethyl phosphite and diethyl chlorophosphate. The mechanism of this reaction is obscure and warrants further study.

Dialkyl chlorophosphates have been prepared in a variety of ways (5), some of which include the reaction of trialkyl phosphates with phosphorus oxychloride, the reaction of two moles of an alcohol with one mole of phosphorus oxychloride, and the more practical chlorination of trialkyl and dialkyl phosphites (5, 6). In addition, several dialkyl phosphites have been converted successfully to dialkyl chorophosphates by treatment with sulfuryl chloride (7).

Because of the decreased stability of these compounds under acidic conditions, it had been necessary to free them of acidic reactants or products before distillation.

In this work the chlorophosphates were prepared under alkaline conditions, so that, except with especially unstable compounds, no precautions were necessary. It was found most convenient to run the reaction without an additional solvent, merely mixing the phosphite with an excess of carbon tetrachloride and 10–15 mole-percent of tertiary base. The reaction mixture was cooled at first, but after the initial vigorous phase had passed, it was stirred at room temperature until the reaction was completed.

The optimum quantity of base was found to be *ca.* 10–15 mole-percent. With less, the reaction was slowed; with more, there was obtained a colored, amine-odored product. In the latter case, distillation over potassium dihydrogen phosphate yielded a pure colorless product. The reaction could be speeded by raising the temperature, but this resulted in a reduction in yield.

It was found unnecessary to purify the phosphite before reaction. In fact, it is present practice to treat the crude phosphite directly with carbon tetrachloride and base, adding a sufficient excess of the latter to neutralize any hydrogen chloride present.

Dimethyl and diallyl chlorophosphates were found to be extremely sensitive to heat, so that modifications of the standard procedure had to be employed in the synthesis of each. Despite all precautions, considerable decomposition occurred during distillation, and there was left in each case a viscous polymer-like residue. In the case of the diallyl chlorophosphate the residue was analyzed and found to contain only 0.93% chlorine. Similar residues were found when the more stable chlorophosphates were redistilled after standing for several months. It seems reasonable to suppose that the residues are long chain compounds formed by the splitting out of RX between molecules.

4. $$\begin{array}{c} \mathrm{O} \\ \uparrow \\ \mathrm{ROPX} \\ \mathrm{O} \\ \mathrm{R} \end{array} + \begin{array}{c} \mathrm{O} \\ \uparrow \\ \mathrm{ROPX} \\ \mathrm{O} \\ \mathrm{R} \end{array} \rightarrow \begin{array}{cc} \mathrm{O} & \mathrm{O} \\ \uparrow & \uparrow \\ \mathrm{ROP{-}O{-}P{-}X} & \\ \mathrm{O} & \mathrm{O} \\ \mathrm{R} & \mathrm{R} \end{array} + \mathrm{RX}, \text{ etc.}$$

On the basis of this hypothesis it is calculated that the diallyl chlorophosphate residue contained polymeric molecules having an average molecular weight of 3800 and containing an average of 36 repeating units per molecule.

Several attempts to prepare pure diethyl bromophosphate by an analogous reaction using carbon tetrabromide, bromoform or bromotrichloromethane in place of carbon tetrachloride were unsuccessful. In each case there was evidence of the formation of the desired product, for on distillation there was obtained the familiar sweet-smelling oil, and a viscous yellow-orange residue (polymer?). However, analysis indicated that halogen-containing impurities were always present. Apparently the by-products of the reaction were too high-boiling to be removed from this highly thermosensitive compound by the methods employed in this work.

In a recent paper, Toy (8) reviewed the methods that had previously been used for the preparation of tetraalkyl pyrophosphates and reported a new and far superior process for their preparation. He found that by the controlled hydrolysis of a dialkyl chlorophosphate in the presence of a base, he could prepare pure "pyro" compounds in high yield. Atherton and Todd (1b) prepared tetrabenzyl pyrophosphate by reaction of dibenzyl phosphite and carbon tetrachloride in the presence of an aqueous solution of potassium hydroxide.

Since the dialkyl chlorophosphates are here prepared under alkaline conditions, it seemed probable that if there was added to the "usual" mixture of dialkyl phosphite, carbon tetrachloride, and base, the correct quantity of water and sufficient base to neutralize the acid formed, the corresponding tetraalkyl pyrophosphate should be produced. This was indeed found to be the case.

A slight excess of water caused no difficulty under the conditions employed. When the organic base was replaced completely by sodium bicarbonate the reaction failed to take place. On partial replacement, there was obtained a product of somewhat lower purity.

Mixed orthophosphate esters have been prepared by several methods. Weger (9) reacted silver diethyl phosphate with methyl iodide to yield diethylmethyl phosphate. Dibutylethyl phosphate was prepared by Gerrard (10) by the reaction of dibutyl chlorophosphate with ethanol in the presence of pyridine. It was shown by Rueggeberg and Chernack (11) that when triethyl phosphate was warmed with sodium butoxide there was formed a mixture of dibutylethyl phosphate and butyldiethyl phosphate. Atherton and Todd (1b) found that dibenzyl phosphite could be reacted with ethanol at room temperature in the presence of bromotrichloromethane and a tertiary base to yield dibenzylethyl phosphate, but reported that the reaction did not take place in the presence of carbon tetrachloride.

In the light of previous experience, it seemed probable that the chlorophosphate formed would react with an alcohol to yield the mixed phosphoric acid esters. By running the reaction at an elevated temperature there was prepared, in good yield, butyldiethyl phosphate. Due to the greater reactivity induced by the allyl groups, diallylethyl phosphate could be prepared by reaction at room temperature. This compound could be polymerized by heating with benzoyl peroxide.

Reaction mechanism. A kinetic study was undertaken on the reaction between diethyl phosphite and carbon tetrachloride in the presence of triethylamine, equations 2 and 3, in order to ascertain the effect of varying the initial concen-

trations of the various reactants on the over-all rate of reaction, so that a reasonable mechanism might be proposed. In view of the complex nature of the reaction, an accuracy of $\pm 5\%$ was considered adequate.

It was planned to follow the course of the reaction by determinations of chloride in the solid (triethylamine hydrochloride) and of total hydrolyzable chlorine in the reaction mixture (triethylamine hydrochloride + diethyl chlorophosphate). This would give, by difference, the concentration of diethyl chlorophosphate in the liquid phase. In order to precipitate the triethylamine hydrochloride completely, ligroin was selected as the reaction solvent.

The effect of varying the concentrations of each of the reactants on the rate of formation of total hydrolyzable chlorine is shown in Fig. 1. In Fig. 2, there is

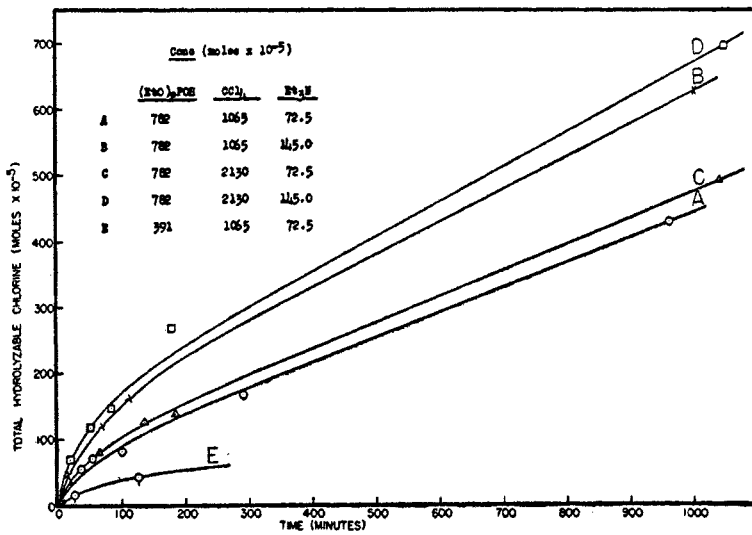

FIG. 1. RATE OF FORMATION OF TOTAL HYDROLYZABLE CHLORINE [$(EtO)_2POCl + Et_3N \cdot HCl$]

plotted the rate of formation of triethylamine hydrochloride. The erratic nature of the results shown in Fig. 2 led to an investigation of possible faults in the analytical procedure. None could be found. The variations might be explained by a variable induction period for the side reaction, by a complex mechanism for the formation of triethylamine hydrochloride involving both formation and simultaneous reaction of that compound, or by the presence of variable quantities of an unknown catalyst from outside the system. The first supposition seems least reasonable for in each of 5 identical runs, it was determined that the white precipitate formed during the time interval between $3\frac{1}{4}$ and $4\frac{3}{4}$ minutes after the start of the reaction, hence, if it were only a matter of induction period, the percentage error would fall off quickly with time, so that after 100 or 200 minutes the curve would be uniform.

An investigation of the literature led to the discovery of a reported reaction between bromoform or carbon tetrabromide, and amines, in the presence of air

which yields aldehydes and base hydrobromide (12). Chloroform and carbon tetrachloride were reported to be unreactive. It was found in these laboratories that when carbon tetrachloride and triethylamine were mixed there was always obtained a small precipitate of triethylamine hydrochloride. The results of a light-absorption study, Fig. 3, indicate that association or reaction between triethyl-

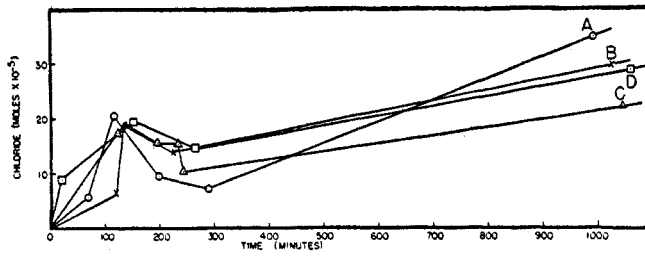

FIG. 2. RATE OF FORMATION OF CHLORIDE ($Et_3N \cdot HCl$)

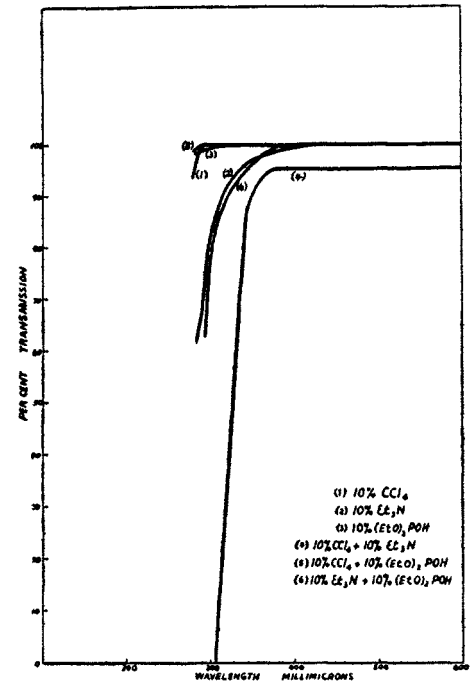

FIG. 3. LIGHT ABSORPTION OF REACTANTS

amine and carbon tetrachloride does occur. However, under the conditions of the kinetic study, in the absence of phosphite, no measurable amounts of triethylamine hydrochloride were formed in four hours. The possibility that triethylamine hydrochloride might act as a catalyst and so might affect the course of reaction when present in only trace amounts was shown to be invalid, for if the free base was replaced by the hydrochloride, the reaction did not take place.

Variation of the concentration of the chlorophosphate with time could not be accurately calculated, and as was to be expected on the basis of simultaneous reactions, the over-all rate of reaction based on total hydrolyzable chlorine did not follow a constant order of reaction. It can be observed from Fig. 1 that the rate of formation of total hydrolyzable chlorine is affected differently by equivalent changes in the initial concentrations of each of the reactants. In each case, the rate of reaction appears to vary considerably with reactant concentration during its early stages, and to fall off to zero order later on. For the early part of the reaction, doubling the concentration of diethyl phosphite increased the rate of formation of the total hydrolyzable chlorine by a factor of 2.3, whereas doubling the concentration of triethylamine increased it only by 1.6 and of carbon tetrachloride by 1.15. Although the rate of the side reaction could not be determined, it will be seen by comparison of Figs. 1 and 2 that its magnitude is comparatively small. Hence, for the purpose of analysis it will be ignored.

The evidence obtained favors an ionic mechanism. In the absence of base, the reaction failed to occur. Catalysts for free radical reactions such as ultraviolet light and benzoyl peroxide were ineffective. The rate of reaction appears to be strongly dependent on the strength of the base. Triethylamine was only slightly more effective as a catalyst than tributylamine or triamylamine, but was more than 1000 times more effective than pyridine.

Since a zero order reaction in the liquid phase is so strongly indicative of a free radical mechanism, the possibility of a series of reactions involving the formation of an ion or unionized complex between phosphite and base followed by breakdown to free radicals was considered. But this mechanism was found to be highly improbable for in the presence of triethylamine, neither ultraviolet light nor benzoyl peroxide increased the rate of reaction. In fact, in the latter case, the reaction was slowed down, probably because of partial neutralization of the base.

Two possible mechanisms are proposed:

5. $$(RO)_2POH + B \underset{K_2}{\overset{K_1}{\rightleftharpoons}} [(RO)PO]^- + B\cdot H^+; \quad \frac{K_2}{K_1} = K_A \qquad (a)$$

$$CCl_4 + B \underset{K_4}{\overset{K_3}{\rightleftharpoons}} CCl_3^- + B\cdot Cl^+; \quad \frac{K_4}{K_3} = K_B \qquad (b)$$

$$B\cdot Cl^+ + [(RO)_2PO]^- \xrightarrow{K_5} (RO)_2POCl + B \qquad (c)$$

$$B\cdot H^+ + CCl_3^- \underset{K_7}{\overset{K_6}{\rightleftharpoons}} HCCl_3 + B; \quad \frac{K_6}{K_7} = K_D \qquad (d)$$

Side reaction: $(RO)_2POH + (RO)_2POCl + B \rightarrow$

$$(RO)_2P{-}O{-}\overset{\overset{O}{\uparrow}}{P}(OR)_2(?) + B\cdot HCl$$

6.
$$(RO)_2POH + B \rightleftharpoons [(RO)_2PO]^- + B\cdot H^+$$
$$[(RO)_2PO]^- + CCl_4 \rightleftharpoons (RO)_2POCl + CCl_3^-$$
$$CCl_3^- + (RO)_2POH \rightleftharpoons [(RO)_2PO]^- + HCCl_3$$
$$B\cdot H^+ + CCl_3^- \rightleftharpoons HCCl_3 + B$$

Side reaction: $(RO)_2POH + (RO)_2POCl + B \rightarrow$

$$(RO)_2P{-}O{-}\overset{\overset{O}{\uparrow}}{P}(OR)_2(?) + B\cdot HCl$$

On the basis of the available information the mechanism of this reaction cannot be stated. However, it is interesting that if several reasonably plausible assumptions are applied to the first of the proposed mechanisms, the relationship between rate of reaction and initial concentration of reactants that was found for the early part of the reaction can be explained.

If one simply assumes that step (a) is the "slow" or rate-determining step and that the equilibrium constants K_A, K_B, and K_D are equal, then doubling the concentration of diethyl phosphite should increase the rate of reaction by a factor of nearly 2, triethylamine by 1.4, and carbon tetrachloride by 1.2.

Thus, the availability of $[(EtO)_2PO]^-$ for reaction in (c) will be a function of the relative concentrations of diethyl phosphite, triethylamine, and the triethylammonium ion. If the concentration of diethyl phosphite were doubled, the rate of formation of $[(EtO)_2PO)]^-$, and hence, the over-all rate of reaction should be nearly doubled; the concentration of triethylammonium ion being kept almost constant by (d) and (b). If the concentration of carbon tetrachloride were doubled, the concentration of CCl_3^- would be increased by (b) and in turn, $Et_3N\cdot H^+$ would be decreased by (d) to about 50% of its former value. This in turn, should increase the availability of $[(EtO)_2PO]^-$ and hence the rate of reaction by a factor of 1.2. If the concentration of triethylamine were doubled, the concentration of $Et_3N\cdot H^+$ would be increased by a factor of 1.4 by (d) and (b) and hence by (a) the availability of $[(EtO)_2PO]^-$ should be increased by a factor of 1.4.

However, if the more reasonable assumption is made that $K_A > K_D > K_B$, and there is added the assumption that either reaction (b) or (c) is sufficiently slow to contribute 10–15% of its weight to the rate of the reaction, so that changes in the concentration of $Et_3N\cdot Cl^+$ become important, the rate of reaction should be affected by the more closely agreeing factors of 2.1–2.3 for diethyl phosphite, 1.4–1.6 for triethylamine, and 1.1–1.2 for carbon tetrachloride.

EXPERIMENTAL

Dialkyl chlorophosphates. With the exception of the two specific cases listed below, the preparation of diethyl chlorophosphate may be considered typical and will serve to illustrate the procedure used for the preparation of the more stable chlorophosphates, which are listed in Table I. In the case of the diallyl and the dimethyl chlorophosphates, it is felt that the

yields could be considerably improved with a more thorough study of the individual reactions.

Diethyl chlorophosphate. To a cooled (0°), stirred mixture of 27.6 g. (0.20 mole) of diethyl phosphite and 35 ml. (0.4 mole) of carbon tetrachloride, there was slowly added 3.2 ml. (0.023 mole) of triethylamine. The temperature was maintained at 0° for 15 minutes, then allowed to rise to room temperature and stirred for 3 hours. The reaction mixture was filtered, stripped completely of low-boiling components at room temperature (pressure *ca.* 20 mm.) and vacuum-distilled. Yield, 28 g. of a colorless, sweet-smelling oil.

It was found unnecessary to use a rectifying column for purification. In fact, the highest yields were obtained when distillation was done rapidly and at low temperature.

In one run, the by-products of reaction were examined. A distillation curve of the low-boiling fraction indicated the presence of considerable quantities of chloroform. The white precipitate was recrystallized from methyl ethyl ketone, m.p. 246–251° (uncorr.). Reported for *triethylamine hydrochloride*, 253–254°.

TABLE I

DIALKYL CHLOROPHOSPHATES

ALKYL GROUP	REACTION TEMP.	TIME, HRS.	YIELD, %	B.P., °C. (MM.)	n_D^{20}	ANALYSIS Cl	
						Calc'd	Found
Ethyl.....	Room temp.	3	81	64 (6–7)	1.4167	20.58	20.39, 20.42
Ethyl.....	Reflux[a]	¼	70	64 (6–7)	1.4169	—	—
n-Propyl.....	Room temp.	6	80	65 (3–4)	1.4246	17.72	17.59, 17.61
n-Butyl.....	Room temp.	6	55[b]	110–3 (6)	1.4308	15.54	15.61, 15.73

[a] Triethylamine added dropwise to refluxing mixture.

[b] Decomposed in part due to high temperature of distillation.

Anal. Calc'd for $C_6H_{16}ClN$: N, 10.18; Cl, 25.8.
Found: N, 10.06, 9.72; Cl, 25.38, 25.21.

When an attempt was made to distill the dark high-boiling residue, there was obtained a small quantity, less than one gram, of a colorless oil distilling at 97–104°/0.01–0.04 mm. Some decomposition had probably occurred during this process. Yet, it is interesting that the analysis indicated the presence of a compound or compounds having a high percentage of phosphorus.

Anal. Calc'd for tetraethyl hypophosphate, $C_8H_{20}O_6P_2$: C, 35.05; H, 7.3; P, 22.6.
Found: C, 34.3; H, 7.3; P, 19.9, 20.0.

Diallyl chlorophosphate. To a cooled (0°), stirred mixture of 32.4 g. (0.20 mole) of diallyl phosphite and 35 ml. (0.4 mole) of carbon tetrachloride, there was slowly added 3.2 ml. (0.023 mole) of triethylamine. A very vigorous reaction ensued. The temperature was maintained at 0° for one hour and then slowly allowed to rise to room temperature. The mixture was stirred overnight. The solid was filtered off, 0.5 g. of hydroquinone was added to the filtrate and the low-boiling substances were carefully stripped off under a vacuum (10 mm.) at room temperature. The residue was vacuum-distilled on a high vacuum system, the pressure in which can ordinarily be reduced to 0.001 mm. As soon as distillation began, the pressure rose quickly and the McLeod gauge went "off scale". The sample distilled at 65°; pot 85°. By comparison with the data for di-*n*-propyl chlorophosphate, it is estimated that the pressure rose to 3–4 mm. There was obtained 8.5 g. of a sweet-smelling oil, n_D^{20} 1.4504; yield 22%.

Anal. Calc'd for $C_6H_{10}ClO_3P$: Cl, 18.05. Found: Cl, 18.03, 18.09.

A large quantity of "chlorine-free" brownish-yellow material remained as residue.

Dimethyl chlorophosphate. To a cooled (0°) stirred mixture of 22.0 g. (0.20 mole) of di-

methyl phosphite in 35 ml. (0.4 mole) of carbon tetrachloride, there was slowly added 2.8 ml. (0.020 mole) of triethylamine. The reaction mixture was stirred for one hour at 0° and then for one-half hour at room temperature. The solid was filtered off, the filtrate vacuum-stripped at room temperature (40 min.) and distilled under a vacuum. There was obtained 9 g. of sweet-smelling liquid, b.p. 70°/10 mm.; yield 28%, and a large residue of a viscous light colored oil. A determination of hydrolyzable chlorine indicated that the purity of the sample obtained was only 93%. By analogy with the results of earlier runs with similar products, it was assumed that the impurity was a low-boiling compound that had not been completely removed during the stripping operation.

TETRAALKYL PYROPHOSPHATES

Tetraethyl pyrophosphate. (a) *Reaction in presence of triethylamine.* To a stirred mixture of 27.6 g. (0.20 mole) of diethyl phosphite and 35.6 ml. (0.40 mole) of carbon tetrachloride cooled to 5°, there was added 3.25 ml. (0.18 mole) of water and then dropwise 55.6 ml. (0.40 mole) of triethylamine. The temperature was allowed to rise slowly to 25° (½ hr.), and the mixture was maintained at that temperature for 3½ hours. The slurry was filtered and the filtrate vacuum-stripped and distilled. Yield, 21 g. (73%) of tetraethyl pyrophosphate, n_D^{25} 1.4180, b.p. 105–109°/0.03 mm.

Anal. Calc'd for $(EtO)_4P_2O_3$: Ethoxyl, 62.11. Found: Ethoxyl, 61.92, 61.94.

Determination of P^{III} (0.09%) indicated the presence of less than 1% of tetraethyl hypophosphate or similar impurity. When the order of addition of water and base was reversed, there resulted a less pure product.

(b) *Reaction in presence of triethylamine and sodium bicarbonate.* To a stirred mixture of 27.6 g. (0.20 mole) of diethyl phosphite, 35.6 ml. (0.40 mole) of carbon tetrachloride, ½ ml. of water, and 25.2 g. (0.30 mole) of sodium bicarbonate, there was added 3.2 ml. (0.023 mole) of triethylamine, keeping the temperature at 20–25.° The reaction mixture was stirred for 4 hours, filtered, and the filtrate vacuum-stripped and distilled. There was obtained 3 g. of recovered phosphite and 15 g. of tetraethyl pyrophosphate; yield 52%, conversion, 58% n_D^{25} 1.4176.

The values for the index of refraction of tetraethyl pyrophosphate reported by Toy (8) varied between n_D^{25} 1.4182 and 1.4172. Since his value for diethylphosphoric acid, the most probable impurity, is n_D^{25} 1.4146–1.4152, it is assumed that the purer product has the higher index of refraction.

Tetraisopropyl pyrophosphate. This compound was prepared by the procedure described for tetraethyl pyrophosphate, method (a). Before stripping, however, it was found necessary to wash the mixture quickly with a cold dilute solution of sodium bicarbonate in order to prevent the distillation of solid impurities (probably $Et_3N \cdot HCl$) along with the reaction product. There was obtained 26.5 g. of tetraisopropyl pyrophosphate, b.p. 94–99°/0.01–0.02, n_D^{25} 1.4165, yield 73.3%.

Anal. Calc'd for $(C_3H_7O)_4P_2O_3$: Isopropoxyl, 68.25; P, 17.89.
Found: Isopropoxyl, 67.97, 68.00; P, 17.82.

MIXED ORTHOPHOSPHATE ESTERS

n-Butyldiethyl phosphate. To a mixture of 27.6 g. (0.20 mole) of diethyl phosphite, 35.6 ml. (0.40 mole) of carbon tetrachloride, and 16.3 g. (0.21 mole) of *n*-butanol, there was added 31.6 ml. (0.22 mole) of triethylamine. The reaction mixture was stirred and refluxed for 3 hours, then filtered, and the filtrate vacuum-stripped (25°/5) and distilled over potassium dihydrogen phosphate. There was obtained 22 g. of *n*-butyldiethyl phosphate, n_D^{25} 1.4085, b.p. 100–101°/2–3, yield, 52%.

Anal. Calc'd for $C_8H_{19}O_4P$: P, 14.74. Found: P, 14.70, 14.73.

Diallylethyl phosphate. To a stirred mixture of 32.4 g. (0.20 mole) of diallyl phosphite, 20 ml. (0.22 mole) of carbon tetrachloride, and 12 ml. (0.21 mole) of ethanol cooled to 0°, there was added dropwise 41.7 ml. (0.3 mole) of triethylamine. The mixture was kept at 0°

for 30 minutes and then stirred overnight at room temperature. The reaction mixture was filtered, the filtrate vacuum-stripped, and distilled over hydroquinone and potassium dihydrogen phosphate. There was obtained 14 g. of diallylethyl phosphate, b.p. 72°/1-2, n_D^{25} 1.4350, yield, 34%. A considerable quantity of a tan-colored viscous residue remained.

Anal. Calc'd for $C_8H_{15}O_4P$: Bromine no., 154.8; P, 15.02.

Found: Bromine no., 152.7, 152.7; P, 14.84, 14.86.

Reaction between diethyl phosphite and diethyl chlorophosphate. To a stirred mixture of 50 ml. of benzene, 34.5 g. (0.20 mole), of diethyl chlorophosphate, and 27.6 g. (0.20 mole) of diethyl phosphite, there was added 29 ml. (0.22 mole) of triethylamine. A considerable volume of white fumes was produced. The reaction mixture was stirred and refluxed for two hours. The white precipitate was filtered, the filtrate vacuum-stripped, and the residue distilled under a high vacuum. There was obtained a considerable quantity of a colorless liquid that distilled from 91–100°/0.06 (pot temperature 134–144°). On the same system, pure tetraethyl pyrophosphate distilled at a slightly higher temperature; 105–109°/0.03 (pot temperature 120–125°).

ANALYSIS

	CALC'D FOR TETRAETHYL PYROPHOSPHATE	CALC'D FOR TETRAETHYL HYPOPHOSPHATE	FOUND
EtO	62.11	65.69	62.72
Total P	21.41	22.62	21.15
P^{III}	0.00	11.32	1.94

Based on the assumption that the most discriminatory determination was that for P^{III}, and that the product was a mixture of tetraethyl hypophosphate and tetraethyl pyrophosphate, it was calulated that there was present 17% of the former product.

KINETIC STUDY

Reagents. The reagents were freshly distilled, a middle fraction of each being used for the study. These include: diethyl phosphite, b.p. 66–67°/6 prepared according to method (a) of McCombie, Saunders, and Stacey (5); triethylamine Eastman, C.P.; ligroin, Eastman Pract., 90–120°; carbon tetrachloride, Eimer and Amend C.P.

Apparatus. A large-scale run proved difficult to handle, for the solid settled and true aliquots could not be taken. The study was therefore made on individual 10-ml. runs that were maintained at 75 ± 1° F. in a thermostatically-controlled room. Each reaction was run in an Erlenmeyer flask of 20 ml. capacity fitted with a ground-glass-joint drying tube. The reaction mixture was stirred by a magnetic stirrer, and in order to keep the system from being heated by the stirrer motor, insulation or an air gap was provided. Stock solutions were prepared by diluting 100 ml. each of diethyl phosphite and carbon tetrachloride and 25 ml. of triethylamine to 250 ml. with ligroin. The three stock solutions and the solvent were dispensed from 5-ml. microburettes reading to 0.01 ml. The order of addition was ligroin, diethyl phosphite, carbon tetrachloride, and triethylamine; the time of reaction being calculated from the time at which the amine was added.

Analysis. To determine the quantity of solid formed, the samples were filtered on a Gooch crucible, washed with ligroin, then dissolved in water, and titrated for chloride by the Volhard method. Total hydrolyzable chlorine was determined by shaking the reaction mixture for 10 min. with 100 ml. of 2% aqueous sodium hydroxide, acidifying, and proceeding as above. Concentrated alkali was found to attack the carbon tetrachloride.

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SUMMARY

1. Dialkyl chlorophosphates were prepared by the reaction of the corresponding dialkyl phosphites and carbon tetrachloride in the presence of a tertiary base. These include: the dimethyl, diethyl, di-*n*-propyl, di-*n*-butyl, and diallyl chlorophosphates.

2. The mechanism of this reaction was studied.

3. Tetraalkyl pyrophosphates were prepared by the reaction of a dialkyl phosphite, carbon tetrachloride, water, and a tertiary base. These include the ethyl and isopropyl pyrophosphates.

4. Mixed orthophosphate esters were prepared by the reaction of a dialkyl phosphite, carbon tetrachloride, an alcohol, and a tertiary base. These include the butyldiethyl and the diallylethyl phosphate. The latter compound can be polymerized.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, QUEEN'S UNIVERSITY]

SYNTHESES OF SUBSTITUTED β,β'-DICHLORODIETHYLAMINES

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The nitrogen mustards, as chemotherapeutic agents for cancer, have attracted considerable attention, since their action on living cells closely resembles that of x-rays (1). It has been emphasized by Gilman and Philips (1) that the effects of the nitrogen mustards rival those of short-wave radiation, and that no other class of chemical agents has been found to exhibit the same specificity of action on chromosomal structures.

At the present time only *bis*-(β-chloroethyl)methylamine and *tris*-(β-chloroethyl)amine have been subjected to extensive clinical examination. Both these compounds, administered as the hydrochlorides, have given promising results in the treatment of several neoplastic diseases including Hodgkin's disease and lymphatic leukemia (2). Furthermore, they have been shown to be of value in inducing temporary symptomatic remissions in Hodgkin's disease where x-ray treatment no longer seemed feasible or effective (3). One disadvantage in the use of nitrogen mustards is that they have a general cytotoxic effect. All rapidly proliferating tissue is especially subject to this action. Thus one of the undesirable side reactions of these compounds is their cytotoxic effect on normal hematopoietic tissue (3).

Of particular interest in the selection of specific nitrogen mustards to be synthesized for future testing are those having groups already known to possess special biological properties. The resulting substituted nitrogen mustards might be expected to retain in part some of the biological properties associated with these groups, or perhaps by virtue of these structures to exert a more selective toxic action. It was with these considerations in view that the present work was undertaken.

It was decided to prepare substituted nitrogen mustards containing the phenanthrene nucleus and the diphenylethane structure. This decision was based on the findings of Turner (4) who tested 75 phenanthrene derivatives on transplanted sarcomas in mice. He found tumor regression rates ranging from none to 50%. Phenanthrene itself, when applied to the skin of mice in conjunction with either of the carcinogens 3,4-benzopyrene or 1,2,5,6-dibenzanthracene, reduced the rate of tumor induction (5). On the other hand some mitotic poisons, *e.g.*, α,β-di-(*p*-methoxyphenyl)ethylamine, which warrant the attention of those seeking a chemotherapeutic agent to combat a disease characterized by uncontrolled cell division, possess the diphenylethane structure. The specific compounds prepared were the hydrochlorides of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene, N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine, and N,N-*bis*-(β-chloroethyl)-β,γ-di-*p*-anisyl-*n*-propylamine.

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In order to compare the two methods available for the preparation of *bis*-(β-hydroxyethyl)amines, *n*-butylamine was treated with ethylene oxide, and *n*-butyl bromide was treated with diethanolamine. Although the yields (85%) of *bis*-(β-hydroxyethyl)-*n*-butylamine by these two methods were the same, the more convenient ethylene oxide method was adopted for subsequent preparations. *Bis*-(β-hydroxyethyl)-*n*-butylamine hydrochloride was chlorinated with thionyl chloride giving a 53% yield of *bis*-(β-chloroethyl)-*n*-butylamine hydrochloride.

9-Bromophenanthrene (6, 7), was converted to 9-cyanophenanthrene (8) in 70% yield as described by Mosettig and van de Kamp (9). Hydrolysis of 9-cyanophenanthrene resulted in a 97% yield of phenanthrene-9-carboxylic acid, while reduction in glacial acetic acid with Adams' catalyst gave an 83% yield of 9-aminomethylphenanthrene (10). 9-Aminomethylphenanthrene on treatment with ethylene oxide and isolation of the product as the hydrochloride gave N,N-*bis*-(β-hydroxyethyl)-9-aminomethylphenanthrene (94% yield) which was finally chlorinated with thionyl chloride to give a quantitative yield of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride.

β,γ-Diphenylpropylamine was prepared from α-phenylcinnamonitrile [obtained in 95% yield by condensation of benzaldehyde with benzylcyanide according to Frost (11)] by catalytic reduction in glacial acetic acid with Adams' catalyst. The product was obtained in 46% yield. Unchanged α-phenylcinnamonitrile and some secondary amine were also isolated. The reduction of the nitrile to the amine in 14% yield by use of sodium in ethanol had been reported by Freund and Remse (12), catalytically with nickel in 60% yield by Braun, Bayer, and Cassel (13), and with Raney nickel in ethanol and liquid ammonia in 88% yield by Freeman, Ringk, and Spoerri (14). The amine was readily converted with ethylene oxide to the N,N-*bis*-(β-hydroxyethyl)amine from which N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride was obtained in good yield by treatment with thionyl chloride.

The condensation of anisaldehyde with *p*-methoxybenzyl cyanide to give *p*,*p*′-dimethoxy-α-cyanostilbene as described by Niederl and Ziering (15) was affected in 85% yield. The reduction of *p*,*p*′-dimethoxy-α-cyanostilbene in glacial acetic acid with Adams' catalyst gave the desired β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine (40% yield) along with some unchanged *p*,*p*′-dimethoxy-α-cyanostilbene. β,γ-Di-(*p*-methoxyphenyl)-*n*-propylamine was treated next with ethylene oxide and the product, N,N-*bis*-(β-hydroxyethyl)-β,γ-di-*p*-anisyl-*n*-propylamine, as the hydrochloride was chlorinated with thionyl chloride. The over-all yield of N,N-*bis*-(β-chloroethyl)-β,γ-di-*p*-anisyl-*n*-propylamine hydrochloride from β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine was 92%.

The pharmacological properties of the substituted *bis*-(β-chloroethyl)amines reported in this paper are under investigation at the Massachusetts General Hospital, Boston. The results of these studies will be published elsewhere.

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EXPERIMENTAL[2]

Bis-(β-chloroethyl)-n-butylamine hydrochloride. Method A. Into a mechanically-stirred solution of 38.5 g. (0.526 mole) of *n*-butylamine in 115 cc. of water was bubbled 53.4 g. (1.21 moles) of ethylene oxide over a period of 6½ hours. The reaction product was then fractionated *in vacuo* and 72 g. (85%) of *bis-(β*-hydroxyethyl)-*n*-butylamine (b.p.$_3$ 112–117°) was obtained. The hydrochloride of this amine in 100 cc. of toluene was treated drop-wise with 140 g. (1.18 mole) of thionyl chloride under stirring over a period of 1¼ hours. The solution was then refluxed for two hours, and the toluene and excess thionyl chloride were removed *in vacuo*. The residue was dissolved in acetone and toluene was added to turbidity. On cooling at −20° for several days, a crystalline product (m.p. 67–74°) separated, yield 42.8 g. (52%). Four wasteful crystallizations from acetone-toluene raised the melting point to 95–96°.

Anal. Calc'd for $C_8H_{18}Cl_3N$: C, 40.9; H, 7.73; Cl, 45.3; N, 5.9.
Found: C, 41.0; H, 7.69; Cl, 45.2; N, 6.0.

Method B. A mixture of 43 g. (0.314 mole) of *n*-butyl bromide, 20 g. (0.190 mole) of diethanolamine, and 19.7 g. (0.143 mole) of potassium carbonate was refluxed for eight hours. To facilitate filtration 50 cc. of ethanol was added. The potassium bromide and unchanged potassium carbonate were removed and washed with ethanol (3 × 15 cc.). Vacuum-distillation of the filtrate gave 26.1 g. (85%) of *bis-(β*-hydroxyethyl)-*n*-butylamine. This latter compound was converted to *bis-(β*-chloroethyl)-*n*-butylamine hydrochloride (m.p. 75.5–76.5°) in 53% yield by the above procedure. The pure product melted at 95–96° alone and on admixture with a sample prepared by Method A.

9-Bromophenanthrene (m.p. 63.8–64.8°) was prepared in 52% yield as previously described (7).

9-Cyanophenanthrene was obtained in a purified yield of 70% (m.p. 111.0–111.3°) by heating 9-bromophenanthrene with cuprous cyanide (8, 9).

9-Phenanthroic acid. 9-Cyanophenanthrene was converted to 9-phenanthroic acid (m.p. 256.5–257.5°) in a manner similar to that reported by Goldberg, Ordas, and Carsch (16). They reported m.p. 252–253°.

9-Aminomethylphenanthrene (m.p. 108.2–108.8°) was prepared in 83% yield by the method of van de Kamp, Burger, and Mosettig (10).

N,N-Bis-(β-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride. A solution of 6.9 g. (0.033 mole) of 9-aminomethylphenanthrene in 26 cc. of methanol was held at 56–57° and 3.2 g. (0.073 mole) of ethylene oxide was allowed to slowly bubble into the solution over a period of 2¼ hours. After the addition was complete, the reaction mixture was aged for a further period of one hour at 57° and then left at room temperature for 5½ hours. The methanol and excess ethylene oxide were removed *in vacuo* and the residual viscous oil was treated with 5.5 cc. of conc'd hydrochloric acid. On standing overnight, the solution deposited 10.4 g. (94%) of N,N-*bis-(β*-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride melting at 173.5–174.7°. Three crystallizations from ethanol gave a good yield of product melting at 176.2–176.8°.

The hydrochloride is soluble in methanol and hot ethanol. It is less soluble in cold ethanol and very slightly soluble in acetone and benzene.

Anal. Calc'd for $C_{19}H_{22}ClNO_2$: C, 68.7; H, 6.68; Cl, 10.70; N, 4.2.
Found: C, 68.9; H, 6.42; Cl, 10.65; N, 4.2.

N,N-Bis-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride. A mixture of 6.32 g. (0.019 mole) of N,N-*bis-(β*-hydroxyethyl)-9-aminomethylphenanthrene hydrochloride and 35 cc. of benzene under a reflux condenser was treated with 6.12 g. (0.0514 mole) of thionyl chloride. When the mixture was warmed to approximately 40°, a vigorous reaction ensued. Heating was then discontinued and after 15 minutes the reaction subsided. On further warming crystals formed and the flask was gently shaken during the crystallization period.

[2] All melting points have been corrected against reliable standards.

After refluxing for a period of one hour, the mixture was kept at room temperature overnight. The crystals were washed with benzene (10 cc.). In this way, 7.03 g. (100%) of N,N-*bis*-(β-chloroethyl)-9-aminomethylphenanthrene hydrochloride (m.p. 182–183.3°) was obtained. One crystallization from ethanol (7.15 cc./g.) failed to raise the melting point, which was found to be somewhat dependent on the rate of heating. The hydrochloride is soluble in hot methanol and hot ethanol but insoluble or slightly soluble in acetone and benzene.

Anal. Calc'd for $C_{19}H_{20}Cl_3N$: C, 61.9; H, 5.47; Cl, 28.8; N, 3.8.
Found: C, 62.2; H, 5.21; Cl, 28.6; N, 4.0.

α-Phenylcinnamonitrile (m.p. 86.0–86.3°) was prepared in 95% yield from benzyl cyanide and benzaldehyde by a procedure similar to that employed by Frost (11).

β,γ-Diphenyl-n-propylamine hydrochloride and di-(β,γ-diphenyl-n-propyl)amine hydrochloride. Seven grams (0.034 mole) of α-phenylcinnamonitrile was dissolved in 100 cc. of glacial acetic acid (distilled over potassium permanganate) and 200 mg. of Adams' catalyst added. The mixture was shaken for 65 hours in a low pressure (55 p.s.i) hydrogenation apparatus. The catalyst was filtered off and the filtrate evaporated *in vacuo* to a viscous oil which was separated into its components through their hydrochlorides. By triturating the hydrochlorides with ether (25 cc.), the unreacted α-phenylcinnamonitrile was extracted. The undissolved material was filtered off and washed with ether (2 × 10 cc.). This left 6.90 g. of a mixture of β,γ-diphenyl-*n*-propylamine hydrochloride, di-(β,γ-diphenyl-*n*-propyl)amine hydrochloride, and ammonium chloride.

The ammonium chloride and the primary amine hydrochloride were extracted from the mixture by stirring with water (2 × 40 cc.) and filtration. The combined filtrates on evaporation *in vacuo* gave 4.6 g. of solid. This mixture was crystallized from 25 cc. of conc'd hydrochloric acid. In this way 3.90 g. (46%) of β,γ-diphenyl-*n*-propylamine hydrochloride (m.p. 194–194.5°) was obtained. Another crystallization from conc'd hydrochloric acid gave 3.66 g. (43%) of pure material melting at 194.7–195.2°.

The crude secondary amine hydrochloride residue, obtained from the above water extraction, melted at 150–198°. One crystallization from ethanol (4 cc.) gave 2.07 g. (27%) melting at 181–204°. A sample of this material was purified by extraction with acetone, and crystallization of the residue from ethanol. Di-(β,γ-diphenyl-*n*-propyl)amine hydrochloride melting at 222.5–225° was thus obtained.

Anal. Calc'd for $C_{30}H_{32}ClN$: Cl, 8.06. Found: Cl, 8.20.

N,N-Bis-(β-chloroethyl)-β,γ-diphenyl-n-propylamine hydrochloride. β,γ-Diphenyl-*n*-propylamine was liberated from a solution of 3.66 g. (0.0147 mole) of the hydrochloride in 40 cc. of water by adding a solution of 1.20 g. (0.029 mole) of sodium hydroxide in 25 cc. of water. The free amine was extracted with ether (3 × 30 cc.) and the combined ethereal extracts were washed with water and evaporated to dryness. The residual yellow oil after solution in methanol (25 cc.) and treatment with ethylene oxide as described above, gave N,N-*bis*-(β-hydroxyethyl)-β,γ-diphenyl-*n*-propylamine. This amine was isolated as the hydrochloride in 97% yield.

A solution of 8.8 g. (0.074 mole) of thionyl chloride in 20 cc. of carbon tetrachloride was added to 4.81 g. (0.014 mole) of the hydrochloride. The reaction mixture was heated to 63° and within 25 minutes it became homogeneous. The resulting solution was held at 80–85° for 1½ hours. After standing overnight at room temperature, the solution was evaporated *in vacuo* at 60–65°, to a viscous yellow oil. This oil was crystallized by redissolving in 10 cc. of dry carbon tetrachloride, cooling to −20°, add seeding with N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride obtained in a previous run. After standing at −20° for five days crystallization appeared to be complete. On filtration 4 g. (75%) of product (m.p. 131.8–133°) was obtained. One crystallization from toluene (19 cc.) gave pure crystals melting at 135.3–137°, yield 3.52 g. (66%).

N,N-*Bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride is very soluble in ethanol, dioxane, and chloroform and soluble in acetone, hot toluene, and hot benzene.

Anal. Calc'd for $C_{19}H_{24}Cl_3N$: C, 61.2; H, 6.49; Cl, 28.5; N, 3.7.

Found: C, 61.4; H, 6.51; Cl, 28.5; N, 3.9.

p-Methoxybenzyl chloride was obtained from *p*-methoxybenzyl alcohol in 94% yield by chlorination with thionyl chloride in benzene.

p-Methoxybenzyl cyanide was prepared in 88% yield by the method of Lee, *et al.* (17).

p,p'-Dimethoxy-α-cyanostilbene (m.p. 107.8–108.7°) was obtained in 85% yield from the condensation of *p*-methoxybenzyl chloride with *p*-methoxybenzyl cyanide. The procedure was the same as that followed in the preparation of α-phenylcinnamonitrile. Niederl and Ziering (15) reported m.p. 108°.

β,γ-Di-(p-methoxyphenyl)-n-propylamine. Adams' catalyst (300 mg.) was added to 10.1 g. (0.038 mole) of *p,p'*-dimethoxy-α-cyanostilbene in 150 cc. of purified glacial acetic acid. This mixture was reduced in a Parr hydrogenator at an initial hydrogen pressure of 60 p.s.i. Shaking under pressure was continued for 42 hours. The solution was filtered and evaporated under reduced pressure, leaving a dark oil. Ether (100 cc.) was added and swirled with the oil. On standing overnight, β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine acetate and di-[β,γ-di(*p*-methoxyphenyl-*n*-propyl)]amine acetate crystallized and were filtered from the ether solution. After washing with ether (50 cc.), the mixture of crystalline acetates was suspended in water (50 cc.), and treated with a solution of 2 g. of sodium hydroxide in water (20 cc.). The liberated amines were extracted with ether (3 × 30 cc.) and the ethereal solution was washed with water (2 × 15 cc.) and evaporated. The residual oil on distillation gave 4.12 g. (40%) of β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine, b.p.$_1$ 204°. Three crystallizations from isopropyl ether (10 cc.) raised the melting point of this amine from 70–73° to 73–74°; yield 3.54 g. (34%).

Anal. Calc'd for $C_{17}H_{21}NO_2$: C, 75.2; H, 7.75; N, 5.1.

Found: C, 75.2; H, 7.65; N, 5.3.

N,N-Bis-(β-chloroethyl)-β,γ-di-(p-methoxyphenyl)-n-propylamine hydrochloride. Ethylene oxide was added to a solution of β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine and the product converted to N,N-*bis*-(β-hydroxyethyl)-β,γ-di-(*p*-methoxyphenyl)-*n*-propylamine hydrochloride as described above for the preparation of N,N-*bis*-(β-hydroxyethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride. In this case the product was also an oil.

When N,N-*bis*-(β-hydroxyethyl)-β,γ-dianisyl-*n*-propylamine hydrochloride in carbon tetrachloride was chlorinated with thionyl chloride as described above a 92% yield of product (m.p. 162–162.5°) was obtained. One crystallization from anisole (7.1 cc./g.) gave an 80% yield of pure material melting at 165–167°.

Anal. Calc'd for $C_{21}H_{28}Cl_3NO_2$: C, 58.2; H, 6.52; Cl, 24.5; N, 3.24.

Found: C, 57.8; H, 6.60; Cl, 24.4; N, 3.16.

SUMMARY

Four new substituted *bis*-(β-chloroethyl)amine hydrochlorides, of interest as possible chemotherapeutic agents for cancer, have been synthesized. They are: *bis*-(β-chloroethyl)-*n*-butylamine hydrochloride, N,N-*bis*-(-β-chloroethyl)-9-aminomethylphenanthrene hydrochloride, N,N-*bis*-(β-chloroethyl)-β,γ-diphenyl-*n*-propylamine hydrochloride, and N,N-*bis*-(β-chloroethyl)-β,γ-dianisyl-*n*-propylamine hydrochloride.

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DEHYDROHALOGENATION OF SEVERAL VINYL HALIDES[1]

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The dehydrohalogenation of unsaturated alcohols containing vinyl halogen atoms has been used since 1872 (1) for the production of acetylenic alcohols, but no attempt has been made to relate either the nature of the halogen atom or its position on the carbon chain with the extent of reaction. The influence of geometrical isomerism has, however, been determined for both 3-chloro-2-propen-1-ol (2) and 3-chloro-2-buten-1-ol (3), and the information obtained has been used to elucidate the structures of these compounds (3, 4, 5) under the assumption that *trans*-elimination takes place more readily than *cis*-elimination.

The present study was made to obtain quantitative data pertaining to the ease of removal by aqueous alkali of a bromine atom and a chlorine atom on the number 2 carbon atom of 2-halo-2-propen-1-ol and to compare these reactivities with those previously reported for the 3-chloro-2-propen-1-ols and the 3-chloro-2-buten-1-ols. The data plotted in Figure 1 show the effect of sodium hydroxide concentration on the extent of reaction, while Figure 2 gives data related to the effect of time on the extent of reaction using a 10% solution of sodium hydroxide at 100°.

The dehydrobromination reaction was expected to take place more readily than the dehydrochlorination reaction but the great ease of dehydrobromination found was surprising. The low yields of propargyl alcohol from 2-bromo-2-propen-1-ol reported in the literature (1) probably resulted from using conditions much more severe than actually were required, with subsequent decomposition of the propargyl alcohol originally formed. It is also possible that the dehydrohalogenation reaction may, in part, involve a hydrogen atom on the number 3 carbon atom, to give hydroxyallene which would rearrange to acrolein. The formation of 2,3-epoxypropene is also a possibility. It is felt, however, that these side reactions are not the main cause for the low yields of propargyl alcohol. It is also obvious that any method of preparation of 2-bromo-2-propen-1-ol involving a basic medium will have dehydrobromination as an important side reaction.

The relationship between the ease of dehydrochlorination and the position of the chlorine atom on the carbon chain can not be ascertained from the available data because 2-chloro-2-propen-1-ol has a reactivity greater than the *trans*-isomer of 3-chloro-2-propen-1-ol and less than the *cis*-isomer and also because

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of the possibility of side reactions with 2-chloro-2-propen-1-ol. In comparison with 3-chloro-2-buten-1-ol (3) it appears that there is only a small difference

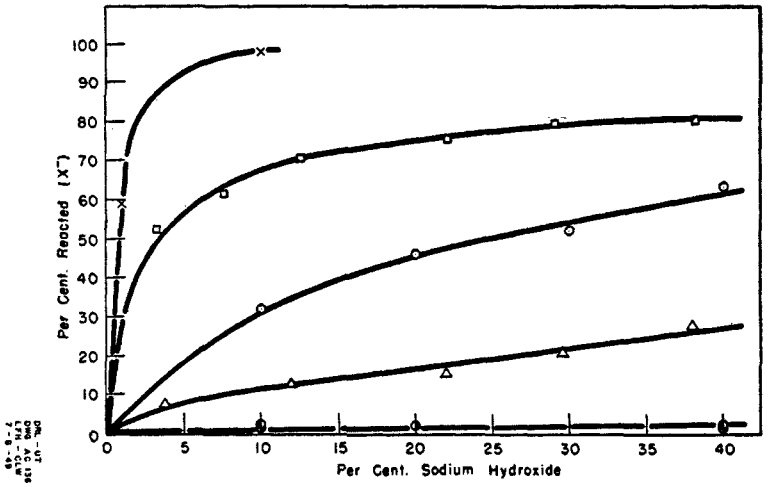

FIGURE 1. EFFECT OF SODIUM HYDROXIDE CONCENTRATION ON THE EXTENT OF REACTION FOR 2 HOURS AT REFLUX TEMPERATURE

2-Bromo-2-propen-1-ol—×; 2-chloro-2-propen-1-ol—○; *cis*-3-chloro-2-propen-1-ol—□; *trans*-3-chloro-2-propen-1-ol—△; *cis*-3-ethoxy-1-chloro-1-propene—◐; *trans*-3-ethoxy-1-chloro-1-propene—◑.

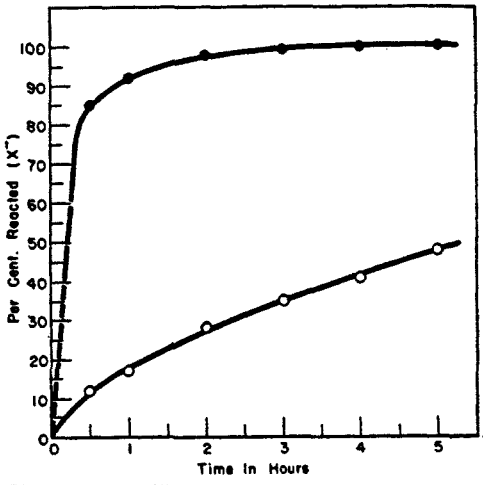

FIGURE 2. EFFECT OF TIME ON THE EXTENT OF REACTION USING 10% SODIUM HYDROXIDE AT 100°

2-Bromo-2-propen-1-ol—●; 2-chloro-2-propen-1-ol—○

in reactivity between the number two position and the number three position when the chlorine atom involved is attached to a carbon atom which in turn is attached to two other carbon atoms. Under comparable conditions of time

(2 hrs.), temperature (101.5°), and sodium hydroxide concentration (10%), 2-chloro-2-propen-1-ol reacted to the extent of 31%, α-3-chloro-2-buten-1-ol 32%, and β-3-chloro-2-buten-1-ol 27%. *trans*-3-Chloro-2-propen-1-ol has been dehydrochlorinated in the course of other work in this laboratory to give a 79% yield of 2-butyn-1-ol, which indicates the substantial absence of side reactions.

The two isomers of 3-ethoxy-1-chloro-1-propene were prepared from the corresponding isomers of 1,3-dichloropropene by reaction with sodium ethoxide. Both *cis*- and *trans*-3-ethoxy-1-chloro-1-propene were very resistant to the action of sodium hydroxide in aqueous solution, but they both developed hydrochloric acid rapidly on standing at room temperature in the presence of moisture. The lack of reaction with aqueous sodium hydroxide is attributable to the very low solubility of the ethers in a solution of this nature. When a 20% solution of potassium hydroxide in a 15% ethyl alcohol-85% water solvent was used as the dehydrochlorination medium, the lower-boiling isomer dehydrochlorinated more extensively than the higher-boiling isomer.

Assuming a greater ease for *trans*-elimination, then the lower-boiling isomer of 3-ethoxy-1-chloro-1-propene would be assigned the *cis*-structure (in respect to the two hydrogen atoms attached to the carbon atoms associated with the carbon-carbon double bond). This assignment of configuration is consistent with the origin of the ether from the lower-boiling isomer of 1,3-dichloropropene to which the *cis*-configuration has been assigned (5). The higher-boiling isomer would then have the *trans*-configuration.

Incidental to this study of dehydrohalogenation there have been obtained more accurate physical data for 2,3-dibromo-1-propene and 2-bromo-2-propen-1-ol and *cis*- and *trans*-3-ethoxy-1-chloro-1-propene have been prepared and characterized for the first time. The two previous references in the literature to these ethers apparently pertained in one incidence (6) to a mixture of the two isomers and in the other (7) to the *trans*-isomer[4].

EXPERIMENTAL

2,3-Dibromo-1-propene. This compound was prepared from 1,2,3-tribromopropane by the action of a concentrated solution of sodium hydroxide in a manner similar to that described in *Organic Syntheses* (8). Yield 72%; b.p. 40.5° (18 mm.), n_D^{25} 1.5416, d_4^{25} 2.0346 [Lit. (9) n_D^{20} 1.5157, d_4^{20} 1.9336]; MR (obs'd), 31.12; MR (calc'd), 30.91.

2-Bromo-2-propen-1-ol. This bromo alcohol was prepared from 2,3-dibromo-1-propene by hydrolysis, using a 10% excess of 10% sodium carbonate solution at 95° for seven hours. The yield was only 47% because of the severity of the conditions; subsequent dehydrobromination studies suggest that there was some loss through removal of both bromine atoms.

The 2-bromo-2-propen-1-ol was separated from the reaction mixture, dried with magnesium sulfate, and distilled through a three-foot glass helix-packed fractionating-column. B.p. 60–61° (18 mm.), n_D^{25} 1.4973, d_4^{25} 1.6360; MR (obs'd), 24.88; MR (calc'd), 24.52.

[4] While this paper was in press Smith and King, *J. Am. Chem. Soc.*, **72**, 95 (1950) published the following data on these ethers: "product from the 112° 1,3-dichloropropene-1, b.p. 128.0° (740 mm.), n_D^{25} 1.4306; product from the 104° 1,3-dichloropropene-1, b.p. 120–121° (740 mm.), n_D^{25} 1.4282".

2-Chloro-2-propen-1-ol. The 2-chloro-2-propen-1-ol used in this investigation was furnished by Shell Development Co., Emeryville, California and had the following constants: b.p. 134°, n_D^{20} 1.460, d_4^{20} 1.162. It was used without further purification other than simple distillation.

cis- and trans-3-Ethoxy-1-chloro-1-propene. Both isomers of 3-ethoxy-1-chloro-1-propene were prepared in a similar manner by treating the appropriate isomer of 1,3-dichloropropene with sodium ethoxide in ethanol. *cis-* and *trans*-1,3-Dichloropropene were isolated from D-D (furnished by Shell Chemical Co., Houston, Texas) by fractionation. *cis*-1,3-Dichloropropene: b.p. 103.5–104.5° (746 mm.), n_D^{25} 1.4650 [Lit. (5) n_D^{25}1.4652]. *trans*-1,3-Dichloropropene: b.p. 112.0–112.3° (745 mm.), n_D^{25} 1.4696 [Lit. (5) n_D^{25} 1.4712].

One mole (111 g.) of 1,3-dichloropropene and one mole of sodium ethoxide in 500 ml. of ethanol were mixed at room temperature in a one-liter three-necked flask fitted with a thermometer, stirrer, and reflux condenser. The heat of the reaction caused the temperature of the mixture to rise to 75° within 30 minutes. Stirring was continued for another 1½ hours, during which time the temperature dropped to 40°. The sodium chloride was removed; then distilled water was added until two layers were formed. The organic layer was separated and dried with calcium chloride which removed both the water and the ethanol. After a 24-hour treatment with calcium chloride, the ether was distilled through an 18-inch glass helix-packed column.

cis-3-Ethoxy-1-chloro-1-propene[4]: Yield 71%; b.p. 120.5° (749 mm.), n_D^{25} 1.4290, n_D^{30} 1.4270; d_4^{25} 0.9941; MR (obs'd), 31.36; MR (calc'd), 31.33.

Anal. (10) Calc'd: Cl, 29.40. Found: Cl, 29.31, 29.26.

trans-3-Ethoxy-1-chloro-1-propene[4]: Yield 76%; b.p. 126° (747 mm.), n_D^{25} 1.4310, n_D^{30} 1.4291; d_4^{25} 0.9935; MR (obs'd), 31.34; MR (calc'd), 31.33.

Anal. (10) Calc'd: Cl, 29.40. Found: Cl, 29.49, 29.56.

Dehydrohalogenation of 2-chloro-2-propen-1-ol and 2-bromo-2-propen-1-ol. Two series of dehydrohalogenation runs were made with the chloro and bromo alcohols to evaluate the influence of both sodium hydroxide concentration and time on this reaction. The procedure used was essentially the same as that previously described by Hatch and Moore (2).

The first series of runs used 2-chloro-2-propen-1-ol and sodium hydroxide concentrations of 10%, 20%, 30%, and 40% for two hours at the reflux temperature of the solution. These conditions permitted a direct comparison of the reactivity of a chlorine atom on the number 2 carbon atom with data previously reported (2) pertaining to the reactivity of a chlorine atom on the number 3 carbon atom under these conditions. This comparison is made in Figure 1. Two runs under similar conditions using 2-bromo-2-propen-1-ol are also plotted in Figure 1.

A second series of runs was made at 100° using 2-chloro-2-propen-1-ol and a 10% sodium hydroxide solution with time as a variable. These data are given in Figure 2 along with comparable data for 2-bromo-2-propen-1-ol.

The reaction mixtures from the various runs were combined and a low yield (30%) of propargyl alcohol was obtained which had the following constants: b.p. 113.0° (747 mm.), n_D^{25} 1.4292, d_4^{25} 0.9446; MR (obs'd), 15.31; MR (calc'd), 15.58 [Lit. (11) b.p. 113.6° (760 mm.), n_D^{20} 1.4320, d_4^{20} 0.9478; MR (obs'd), 15.33; MR (calc'd), 15.58).

Dehydrochlorination of cis- and trans-3-ethoxy-1-chloro-1-propene. Several attempts were made to dehydrochlorinate both *cis-* and *trans*-3-ethoxy-1-chloro-1-propene using aqueous sodium hydroxide solutions. The amount of chloride ion produced in every case was negligible as indicated in Figure 1.

Under the assumption that the lack of reactivity was primarily caused by the low solubility of the ethers in the reaction medium, an alcohol (15%)-water (85%) solution of 20% potassium hydroxide was used. The following results were obtained: *cis*-3-ethoxy-1-chloro-1-propene—2 hrs. 8.5% (Cl^-), 4 hrs. 10.9% (Cl^-); *trans*-3-ethoxy-1-chloro-1-propene —4 hrs. 2.2% (Cl^-). Although the extent of reaction is not great in any case, a distinct

difference in reactivity is shown between the two isomers with the lower-boiling isomer being the more reactive.

SUMMARY

Both 2-chloro-2-propen-1-ol and 2-bromo-2-propen-1-ol have been dehydrohalogenated under various conditions of time and sodium hydroxide concentration.

The 2-bromo-2-propen-1-ol was shown to be appreciably more reactive than either the 2-chloro-2-propen-1-ol or the two isomers of 3-chloro-2-propen-1-ol previously reported while 2-chloro-2-propen-1-ol has a reactivity between those of the two isomers of 3-chloro-2-propen-1-ol and about the same reactivity as the two isomers of 3-chloro-2-buten-1-ol.

More accurate physical constants have been obtained for 2,3-dibromo-1-propene and 2-bromo-2-propen-1-ol.

cis- and *trans*-3-Ethoxy-1-chloro-1-propene have been prepared and characterized.

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[CONTRIBUTION FROM THE WELLCOME RESEARCH LABORATORIES]

CATALYTIC HYDROGENATION OF NITROBENZYL ALCOHOLS AND NITROBENZALDEHYDES

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Debenzylation type hydrogenations such as those illustrated below are now well-established (1) using palladized charcoal. Hartung and Crossley (1b) stated

$$\mathrm{ArCHX}\,(\mathrm{R}) \xrightarrow[\mathrm{H_2}]{\text{Pd-C}} \mathrm{ArCH_2}\,(\mathrm{R}) + \mathrm{HX}$$

R = H, alkyl, or aryl
X = Halogen, OH, O-alkyl, OCOZ, $\mathrm{NR'_2}$, or similar functions

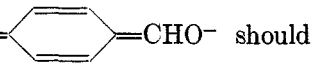
that a platinum catalyst prepared in essentially the same fashion as their active palladium catalyst did not readily reduce propiophenone to propylbenzene. In these laboratories we have found (2) that whereas the rate of catalytic hydrogenation of benzyl alcohol to toluene can serve as a practical control for determining the activity of a batch of palladized charcoal catalyst, it cannot be used as a control for Adams' catalyst. Such reduction as occurs is slow and may involve other than debenzylating action.

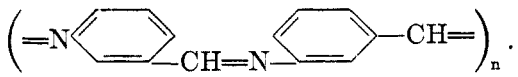
It became desirable to obtain *m*- and *p*-aminobenzyl alcohols for other work. These are described in the literature, prepared by laborious procedures. The rapid catalytic reduction of aromatic nitro to amino groups, the slower reduction of aldehydic carbonyl to alcohol, and the non-debenzylating character of Adams' catalyst made it seem reasonable that the products sought might be obtained in a single, smooth hydrogenation of the *m*- or *p*-nitrobenzyl alcohols or of the *m*- or *p*-nitrobenzaldehydes over this catalyst.

m-Nitrobenzyl alcohol over Adams' catalyst rapidly absorbed just the calculated amount of hydrogen (three moles) and gave a nearly quantitative yield of *m*-aminobenzyl alcohol. *p*-Nitrobenzyl alcohol likewise took up the same amount of hydrogen rapidly, but the clear and colorless methanol solution, obtained after removal of the platinum, on evaporation even at room temperature *in vacuo* gave only an insoluble polymer. This tendency of *p*-aminobenzyl alcohol to polymerize is well-known (3) and is catalyzed by acids, both acetic and hydrochloric acid having been used for this purpose. We have found no report of similar behavior for *m*-aminobenzyl alcohol, in fact it can be vacuum-distilled without appreciable decomposition, and forms a stable hydrochloride, m.p. 121° (4). The difference in reactivity (as for polymerization) between the *meta* and *para* isomers is explicable in terms of the activation or labilization of the methylol group by the strong mesomeric effect of a *para*, but not a *meta*, amino. This difference extends to the ability of the *para* isomer to condense readily with a variety of activated hydrogen compounds (such as undergo the Mannich reaction) in weakly acidic media to give *p*-aminobenzyl derivatives. With α-naphthol the product is 4-(*p*-aminobenzyl)-1-naphthol (5).

An authentic sample of *p*-aminobenzyl alcohol, prepared by lithium aluminum hydride reduction of *p*-aminobenzoic acid, when evaporated in methanol solution with a trace of acetic acid gave an insoluble yellow polymer.

Hydrogenations of the corresponding nitrobenzaldehydes were attempted because of their greater availability as compared with the nitro alcohols. *p*-Nitrobenzaldehyde took up the calculated volume of hydrogen (4 moles) quickly but *p*-aminobenzyl alcohol was isolated only as the polymer. In contrast, *m*-nitrobenzaldehyde reduced only slowly and uptake stopped after absorption of about one-half the calculated amount. At this point an insoluble, viscous polymer precipitated, coating thoroughly the catalyst and reduction bottle.

The difference in behavior of the two nitrobenzaldehydes can be explained in terms of the mesomeric effect. In each case the nitro group will undoubtedly be reduced preferentially leading to the corresponding aminobenzaldehydes as intermediates. That the *p*-isomer reduced smoothly with a hydrogen uptake corresponding to the formation of *p*-aminobenzyl alcohol we interpret as due to the resonance stabilization of the intermediate aminoaldehyde. Contributions of the type  should stabilize the molecule by diminishing the reactivity of both the amino and carbonyl functions for their characteristic condensations (in this case Schiff's base formation) as compared with the isolated, uncoordinated groups (aniline and benzaldehyde react rapidly to give a Schiff's base). With the *meta* isomer no such favorable resonance interaction can occur and the individual group reactivities will be closer to their normal values, presumably reacting to give a Schiff's base type polymer



Certainly *m*-aminobenzaldehyde is much less well characterized than its *o*- or *p*-isomers. Although several papers (6a, b, c, d) report the preparation and derivatives of this compound no well-defined identification of it by melting point or other properties has been made. Even *m*-acetylaminobenzaldehyde is reported by different authors as having the melting point 84° (6c) and 122° (6b) respectively.

EXPERIMENTAL

Reductions. Catalytic hydrogenations were carried out in a Burgess-Parr type apparatus in methanol solution, at room temperature, 2-3 atmospheres over-pressure of hydrogen, and with Adams' catalyst. When the hydrogn uptake was complete, the platinum-free solvent was evaporated on a steam-bath or in some cases at room temperature *in vacuo*.

m-Nitrobenzyl alcohol. *m*-Nitrobenzyl alcohol (15 g., 0.1 mole) absorbed just 0.3 mole of hydrogen in 40 minutes. The yield of *m*-aminobenzyl alcohol recrystallized from benzene was 12.4 g. (100%); m.p. 95-96°.

p-Nitrobenzyl alcohol. *p*-Nitrobenzyl alcohol (15 g., 0.1 mole) absorbed just 0.3 mole of hydrogen in 40 minutes. After removal of platinum the reduction mixture was a clear, colorless solution. Evaporation of methanol either on the steam-bath or at room temperature *in vacuo* gave only an insoluble yellow polymer which started to come out when about

one-half the solvent had been removed; yield 10 g. (80%); m.p. > 250°. This polymer was practically insoluble in water, methanol, benzene, or mineral acids.

This hydrogenation was repeated a number of times and always took up the proper amount of hydrogen rapidly, but all attempts to isolate the desired *p*-aminobenzyl alcohol yielded only insoluble polymers of the type described.

p-Aminobenzyl alcohol. By the procedure of Nystrom and Brown (7) *p*-aminobenzyl alcohol; m.p. 63–64° (recrystallized five times from benzene), was prepared in 20% yield by reduction of *p*-aminobenzoic acid with lithium aluminum hydride. A small sample of this pure *p*-aminobenzyl alcohol on warming in methanol solution in the presence of a trace of acetic acid gave an insoluble high-melting yellow polymer; m.p. >250°.

m-Nitrobenzaldehyde. Hydrogenation of 7.6 g. (0.05 mole) of *m*-nitrobenzaldehyde proceeded at only a moderate rate, and stopped after about one-half the calculated hydrogen uptake (took 0.1 mole, calc'd 0.2 mole) during which time a very insoluble viscous polymer precipitated coating catalyst and bottle completely. This substance was insoluble in hot water, methanol, or hot glacial acetic acid.

p-Nitrobenzaldehyde. Several samples of *p*-nitrobenzaldehyde, 3.0 g. (0.02 mole), were reduced and always took up the calculated amount of hydrogen (0.08 mole) rapidly (within less than 45 minutes). All attempts to isolate *p*-aminobenzyl alcohol from the clear filtrate from platinum gave only insoluble yellow polymers (in good yields) of the type described under the reduction of *p*-nitrobenzyl alcohol.

SUMMARY

m- and *p*-Nitrobenzyl alcohols and *m*- and *p*-nitrobenzaldehydes have been reduced catalytically using Adams' catalyst. A reasonable theoretical explanation has been given for the different results obtained in the individual cases.

TUCKAHOE 7, NEW YORK

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THE SYNTHESIS OF 1,5-DISUBSTITUTED TETRAZOLES

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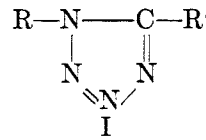
In a previous communication the synthesis of various alkylated pentamethylenetetrazoles was described (1). The activity of pentamethylenetetrazole (Metrazol) as an analeptic and respiratory stimulant was enhanced by the substitution of alkyl groups in the pentamethylene ring (2). In continuing our studies of the effect of structure on the pharmacologic activity in the tetrazole series it became of interest to determine whether similar relationships existed in a series of simple 1,5-disubstituted tetrazoles (I). Although a number of such structures in which one of the substituents on the tetrazole ring is an aromatic group are known (3), only a single example, 1,5-dimethyltetrazole, in which both substituents are aliphatic in character has been described.



I

Initially the scope of this investigation was limited to a group of compounds in which R and R′ were groups such as methyl, ethyl, butyl, isobutyl, cyclohexyl, and phenyl. A series of tetrazoles exhibiting systematic variations of the foregoing substituents in both positions was prepared so that the pharmacologic effects of lengthened and branched chains in the aliphatic series, of cycloaliphatic, and of aromatic groups could be correlated. As the work progressed the results of pharmacologic tests indicated the desirability of synthesizing a number of other structures to elaborate more completely the trends.

Several methods for the synthesis of 1,5-disubstituted tetrazoles have been described (3). Schmidt (4) has described an apparently simple method for the conversion of ketones into tetrazoles by interaction with hydrazoic acid in the presence of sulfuric acid. The process appears to be an elaboration of the Schmidt reaction (5) for the conversion of ketones to amides and is said to take place when the ketone reacts with two moles of hydrazoic acid. According to Schmidt (6) hydrazoic acid will decompose in the presence of concentrated sulfuric acid with liberation of nitrogen and formation of an imine radical. Through interaction of the ketone with this radical an oxime is assumed to form and undergo rearrangement to the amide under the influence of sulfuric acid (7). Tetrazole

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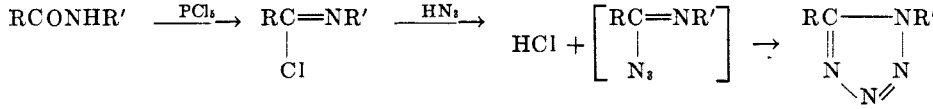
formation is explained by the interaction of a second mole of hydrazoic acid with the oxime or some intermediate during the rearrangement. In support of these suggestions the formation of 1,5-dimethyltetrazole by interaction of the benzenesulfonic ester of acetoxime and sodium azide (8), and the failure of amides to yield tetrazoles under the conditions of the Schmidt reaction have been cited. The formation of a compound said to be 1-benzyl-5-methyltetrazole by interaction of the toluenesulfonate of methyl benzyl ketoxime and sodium azide has also been described (8). Smith (9) has recently subjected that aspect of the Schmidt reaction involving the interaction of ketones and hydrazoic acid to a critical study and has developed a more acceptable interpretation of the mechanism involved in both amide and tetrazole formation.

In attempts to apply Schmidt's procedure to the synthesis of symmetrically substituted 1,5-dialkyltetrazoles it was not possible to confirm his results completely. Under the conditions set forth by this author we obtained 1,5-dimethyltetrazole in 12% yield from acetone, N-methylacetamide being the major product of the reaction. Schmidt (4) reported an 80% yield of the tetrazole in this case. Similarly, from diethyl ketone, N-ethylpropionamide was formed in 88% yield, together with correspondingly small amounts of the tetrazole, while diisobutyl ketone under similar conditions gave 46% of N-isobutylisovaleramide and 24% of 1,5-diisobutyltetrazole. Although the conditions of the reactions were subjected to considerable variation, in our hands the procedure failed to lead to a tetrazole as the major product in any instance.

Lack of success in duplicating Schmidt's claims prompted the investigation of procedures for the preparation of 1,5-disubstituted tetrazoles from N-substituted amides. Forster (10) had demonstrated the possibility of synthesizing 1-hydroxy-5-phenyltetrazole by interaction of benzhydroximidyl chloride and sodium azide. At about the same time Schroeter (11) succeeded in converting the imide chloride of benzanilide into 1,5-diphenyltetrazole by warming the chloride with sodium azide suspended in amyl ether. von Braun and Rudolph (12) improved the procedure by treating the imide chlorides with hydrazoic acid in benzene or chloroform solution. Most imide chlorides, R'C(Cl)=NR, excepting those derived from N-aryl aromatic amides in which both R and R' are aryl groups, are rather unstable substances which undergo thermal decomposition quite readily. For instance, imide chlorides in which R' is aromatic and R is aliphatic decompose readily on warming with the formation of an alkyl chloride and an aromatic nitrile (13). Since the use of hydrazoic acid solutions permitted the reaction with the imide chlorides to take place at room temperature or only slightly above, von Braun and Rudolph were able to increase the scope of the



procedure to include many imide chlorides which had not been susceptible to reaction at the higher temperatures required when sodium azide was employed.

The foregoing sequence of reactions was applied by von Braun and Rudolph

only to imide chlorides in which R′ was aromatic and R was either aliphatic or aromatic. The restriction to imide chlorides derived from anilides appeared to be based on earlier work by von Braun and his co-workers (14, 16) in which it was shown that the chlorides of aliphatic amides of the type $RCH_2C(Cl)=NR'$, where R was either hydrogen or an aliphatic group and R′ was either aliphatic or aromatic, were characterized by such great reactivity that they could not be isolated. Such imide chlorides readily formed amidine-like condensation products apparently due to a primary shift of hydrogen from the *alpha*-carbon to nitrogen followed by a reaction between the tautomeric forms with elimination of hydrogen chloride (15).

$$RCH_2C(Cl)=NR' \rightleftarrows RCH=C(Cl)NHR'$$

$$\begin{matrix} RCH_2C(Cl)=NR' \\ + \\ RCH=C(Cl)NHR' \end{matrix} \rightarrow \begin{matrix} RCH_2C=NR' \\ | \\ RCH=C(Cl)NR' \end{matrix} + HCl$$

The same authors also indicated that imide chlorides of the type $R_2CHC(Cl)=NR'$, where R and R′ are both aliphatic, are likewise unstable, but that the complete replacement of the hydrogen on the *alpha*-carbon by alkyl groups would lead to stable products.

Although von Braun attributed a rather high degree of instability to most imide chlorides, this conclusion was based on attempts to isolate these compounds. Our experience with a variety of purely aliphatic, as well as mixed aliphatic-aromatic N-substituted amides, indicates that all of these compounds can easily be converted into derivatives that behave like imide chlorides by interaction with phosphorus pentachloride in an inert solvent, provided the reaction mixtures are kept near or only slightly above room temperature. Although von Braun and his coworkers frequently employed inert solvents or diluents, their reactions were always carried out with a large excess (2–3 moles) of phosphorus pentachloride. Our experience has indicated that the addition of an equimolar quantity of phosphorus pentachloride to a benzene solution or suspension of the substituted amide sufficed for complete conversion of the latter to the corresponding imide chloride. The resulting benzene solution of the imide chloride upon treatment with a solution of hydrazoic acid in the same solvent gave evidence of further reaction by the elimination of hydrogen chloride. It was generally found desirable to heat the reaction mixture slowly to boiling after complete addition of the hydrazoic acid, and to maintain this temperature for some time in order to obtain the maximum yield of tetrazole. Throughout this period hydrogen chloride evolution continued at a gradually decreasing rate. These observations suggest the possibility of the initial formation of an imide azide which slowly cyclizes to the tetrazole, although we have not attempted to isolate such intermediates. The presence of hydrogen chloride to the extent that it was soluble in the benzene solution and of phosphorus oxychloride, formed by interaction of the amides with the pentachloride, did not appear to interfere with the reaction

of the imide chlorides and hydrazoic acid. In several experiments in which the benzene solution of the imide chloride was concentrated to remove hydrogen chloride and at least part of the oxychloride, no improvement in the yield of tetrazole was noted. In fact, with the more heat-sensitive imide chlorides the best results were obtained when all procedures that involved warming prior to treatment with hydrazoic acid were avoided insofar as possible.

In Table II are recorded the code numbers, names, and other pertinent data for all the 1,5-disubstituted tetrazoles prepared during the course of this work. All the products were colorless, crystalline solids, insoluble in cold water excepting those having relatively small aliphatic substituent groups. Both 1,5-dimethyl and 1-isobutyl-5-methyltetrazole were quite soluble in cold water, 10% solutions in water being used for testing purposes. When one of the substituents was a cyclic group and the other a methyl group, the compounds usually exhibited a slight solubility in cold water and a sufficiently increased solubility in hot water to permit satisfactory recrystallization. Most of the compounds were readily soluble in organic solvents such as benzene, toluene, ether, ethanol, ethyl acetate, and acetone, especially on warming, but they were practically insoluble in petroleum ether. Only 1,5-diphenyltetrazole failed to exhibit moderate solubility in most of these solvents. All of the compounds were heat-stable and those of lower molecular weight could be distilled under reduced pressure. They failed to form salts with aqueous acids or bases and withstood treatment with hot 50% sulfuric acid or 40% sodium hydroxide solution.

The results of screening tests of the pharmacologic action of the compounds have been reported by Gross and Featherstone (17). They concluded that the optimal structural features for maximum stimulatory action were the presence of a saturated cyclic group or a comparably large aliphatic group in position 1 and a small group, preferably methyl, in the 5 position of the tetrazole ring. Potent stimulatory effects were exhibited by 1-cyclohexyl-5-methyl-, 1-cyclohexyl-5-ethyl-, 1-cyclopentyl-5-methyl-, and 1-isobutyl-5-methyl-tetrazole. The first two also exhibited marked respiratory stimulation and analeptic action, the methyl compound being effective at much lower dosage than the ethyl compound.

EXPERIMENTAL[5]

Amides. The N-substituted amides were prepared by treatment of the appropriate primary amines with suitable acid anhydrides or acid chlorides. When acid anhydrides were used, the amine was treated with an excess of the anhydride usually with the corresponding acid as solvent. When acid chlorides were used, these were added dropwise to a benzene solution of two moles of amine or one mole of amine together with one mole of pyridine. External cooling was applied when needed. After washing the benzene solution of the amide with water and drying over sodium sulfate, the solvent was removed by distillation and the residual amide was purified either by crystallization from the appropriate solvent or by distillation under reduced pressure. In Table I are listed the amides used or prepared

[5] Microanalyses were carried out on all compounds described in this communication by Mr. William Saschek.

as intermediates together with their physical constants, analyses, and other pertinent data in those instances where the products have not been previously described in the literature.

Tetrazoles from ketones. Caution: Hydrazoic acid vapors are highly toxic and all reactions involving its use should be carried out in a good hood. The use of heavy metals such as mercury in thermometers or seals should be avoided. Although the preparation of 1,5-diisobutyl-

TABLE I

N-SUBSTITUTED AMIDES $R_1NH—COR_2$

AMIDE	R_1	R_2	M.P. (B.P.), °C.[i]	REFERENCE
N-Methylacetamide	CH_3	CH_3	(206)	18
N-Isobutylacetamide	iso-C_4H_9	CH_3	(219.5–224)	19
Acetanilide	C_6H_5[j]	CH_3	114	20
Propionanilide	C_6H_5[j]	C_2H_5	103.5–104	21
Isobutyranilide	C_6H_5	iso-C_4H_9	109–110	22
Hexahydrobenzanilide	C_6H_5	cyclo-C_6H_{11}	131–132	23
Benzanilide	C_6H_5[j]	C_6H_5	160–161	24
N-Methylbenzamide	CH_3	C_6H_5	77	25
N-Ethylbenzamide	C_2H_5	C_6H_5	68.5	25
N-Isobutylbenzamide	iso-C_4H_9	C_6H_5	(180–181/ 11 mm.)	26
N-Cyclohexylbenzamide	cyclo-C_6H_{11}	C_6H_5	149.5	27, 28
N-Cyclohexylacetamide	cyclo-C_6H_{11}	CH_3	107–109	28
N-Cyclohexylpropionamide	cyclo-C_6H_{11}	C_2H_5	92	23
N-Cyclohexyl-*n*-butyramide	cyclo-C_6H_{11}	*n*-C_3H_7	66–67	[a]
N-Cyclohexylisobutyramide	cyclo-C_6H_{11}	iso-C_3H_7	119	[b]
N-Cyclohexyl-*n*-valeramide	cyclo-C_6H_{11}	*n*-$_4CH_9$	68	[c]
N-Cyclohexylisovaleramide	cyclo-C_6H_{11}	iso-C_4H_9	105.5–107	[d]
N-Cyclohexylhexahydrobenzamide	cyclo-C_6H_{11}	cyclo-C_6H_{11}	172–173	[e]
N-Methylhexahydrobenzamide	CH_3	cyclo-C_6H_{11}	115–116	[f]
N-Ethylhexahydrobenzamide	C_2H_5	cyclo-C_6H_{11}	94–95	14
N-Isobutylhexahydrobenzamide	iso-C_4H_9	cyclo-C_6H_{11}	127–128	[g]
N-Cyclopentylacetamide	cyclo-C_5H_9	CH_3	(146–149/ 22 mm.)	[h]
Acetyl-*p*-anisidine	*p*-$CH_3OC_6H_4$[j]	CH_3	127	29

[a] Crystallized from heptane. *Anal.* Calc'd for $C_{10}H_{19}NO$: N, 8.3. Found: N, 8.2. [b] Crystallized from heptane. *Anal.* Calc'd for $C_{10}H_{19}$:NO: N, 8.3. Found: N, 8.2. [c] Crystallized from ether. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.8. [d] Crystallized from benzene. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.7. [e] Crystallized from 87% isopropyl alcohol. *Anal.* Calc'd for $C_{13}H_{23}NO$: N, 6.7. Found: N, 6.8. [f] Crystallized from aqueous methanol. *Anal.* Calc'd for $C_8H_{15}NO$: N, 9.9. Found: N, 10.1. [g] Crystallized from heptane. *Anal.* Calc'd for $C_{11}H_{21}NO$: N, 7.6. Found: N, 7.6. [h] *Anal.* Calc'd for $C_7H_{13}NO$: N, 11.0. Found: N, 10.9. [i] Boiling points are indicated by temperatures enclosed in parentheses. [j] Obtained from commercial sources.

tetrazole from diisobutyl ketone is not typical since it represents the only instance in which a moderate yield of tetrazole was obtained, it illustrates the procedure used in the less successful reactions with acetone and diethyl ketone. Powdered sodium azide (98 g., 1.5 moles) was placed in a 3-l. three-necked flask equipped with a stirrer, a dropping-funnel with outlet below the liquid level, an alcohol thermometer with bulb in the reaction mixture,

TABLE II

1,5-Disubstituted Tetrazoles $R_1N{-}CR_2$ (N, N, N)

TT-no.[c]	R_1	R_2	% Yield	M.p., °C.	Crystals	Solvent	Molecular formula	Analyses					
								Calc'd			Found		
								C	H	N	C	H	N
9 (4)	CH_3	CH_3	24[a]	73–74	Prisms, leaflets	Benzene-ether	$C_3H_6N_4$	36.8	6.1	57.2	37.0	5.9	57.1
020	C_4H_9(iso)	CH_3	46	45–45.5	Prisms	Heptane	$C_6H_{12}N_4$	51.4	8.6	40.0	51.8	8.4	39.7
10	C_4H_9(iso)	C_4H_9(iso)	24[b]	41–43.5	Needles	Ether-petroleum ether	$C_9H_{13}N_4$	59.3	9.9	30.8	59.5	9.9	30.4
21 (30)	C_6H_5	CH_3	39	97.5–99	Needles	Water	$C_8H_8N_4$	60.0	5.0	35.0	60.0	5.1	34.9
27	C_6H_5	C_2H_5	66	49	Prisms	Heptane-ethyl acetate	$C_9H_{10}N_4$	62.1	5.7	32.2	61.9	5.7	32.5
47	C_6H_5	C_4H_9(iso)	67	55–56	Long prisms	Benzene-petroleum ether	$C_{11}H_{14}N_4$	65.3	6.9	27.7	65.2	7.2	27.7
44	C_6H_5	C_6H_{11}(cyclo)	50	99.5–100.5	Prisms	Aqueous methanol	$C_{13}H_{16}N_4$	68.4	7.0	24.6	68.4	7.2	24.3
20 (11)	C_6H_5	C_6H_5	75	144–145	Prisms	Ethyl acetate	$C_{13}H_{10}N_4$	70.3	4.5	25.2	70.3	4.6	25.0
19 (12)	CH_3	C_6H_5	43	104–105	Needles	Water	$C_8H_8N_4$	60.0	5.0	35.0	60.0	5.1	34.9
49	C_2H_5	C_6H_5	30	70–71	Prisms	Ether	$C_9H_{10}N_4$	62.1	5.7	32.2	62.1	5.8	32.0
46	C_4H_9(iso)	C_6H_5	66	51–52	Needles	Benzene-petroleum ether	$C_{11}H_{14}N_4$	65.4	6.9	27.7	65.5	6.7	27.8
48	C_6H_{11}(cyclo)	C_6H_5	37	132–133	Leaflets	Methanol	$C_{13}H_{16}N_4$	68.4	7.0	24.6	68.4	7.2	24.4
79	C_6H_{11}(cyclo)	CH_3	51	124–124.5	Heavy needles	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.7	8.7	33.8
18	C_6H_{11}(cyclo)	C_2H_5	33	112–112.5	Needles	Water	$C_9H_{16}N_4$	60.0	8.9	31.1	59.9	8.6	31.1
067	C_6H_{11}(cyclo)	C_3H_7(*n*)	75	79–80	Needles	Heptane	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.8	9.3	28.9
071	C_6H_{11}(cyclo)	C_3H_7(iso)	61	85–86	Needles	Heptane	$C_{10}H_{18}N_4$	61.9	9.3	28.9	61.8	9.4	28.9
073	C_6H_{11}(cyclo)	C_4H_9(*n*)	25	43.5–45	Coarse prisms	Ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	62.8	9.3	27.1
17	C_6H_{11}(cyclo)	C_4H_9(iso)	27	78.5–79	Needles	Petroleum ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.4	9.5	26.9
5	C_6H_{11}(cyclo)	C_6H_{11}(cyclo)	45	179.5–180	Flat prisms	Isopropyl alcohol	$C_{13}H_{22}N_4$	66.7	9.4	23.9	66.4	9.4	23.9
24	CH_3	C_6H_{11}(cyclo)	26	97–98	Leaflets	Water	$C_8H_{14}N_4$	57.8	8.4	33.7	57.9	8.7	33.7
14	C_2H_5	C_6H_{11}(cyclo)	52	84–86	Needles	Ethyl acetate-pet. ether	$C_9H_{16}N_4$	60.0	8.9	31.1	59.8	8.9	31.2
51	C_4H_9(iso)	C_6H_{11}(cyclo)	25	75–76	Needles	Petroleum ether	$C_{11}H_{20}N_4$	63.5	9.6	26.9	63.2	9.4	26.7
09	C_5H_9(cyclo)	CH_3	69	62–63	Needles	Toluene-heptane	$C_7H_{12}N_4$	55.3	8.0	36.6	55.5	7.9	36.8
0103	$C_6H_{11}CH_2$	CH_3	10	87–88	Needles	Heptane	$C_9H_{16}N_4$	60.0	8.9	31.1	60.1	8.8	31.3
69	*p*-$CH_3OC_6H_4$	CH_3	47	93–94	Needles	25% Isopropyl alcohol	$C_9H_{10}N_4O$	56.8	5.3	29.5	57.2	5.1	29.5
70	*p*-HOC_6H_4	CH_3	59	177–179	Needles	Water	$C_8H_8N_4O$	54.5	4.5	31.8	54.5	4.8	32.0

[a] Yield from acetone only 12%. [b] Prepared from diisobutyl ketone. [c] The compounds have been identified by these code numbers in the publications of Gross and Featherstone (17). Figures in parentheses are references in the present article.

and an outlet tube leading to a trap for the absorption of acidic vapors. The sodium azide was covered with 1200 ml. of ethylene dichloride, and with continuous stirring 882 g. of sulfuric acid was added dropwise at such a rate that the reaction mixture remained below 40°. Occasionally, external cooling with a cold-water bath was necessary. Addition of the acid required about 45 minutes, whereupon 71 g. (0.5 mole) of diisobutyl ketone dissolved in 200 ml. of ethylene dichloride was added at such a rate that the addition could be completed within an hour while the temperature could be kept below 45° with only occasional external cooling. Stirring was continued for two hours after complete addition of the ketone while the temperature dropped slowly to 30°, after which the reaction mixture was allowed to stand overnight at room temperature. The reaction mixture was then diluted with 500 ml. of water, with cooling, and the ethylene dichloride layer was separated. The aqueous layer was neutralized by the portionwise addition of sodium carbonate and the oily material which separated was taken up in ethylene dichloride. The saturated salt solution was decanted from the sodium sulfate that crystallized and was extracted once with ethylene dichloride. The combined ethylene dichloride solutions were dried over sodium sulfate, concentrated to a small volume, and the residual material was fractionated under reduced pressure. Thirty-six grams (46%) of N-isobutylisovaleramide distilled at 134–137° at 10 mm. followed by a small intermediate fraction and 22 g. (24%) of 1,5-diisobutyltetrazole was collected at 166–170° at 8 mm. The latter crystallized on cooling and could be recrystallized from ether-petroleum ether mixtures, separating as needles, m.p. 41-43°.

In addition to the procedure outlined, diisobutyl tetrazole could be prepared in slightly lower yield by the treatment of a benzene solution of diisobutyl ketone and hydrazoic acid with concentrated sulfuric acid. Other techniques such as treatment of an ethylene dichloride solution of the ketone with sodium azide and chlorosulfonic acid, treatment of the ketoxime dissolved in ethylene dichloride with sodium azide and either concentrated sulfuric acid or chlorosulfonic acid, and treatment of a benzene solution of the ketoxime and hydrazoic acid with concentrated sulfuric acid led to N-isobutylisovaleramide as the main product and such small amounts of the tetrazole that they could not readily be separated in pure form from the accompanying amide.

Tetrazoles from amides. The following description of the preparation of 1-cyclohexyl-5-methyltetrazole from N-cyclohexylacetamide is typical of the procedure employed for the synthesis of most of the products listed in Table II. N-Cyclohexylacetamide (100 g., 0.71 mole) was dissolved in 500 ml. of dry benzene in a 2-l. three-necked, round-bottom flask, fitted with a stirrer with a benzene seal, and a reflux condenser surmounted by a calcium-chloride tube. The third opening was connected to a 500-ml. Erlenmeyer flask containing 147 g. (0.71 mole) of phosphorus pentachloride. The benzene solution was stirred and cooled while the phosphorus pentachloride was added portionwise, accompanied by vigorous evolution of hydrogen chloride. When formation of the imide chloride was complete, as evidenced by the disappearance of the phosphorus pentachloride, the Erlenmeyer flask was replaced by a dropping-funnel through which 34 g. (0.79 mole) of hydrazoic acid in benzene solution[6] was added. After the initial vigorous reaction had subsided, the reaction mixture was allowed to stand at room temperature for an hour before it was gradually warmed to the boiling point on a water-bath and maintained at this temperature until hydrogen chloride evolution ceased (about three hours). The solvent was then removed under reduced pressure and the residue was treated with ice and water to decompose any phosphorus oxychloride present. After boiling the crude product under reflux for about an hour with water and cooling in an ice-bath, the 1-cyclohexyl-5-methyl tetrazole was filtered off and recrystallized twice from water, from which it separated as colorless needles, m.p. 124–124.5°; yield, 60 g. (51%).

[6] Solutions of hydrazoic acid in benzene were prepared by treatment of a sludge of sodium azide and water under benzene with concentrated sulfuric acid as suggested by von Braun (31).

SUMMARY

1. Reinvestigation of the Schmidt procedure for the preparation of tetrazoles from aliphatic ketones by interaction with hydrazoic acid in the presence of sulfuric acid failed to confirm the claims of that author. The major product of the reaction is a substituted amide accompanied by only small amounts of the anticipated tetrazoles.

2. It has been shown that the preparation of tetrazoles from N-substituted amides by conversion into the imide chloride and interaction of the latter with hydrazoic acid is not limited to anilides as intimated by von Braun and Rudolph, but may be applied successfully to a great variety of substituted amides including completely aliphatic types. The stability of the imide chlorides is such that they can be prepared successfully in benzene solution.

3. A group of twenty-six 1,5-disubstituted tetrazoles, of which twenty-two have not been previously described, many of them having only aliphatic or cycloaliphatic substituents at the 1 and 5 positions of the tetrazole ring, has been prepared from the appropriately substituted amides.

4. A number of N-substituted amides not previously described have been prepared to serve as intermediates for tetrazole syntheses.

ORANGE, NEW JERSEY

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF E. BILHUBER, INC.]

THE SYNTHESIS OF ALKYLATED PENTAMETHYLENE-TETRAZOLE CARBOXYLIC ACIDS

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In a previous paper the preparation of a series of alkylated pentamethylene-tetrazole derivatives was described (1). Although the parent pentamethylene-tetrazole is very easily soluble in water, the substitution of even a single methyl group on the pentamethylene carbon skeleton caused a profound decrease in water-solubility, while larger alkyl groups and di- or tri-methyl substitution caused almost complete disappearance of water-solubility. Since the pentamethylenetetrazole structure, as a 1,5-dialkylated tetrazole derivative, has an essentially neutral reaction and fails to form stable salts with acids or alkalies, it became desirable to attempt the preparation of such bicyclic structures incorporating a salt-forming group to insure the probability of water-solubility. Furthermore, the possibility existed that some of the polyalkylated structures previously prepared owed their lack of pharmacologic action to their insolubility in water. Although the introduction of a carboxyl group frequently serves to reduce the toxicity of the parent structure, this appeared to be the simplest method of incorporating a salt-forming group in the alkylated pentamethylenetetrazole structure.

Suitable intermediates for the synthesis of the desired structures have recently been prepared in this laboratory and described by Whitmore and Roberts (2), who reported the preparation of the esters of a number of 3,5-dialkyl- and 3,5,5-trialkyl-cyclohexanone-3-carboxylic acids. The synthesis of these esters was based upon Knoevenagel's observation (3, 4) that ring-alkylated derivatives of Δ^2-cyclohexenone readily undergo addition of sodium bisulfite at the carbon-carbon double bond, and that the sulfonic acid group so introduced could be replaced by a cyanide group by interaction with sodium or potassium cyanide. Simultaneous hydrolysis and esterification of the cyanoketones led to esters of the polyalkylcyclohexanone carboxylic acids.

The keto esters so obtained were converted into the corresponding pentamethylenetetrazole derivatives by the procedure outlined previously (1), namely, formation of the oxime and treatment of the latter with sodium azide and chlorosulfonic acid in an inert solvent. Since the oximes were usually liquids that solidified only slowly to give products having a rather broad melting range even after several recrystallizations, attempts to purify the oximes were omitted and the crude intermediates were used directly in the second step of the procedure.

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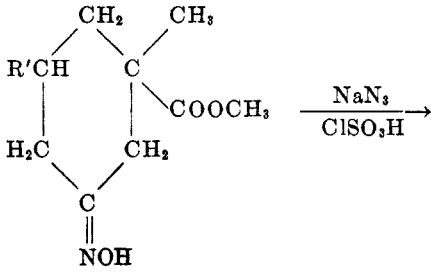
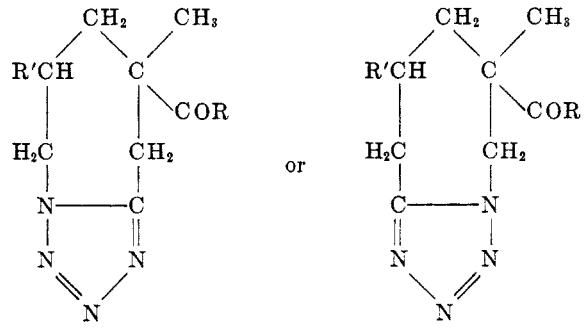
The presence of diastereoisomeric forms could account for the difficulty in purifying the oximes.





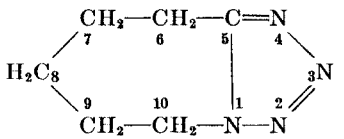
Ia R = OCH_3 Ib R = OCH_3
II R = OH
III R = $N(C_2H_5)_2$; R'H = $(CH_3)_2$

Depending upon the configuration of the individual oximes, the reaction employed in the formation of the tetrazole derivatives could conceivably lead to either of two isomeric structures. The configuration favoring rupture of the bond between C_1 and C_6 of the cyclohexanone ring would form a tetrazole of structure Ia, while the oxime configuration favoring rupture of the bond between C_1 and C_2 would initiate rearrangement and cyclization leading to form Ib. Since no steps were taken to separate the isomeric oximes, it was to be anticipated that mixtures of the configurations I (a and b) might be formed. Although the tetrazole esters appeared to be pure, homogeneous entities, which exhibited constant melting points on recrystallization from several different solvents, the two possible structures could not be distinguished by any simple expedient. For the sake of uniformity the structure Ia has been assigned arbitrarily to all of the new compounds. Employing the same numbering scheme previously suggested for pentamethylenetetrazole derivatives (1), the compounds are methyl esters of 7-methyl-9-alkyl-pentamethylenetetrazole-7-carboxylic acids (Formula Ia), or in the other instance esters of 7-alkyl-9-methyl-pentamethylenetetrazole-9-carboxylic acids.

The free acids were obtained by saponification of the methyl esters with aqueous sodium hydroxide. The yields of acids and the ease with which products of constant melting point were obtained might be considered as further evidence

TABLE I

Pentamethylenetetrazole Carboxylic Acid Derivatives



Code No.[a]	Substituted Pentamethylene Tetrazole[b]	Yield, %	M.P., °C.	Crystals	Solvent	Molecular Formula	Analysis					
							Calc'd			Found		
							C	H	N	C	H	N
TT-8	7,9-Dimethyl-7-carbomethoxy	48	114–115	Prisms	Methanol ether	$C_{10}H_{16}N_4O_2$	53.5	7.1	25.0	53.6	7.0	25.1
TT 54	7,9-Dimethyl-7-carboxy	90	238 (d.)	Small needles	Water	$C_9H_{14}N_4O_2$	51.4	6.7	26.7	51.5	6.6	26.8
TT-63	7-Methyl-9-ethyl-7-carbomethoxy	40	68–69	Needles	Ether-pet. ether	$C_{11}H_{18}N_4O_2$	55.5	7.6	23.5	55.5	7.5	23.7
TT-64	7-Methyl-9-ethyl-7-carboxy	60	161–162	Needles	Water	$C_{10}H_{16}N_4O_2$	53.6	7.1	25.0	53.8	7.1	24.8
TT 59	7-Methyl-9-*n*-propyl-7-carbomethoxy	83	(B.p. 163–165°/1)	—	—	$C_{12}H_{20}N_4O_2$	—	—	—	—	—	—
TT-60	7-Methyl-9-*n*-propyl-7-carboxy	85	174.5–175.5	Prisms	Water	$C_{11}H_{18}N_4O_2$	55.4	7.6	23.5	55.2	7.6	23.4
TT-55	7-Methyl-9-isopropyl-7-carbomethoxy	62	76.5–77.5	Prisms	Ether-pet. ether	$C_{12}H_{20}N_4O_2$	57.1	7.9	22.2	57.2	7.7	22.2
TT-57	7-Methyl-9-isopropyl-7-carboxy	90	201–201.5	Needles	Water	$C_{11}H_{18}N_4O_2$	55.5	7.6	23.5	55.2	7.7	23.1
TT-2	7,9,9-Trimethyl-7-carbomethoxy	43	131–132	Needles	Heptane-benzene	$C_{11}H_{18}N_4O_2$	55.4	7.6	23.5	55.6	7.4	23.6
TT-53	7,9,9-Trimethyl-7-carboxy	75	263–264 (d.)	Leaflets	Water	$C_{10}H_{16}N_4O_2$	53.5	7.1	25.0	53.5	7.0	25.0
TT-56	7,9,9-Trimethyl-7-diethylcarboxamide	67	140–141	Prisms	Water	$C_{14}H_{26}N_6O$	60.2	9.0	25.1	60.2	8.8	25.3

[a] Compounds were identified by these code numbers in the communications of Gross and Featherstone (5). [b] By application of Chemical Abstracts usage the compounds may also be named as 8,6-dialkyl-8-carboxy-6,7,8,9-tetrahydro-5-azepotetrazole derivatives, for example, TT-63 is 8-methyl-6-ethyl-8-carbomethoxy-6,7,8,9-tetrahydro-5-azepotetrazole. Other compounds would be named in an analogous manner.

for the homogeneity of the esters. In one instance the acid was further converted into the diethylamide by way of the acid chloride, which formed readily upon interaction of the acid with thionyl chloride, followed by treatment of the acid chloride with diethylamine. The possibility of isomeric structures is recognized in the arbitrary assignment of formulas for the acids (II) and the diethylamide of 7,9,9-trimethylpentamethylenetetrazole-7-carboxylic acid (III).

Pertinent data regarding the new tetrazole esters and acids are summarized in Table I, where the naming of the compounds as 6,7,8,9-tetrahydro-5-azepotetrazoles according to Chemical Abstracts usage is included.

The pharmacologic actions of these compounds have been described by Gross and Featherstone (5). Neither the esters nor the acids showed profound effects upon rats. Introduction of the carboxyl groups, even in esterified form, markedly decreased the stimulatory action of the compounds on the central nervous system. Toxicity also appeared to be reduced.

EXPERIMENTAL[4]

Methyl 3,5-dialkylcyclohexanone-3-carboxylates. The preparation of the dialkylcyclohexanone carboxylic acid esters used as intermediates was described in an earlier communication by Whitmore and Roberts (2).

Methyl 7,9-dialkylpentamethylenetetrazole-7-carboxylates. The tetrazole esters were prepared by a method analogous to that employed for the synthesis of alkylated pentamethylenetetrazoles (1). The preparation of methyl 7,9-dimethylpentamethylenetetrazole-7-carboxylate may serve as a typical example.

To a solution of 8 g. (0.049 mole) of hydroxylamine sulfate, 3.9 g. (0.098 mole) of sodium hydroxide, and 8 g. (0.098 mole) of anhydrous sodium acetate in 75 ml. of water there was added 16 g. (0.088 mole) of methyl 3,5-dimethylcyclohexanone-3-carboxylate. After thorough shaking at frequent intervals during three hours, the oxime layer was taken up in ether and the aqueous layer was twice extracted with 30-ml. portions of ether. The combined ether solutions were dried over sodium sulfate, and after removal of the solvent, the residual oxime was distilled under reduced pressure. A fraction (13 g., 76%) distilling at 156–158°/11 mm. was collected. The crude oxime was a viscous, colorless liquid. (In some instances the oxime solidified slowly during the preparation and was used in the subsequent step without further purification.)

The conversion of the oxime into the tetrazole was carried out in a good hood. A suspension of 10.8 g. (0.17 mole) of powdered sodium azide in 200 ml. of propylene dichloride (ethylene dichloride may also be used) was prepared in a 1-liter three-necked flask equipped with a stirrer, dropping-funnel, thermometer, and exit tube. An alcohol thermometer is preferable. The bulb of the thermometer and the tip of the dropping-funnel should extend below the surface of the reaction mixture. Provision should be made for the absorption of the hydrogen chloride and hydrazoic acid evolved during the course of the reaction. To the vigorously stirred suspension 116 g. (0.99 mole) of chlorosulfonic acid was added dropwise at such a rate that the temperature of the mixture did not rise above 35°. After complete addition of the chlorosulfonic acid, a solution of 16.5 g. (0.083 mole) of methyl 3,5-dimethylcyclohexanone-3-carboxylate oxime in 25 ml. of propylene dichloride was added with continued vigorous stirring at such a rate that a reaction temperature of 40–45° was maintained. Stirring was continued until the reaction mixture had cooled to room temperature when it was surrounded by an ice-bath, cooled to 5°, and the excess chlorosulfonic acid decomposed by the slow addition of 50 ml. of water taking care that the temperature did not rise above 10°. The propylene dichloride layer was separated

[4] Microanalyses were performed on all compounds by Mr. William Saschek.

from the acid layer and the latter was diluted with 800 ml. of ice and water before extraction with two 250-ml. portions of propylene dichloride. The combined propylene dichloride solutions were washed with 10% potassium carbonate solution and dried over potassium carbonate. After removal of the solvent under reduced pressure on a water-bath, the residue was treated with petroleum ether. On standing, the *7,9-dimethylpentamethylenetetrazole-7-carboxylic acid methyl ester* crystallized and was obtained in the form of colorless, dense prisms on recrystallization from ether-methanol mixtures. Yield, 9 g. (48%); m.p. 114–115°.

The esters of the other dialkyl- and trimethyl-pentamethylenetetrazole carboxylic acids were obtained in an analogous manner. The products are described in Table I where analytical data are also recorded. The 7-methyl-9-*n*-propyl analog failed to crystallize but could be distilled under reduced pressure to effect partial purification. No analyses were carried out on this compound.

7,9-Dialkylpentamethylenetetrazole-7-carboxylic acids. The preparation of 7,9-dimethylpentamethylenetetrazole-7-carboxylic acid is described as typical of the procedure used for the saponification of the esters. A suspension of 9 g. of the methyl ester in 100 ml. of 5% sodium hydroxide was boiled under reflux for 30 minutes during which time the ester dissolved completely. After the hot solution was decolorized with charcoal, it was acidified to Congo Red with hydrochloric acid. On cooling the tetrazole acid crystallized as small, colorless needles. Recrystallization from water gave 8.5 g. (90%) of *7,9-dimethylpentamethylenetetrazole-7-carboxylic acid;* m.p. 238° (d.).

Other acids were prepared in an analogous manner. Analytical data and physical constants of the products are recorded in Table I. All of the acids are moderately soluble in hot water and almost completely insoluble in cold water in which they dissolve readily, however, upon addition of sodium or potassium hydroxide.

7,9,9-Trimethylpentamethylenetetrazole-7-carboxylic acid diethylamide. A suspension of of thionyl chloride in 50 ml. of benzene was boiled under reflux for 2½ hours. Neither the acid nor the acid chloride was completely soluble in benzene, but the character of the solid changed from a light bulky material to a rather dense, heavy, granular product. The benzene and excess thionyl chloride were removed under reduced pressure; then the crude acid chloride was suspended in 50 ml. of dry benzene and treated with an excess of diethylamine. After the suspension had been heated on a water-bath for an hour and allowed to stand at room temperature for 24 hours, the diethylamide was separated from the accompanying diethylammonium chloride by extraction with hot benzene. After recrystallization from water, 9.5 g. of pure diethylamide, melting at 140–141° was obtained. Analytical data are recorded in Table I.

SUMMARY

The preparation of the methyl esters of five di- and tri-alkylpentamethylenetetrazole carboxylic acids and the corresponding free acids has been described. In one instance the diethylamide of the acid was prepared. None of the compounds exhibited marked pharmacologic activity. Evidenty the introduction of the carboxyl group, although it permits the formation of water-soluble salts, severely reduces the activity of the resulting products.

ORANGE, NEW JERSEY

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES, SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

SYNTHESIS OF TETRAHYDROISOQUINOLINE DERIVATIVES

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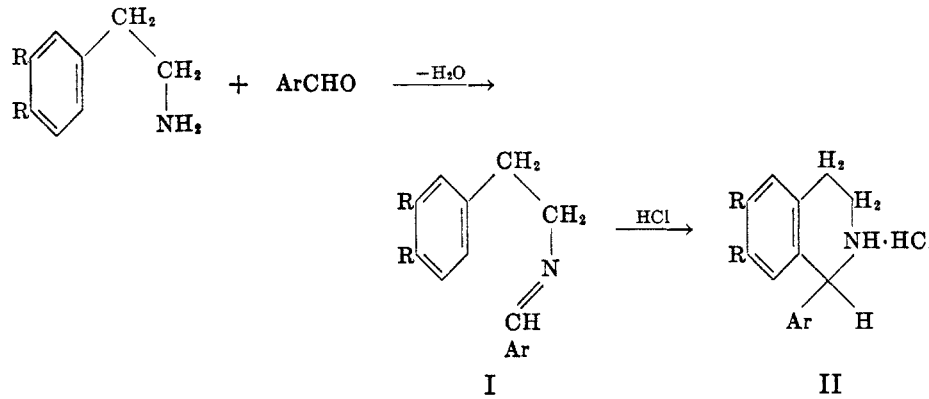
The facility with which β-arethylamines condense with most aldehydes to give the alkylidene derivative (Schiff base) and the cyclization of the resulting Schiff bases into tetrahydroisoquinolines by acidic catalysts led Decker and Becker (1) to synthesize a number of alkaloids of the hydrastinine group:



I II

The intermediate Schiff bases (I) were cyclized to the corresponding tetrahydroisoquinoline (II) by a variety of condensing agents—anhydrous hydrogen chloride, phosphorus oxychloride, zinc chloride, thionyl chloride, and hydrogen bromide (2). Buck (3) prepared a number of tetrahydroisoquinoline hydrochlorides, using formaldehyde, by direct cyclization of the intermediate Schiff base without isolating it. An extension of these earlier studies appears attractive because of the availability of new intermediates which will increase the range of products for pharmacological evaluation.

Table I summarizes the data of the products resulting from the reaction of two β-arethylamines and various aromatic aldehydes. The ease and high degree of purity with which these compounds formed simplified their isolation before the subsequent cyclization reaction.

Biosyntheses of isoquinolines. Schöpf and Bayerle (4) have postulated that isoquinolines can be synthesized under physiological conditions of concentration of reactants, temperature, and *p*H provided that the phenethylamine is activated by a free hydroxyl in the 3-position. This postulate was doubted by Hahn and Schales (5) but their conclusions were shown to be erroneous by Späth, Kuffner, and Kesztler (6). Our own results paralleled those of Späth (6) since, in our hands, homopiperonylamine failed to condense with benzaldehyde at *p*H 5 after standing for 8 days at 25°.

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It soon became apparent that previously described methods for the cyclization of the Schiff base are not always so dependable or facile as indicated. For example, if the group *para* to the point of ring-closure is hydrogen or unsubstituted phenyl, or if *o*-substituted phenyl or *m*, *p*-dialkoxyphenyl, the cylization proceeds less readily, and hydrolysis of the intermediate rather than cyclization has been observed. After a study of the experimental conditions which promote ring-closure in optimum yields, three variations of a general method were evolved. Method I utilized anhydrous hydrogen chloride, Method II used aqueous hydrogen chloride, and Method III utilized ethanolic hydrogen chloride. Table II presents the data on the substituted tetrahydroisoquinoline hydrochlorides.

TABLE I

SCHIFF BASES OF HOMOVERATRYLAMINE

SUBSTITUTED BENZALDEHYDES	APPEARANCE	M.P., °C.	YIELD, %	FORMULA	N	
					Calc'd	Found.[c]
3,4-Diethoxy	Colorless flakes	75–75.5	98	$C_{21}H_{27}NO_4$	3.92	4.14
4-Methoxy	Colorless plates	62	82	$C_{18}H_{21}NO_3$	4.68	4.90
2-Hydroxy	Bright yellow needles	74–74.5	90	$C_{17}H_{19}NO_3$	4.91	5.10
3-Methoxy-4-hydroxy[a]	Orange, bulky plates	120	88	$C_{18}H_{21}NO_4$	4.44	4.50
2-Chloro	Colorless plates	70–70.5	86	$C_{17}H_{18}ClNO_2$	4.61	4.93
3-Nitro	Tiny, felted, white needles	98	83	$C_{17}H_{18}N_2O_4$	8.91	9.03
4-Hydroxy	Light buff plates	161–161.5	87	$C_{18}H_{21}NO_3$	4.91	5.05
2-Hydroxy-5-chloro	Scintillating, yellow platelets	69	98	$C_{17}H_{18}ClNO_3$	4.38	4.29
SCHIFF BASES OF HOMOPIPERONYLAMINE						
3,4-Diethoxy	Lemon-yellow fluffy needles	71–72	85	$C_{20}H_{23}NO_4$	4.10	4.06
Cinnamaldehyde	Snow-white fluffy platelets	64–64.5[b]	86	$C_{18}H_{17}NO_2$	5.02	5.13

[a] Recrystallized from isopropanol. [b] Ref. (1) gives m.p. 61–63°. [c] Microanalyses by Oakwold Laboratories, Alexandria, Virginia.

EXPERIMENTAL

Amines. After exploring rather extensively several of the numerous syntheses of β-phenethylamines described in the literature (7, 8, 9, 10, 11), the following method was selected for the preparation of homoveratrylamine and homopiperonylamine: mandelonitrile acetates were prepared according to Albert (12); these were catalytically reduced to the corresponding β-arethylamines as by Kindler (13). The most effective catalyst was obtained by employing a mixture of recovered palladium and platinum chlorides, depositing the metals on charcoal in the presence of sodium acetate (14). The hydrogenations were carried out in the usual Burgess-Parr apparatus.

Preparation of Schiff bases. The aldehydes were freshly distilled *in vacuo*, or, if solid, were recrystallized, before use in the condensation. The β-phenethylamines were also redistilled (*in vacuo*) immediately prior to the condensation reaction; these amines must be carefully protected from the atmosphere as they easily form carbonates.

Method A (for liquid aldehydes): The aldehyde (0.03 mole) was added to 0.03 mole of the amine. Heat was evolved and a yellow to orange color developed. The mixture was stirred manually until it became viscous and finally set into a hard, dry mass, accompanied by the evolution of heat. Heating on a water-bath was not necessary (with freshly

TABLE II

1-PHENYLTETRAHYDROISOQUINOLINE HYDROCHLORIDES

1-PHENYLTETRAHYDROISOQUINOLINE DERIVATIVE	PREPN. METHOD	APPEARANCE	M.P., °C.	YIELD, %	FORMULA	Cl[g]	
						Calc'd	Found
6,7-Dimethoxy-3′,4′-diethoxy	II[a]	Fluffy white needles	222–223	81	$C_{21}H_{28}ClNO_4$	9.00	9.03
4′,6,7-Trimethoxy	I[b]	White, felted needles	151–152	75	$C_{18}H_{22}ClNO_3$	10.56	10.51
6,7-Dimethoxy-2′-hydroxy	II[c]	White, tiny needles	242	78	$C_{17}H_{20}ClNO_3$	11.02	10.80
6,7-Dimethoxy-2′-hydroxy-5′-chloro	II[d]	White platelets	258–260	68	$C_{17}H_{19}Cl_2NO_3$	9.95	10.21
6,7-Dimethoxy-2′-chloro	II[e]	White plates	210–212	74	$C_{17}H_{19}Cl_2NO_2$	10.42	10.24
6,7-Dimethoxy-4′-hydroxy	III[f]	Druse of white needles	237	83	$C_{17}H_{20}ClNO_3$	11.02	10.89
6,7-Dimethoxy-3′-nitro	II	White plates	253–254	80	$C_{17}H_{19}ClN_2O_4$	10.12	9.89

[a] Method I gave homoveratrylamine hydrochloride. Method III gave negligible yields of the isoquinoline. [b] Method II caused hydrolysis instead of cyclization. Method III gave a 20% yield of the isoquinoline. [c] Method I yielded the Schiff base hydrochloride. Method III gave a 35% yield of the isoquinoline. [d] Method I gave a negligible yield and Method III gave a 34% yield of the isoquinoline. [e] Method I gave a gummy, unidentified product. Method III caused hydrolysis instead of cyclization. [f] Method II gave a 75% yield of the isoquinoline. Method I gave a gummy, unidentified product. [g] Volhard analysis.

distilled reactants) to complete the reaction. The products were recrystallized from dilute ethanol, usually in quantitative yields.

Method B (for solid aldehydes): The aldehyde (0.03 mole) was dissolved in 30 ml. of commercial absolute ethanol (in some instances more ethanol and a gentle warming was required for complete solution). To this alcoholic solution, 0.03 mole of the amine was added, accompanied by the development of color. After gentle heating on a water-bath to drive off most of the alcohol, the mixture was set aside to cool. On cooling, the entire mixture set to a druse of crystals. The product was recrystallized from dilute ethanol.

Cyclization of the Schiff bases. Numerous attempts to effect cyclization (including variations of solvent and temperature) with condensing agents such as boron trifluoride and

thionyl chloride were without success. Hydrogen chloride was the agent of choice and three methods for its use were developed.

Method I: In a 200-ml., three-necked flask, equipped with stirrer, drying-tube, and a glass tube which ended 2 cm. above the surface of the reaction mixture, was placed a solution of 0.02 mole of the Schiff base in 25 ml. of anhydrous benzene. During vigorous stirring of the solution, anhydrous hydrogen chloride was blown over the surface of the reaction mixture. Separation of a yellow precipitate (Schiff base hydrochloride) immediately ensued. After the reaction flask was saturated with hydrogen chloride, the flow of the gas was stopped; upon gentle heating the yellow color disappeared (indicative of cyclization) and the clear solution was allowed to cool in a refrigerator. The precipitated isoquinoline hydrochloride was recrystallized from anhydrous alcohol-ether.

Method II: In a 200-ml., three-necked flask, fitted with a stirrer and reflux condenser, was placed 0.03 mole of the Schiff base and during vigorous stirring, 40-ml. of 24% hydrochloric acid was added. The flask was heated on a water-bath and stirring was continued for 40–60 minutes. If, after cooling, the product separated it was collected and recrystallized. Frequently the product did not separate upon cooling; if this occurred, the reaction mixture was evaporated to dryness *in vacuo*, and the residue was dissolved in the minimum amount of hot absolute ethanol, cooled, and anhydrous ether added to initiate precipitation of the isoquinoline hydrochloride.

Method III: To a solution of 0.02 mole of the Schiff base and 20-ml. of 95% ethanol was added 25-ml. of a saturated ether solution of hydrogen chloride and the whole was concentrated to approximately one-eighth its volume on a water-bath. After cooling, anhydrous ether was added to initiate precipitation. The tetrahydroisoquinoline hydrochloride was recrystallized from anhydrous alcohol-ether.

The hydrochlorides are white and well-crystallized. They are soluble in water, moderately soluble in alcohol, and sparingly soluble in ethyl acetate. They are insoluble in anhydrous ether.

SUMMARY

A study is reported of the synthesis of 1-phenyltetrahydroisoquinoline hydrochlorides *via* the formation and isolation of Schiff bases, from substituted β-arethylamines and aromatic aldehydes, and of their subsequent cyclization.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE STATE UNIVERSITY OF IOWA]

THE PREPARATION OF TIGLIC AND ANGELIC ACIDS AND ESTERS[1]

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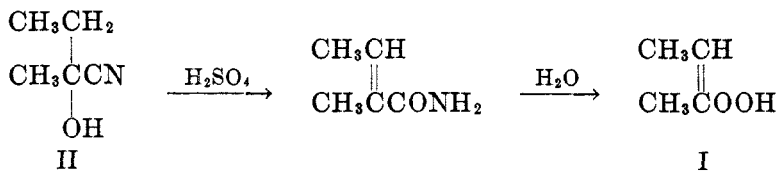
The methods of preparation most commonly applied to the synthesis of the isomeric α,β-dimethylacrylic acids, tiglic (I) and angelic (II) acids, involve the elimination of water from α-hydroxy-α-methylbutyric acid (1, 2, 3) or the elimination of acetic acid from β-acetoxy-α-methylbutyric acid (4). These methods were investigated but were found to be relatively unsatisfactory because of difficulties in separating the isomeric acids and because of low yields. It was desirable, therefore, to develop methods of preparation in which the acids could be isolated in the pure state in relatively high yields.

It was found that pure tiglic acid, the stable isomer, could be prepared in relatively large amounts by the action of 100% sulfuric acid on α-hydroxy-α-methylbutyronitrile (III) followed by hydrolysis to tiglic acid (I). This procedure is analogous to that used for the preparation of methacrylic acid and its derivatives (5, 6). The resulting tiglic acid (m.p. 61–64°) was easily isolated by steam-distillation from the reaction mixture. Yields of 40–53% based on 2-butanone were obtained in experiments involving 10 moles of ketone. If the acid was prepared by this method from α-hydroxy-α-methylbutyronitrile free of appreciable amounts of unchanged ketone, it was not contaminated with angelic acid. In some preparations of tiglic acid where unchanged ketone was present in the cyanohydrin large amounts of oily mixture were isolated along with lowered yields of tiglic acid. Tiglic acid and a small amount of angelic acid were isolated with some difficulty from one such oily mixture.

Tiglic acid (I) was converted by a three-step process to its labile isomer, angelic acid (II) in 33% yield. The addition of bromine to tiglic acid gave an 86% yield of α,β-dibromo-α-methylbutyric acid (IV) (7, 8), which in turn was treated with 25% methanolic potassium hydroxide to yield (62.5%) β-bromoangelic acid (V) (9). Reduction of the bromo acid with 9% sodium amalgam in water gave 61% yield of angelic acid (m.p. 44–46°) (10, 11). This synthesis represents an improvement over the methods reported in the literature. The angelic acid obtained was uncontaminated by tiglic acid and thus was easily purified.



II I

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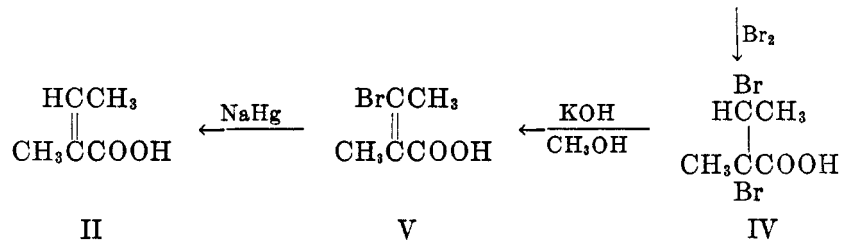

II V IV

The methyl and ethyl esters of tiglic acid were prepared most conveniently by direct esterification of the acid. The dehydration of ethyl α-hydroxy-α-methylbutyrate (12) was relatively unsatisfactory for the synthesis of ethyl tiglate. Complex mixtures, which presumably contained all the possible dehydration products as well as the starting material, were obtained. These mixtures could be separated only by careful fractionation to give ethyl tiglate in relatively low yields and of questionable purity.

Methyl angelate was prepared in 70% yield by the reaction of potassium angelate with methyl iodide as reported by Naster and Gavriloff (3). The identity of the product was established by saponification to angelic acid. One sample of the oily by-product (known to contain angelic acid) from the synthesis of tiglic acid was esterified with ethyl alcohol. The mixture of esters was fractionated carefully. The product with properties identifying it as ethyl angelate (13) yielded very impure tiglic acid when saponified. Thus, it is not possible to guarantee the identity and purity of these esters on the basis of physical properties alone.

EXPERIMENTAL

Tiglic acid (I). A mixture of 720 g. (894 ml., 10 moles) of 2-butanone and 10 ml. of a saturated aqueous solution of potassium cyanide was warmed to 30–35°, and 310 g. (11.5 moles) of anhydrous hydrogen cyanide was distilled into the mixture. The reaction was exothermic and frequently the temperature rose to 60–80° during the addition. After the reaction was complete the solution was cooled to 0° and the potassium cyanide was neutralized with a slight excess (about 10 ml.) of concentrated sulfuric acid so that the decomposition of the cyanohydrin would be suppressed.

This crude α-hydroxy-α-methylbutyronitrile was added slowly to 1470 g. (15 moles) of 100% sulfuric acid (m.p. 10.5°) maintained at 75–80°. The reaction was exothermic and required rapid stirring. The resulting mixture was usually orange-red. The mixture was heated to 125–130° for one hour while being rapidly stirred. Any foaming and blackening observed during this heating signified a lower yield of tiglic acid and the production of an oily mixture as a by-product. The reaction mixture was boiled under reflux for two hours after 720 ml. (40 moles) of water was added. To the solution 500 g. of anhydrous sodium sulfate was added, and the mixture was distilled with steam. The distillate was collected in a receiver cooled in an ice-bath. The solid tiglic acid was collected to give a 400–525-g. (40–53%) yield of product, m.p. 62–64°.

In one experiment 168 g. of the oily by-product was obtained along with 316 g. of tiglic acid. Two fractional distillations of the oil yielded 38 g. of tiglic acid, b.p. 95–97° (12 mm.) and 129 g. of an oil, b.p. 88–95° (12 mm.) from which 11.0 g. of angelic acid, m.p. 42–45°, crystallized. Thus, a 35% yield of tiglic acid and a 1.1% yield of angelic acid were obtained.

In another experiment 295 g. of crude tiglic acid and 249 g. of oily by-product were

obtained. The by-product was esterified as described for the synthesis of ethyl tiglate. Fractionation yielded 60 ml. of ethyl tiglate, b.p. 152–154°, n_D^{20} 1.4340, and 73 g. of ester, b.p. 140–144°, n_D^{20} 1.4284, d_4^{20} 0.916. This latter product has the reported properties of ethyl angelate (13). Saponification of 72 g. (0.56 mole) of this ester yielded 35 g. (63%) of crude tiglic acid, m.p. 48–60°.

α-Hydroxy-α-methylbutyronitrile (III). To a mixture of 886 g. (1101 ml., 12.3 moles) of 2-butanone and a solution of 500 g. (9.7 moles) of sodium cyanide in 1200 ml. of water was added slowly 2100 ml. (8.5 moles) of 40% sulfuric acid. After the addition the organic layer was separated from the aqueous layer which was extracted with ether. The ether solution of cyanohydrin was dried over sodium sulfate and distilled under reduced pressure. An 878-g. yield (72%) of the cyanohydrin, b.p. 92–93° (20 mm.), was obtained. This method is similar to that used in the synthesis of acetone cyanohydrin (14). α-Hydroxy-α-methylbutyronitrile was also prepared in 70% yield by the action of a sodium cyanide-sodium bisulfite mixture on 2-butanone (2).

The pure cyanohydrin could be used in the synthesis of tiglic acid, but the yields were no better than those obtained directly from the ketone.

α,β-Dibromo-α-methylbutyric acid (IV). A mixture of 100 g. (1.0 mole) of tiglic acid in 200 ml. of anhydrous carbon tetrachloride and 160 g. (1.0 mole) of bromine was allowed to stand overnight and was then boiled under reflux until the solution was light orange. The solvent was removed by evaporation and the solid residue was crystallized from ligroin to yield 222 g. (86%) of α,β-dibromo-α-methylbutyric acid, m.p. 82–88°.

β-Bromoangelic acid (V). To a solution of 130 g. (0.50 mole) of α,β-dibromo-α-methylbutyric acid in 70 ml. of methanol was added slowly 700 g. of a 25% solution of potassium hydroxide in methanol. Anhydrous potassium carbonate (13 g.) was added to suppress decarboxylation. The temperature of the reaction mixture was raised to 55° where it was held for two hours. Excess potassium hydroxide was removed by bubbling carbon dioxide through the reaction mixture. The mixture was filtered while warm and the filtered salt was washed with 500 ml. of warm methanol. The methanol solutions were combined and most of the solvent removed by distillation. The residue was evaporated to dryness, dissolved in 100 ml. of water, and acidified to Congo Red with 6 *N* hydrochloric acid. The product was filtered, dried, and crystallized from ligroin to yield 56.4 g. (62.5%) of β-bromoangelic acid, m.p. 92–94.5°.

Angelic acid (II). To a mixture of 18 g. (0.1 mole) of β-bromoangelic acid in 135 ml. of water cooled to 5° was added in small pieces 396 g. (1.57 gram-atoms of sodium) of 9% sodium amalgam. The mixture was stirred slowly for 48 hours. The aqueous layer was separated from the mercury which was washed with 10 ml. of water. The combined aqueous solutions were acidified to Congo Red with concentrated hydrochloric acid. The precipitated product was dried, and crystallized from ligroin to yield 6.1 g. (61%) of angelic acid, m.p. 44–46°.

Ethyl tiglate. A mixture of 50 g. (0.50 mole) of tiglic acid, 92 g. (2 moles) of absolute ethanol, 234 g. of benzene, and 10 ml. of concentrated sulfuric acid was boiled for 24 hours under reflux in a Soxhlet extraction apparatus. The Soxhlet thimble contained 50 g. of calcium carbide. Excess alcohol and benzene were removed by distillation. The residue was treated with an equal volume of water and the organic product was extracted with ether. The ether extract was washed with 10% sodium bicarbonate and dried over sodium sulfate. Fractional distillation yielded 47–52 g. (74–80%) of ethyl tiglate, b.p. 153–156° (760 mm.), n_D^{20} 1.4347, d_4^{20} 0.9226. These properties check those found by von Auwers (13). This general method of esterification is that of Thielepape (15).

Dehydration of ethyl α-hydroxy-α-methylbutyrate. A sample of 150 g. (1.03 moles) of ethyl α-hydroxy-α-methylbutyrate[2] was treated with 90 g. (0.66 mole) of phosphorus trichloride at 5° according to the method of Higginbotham and Lapworth (12). After two fractional distillations 63 g. (48%) of ethyl tiglate, b.p. 71–75° (40 mm.), n_D^{20} 1.4329 was obtained.

[2] This compound was kindly supplied by Rohm and Haas Co. Philadelphia, Pa.

The saponification of 10 g. (0.078 mole) of this ester yielded 2.0 g. (26%) of tiglic acid, m.p. 63–64°.

Similar dehydrations of ethyl α-hydroxy-α-methylbutyrate with chlorosulfonic acid, phosphorus pentoxide, phosphorus oxychloride, and thionyl chloride gave much lower yields of impure ethyl tiglate along with unidentified fractions.

Methyl tiglate. A mixture of 100 g. (1 mole) of tiglic acid, 256 g. (8 moles) of methanol, and 20 ml. of concentrated sulfuric acid was boiled under reflux for 12 hours. The ester was isolated in a manner similar to that used for ethyl tiglate. A 74.2-g. (65%) yield of methyl tiglate, b.p. 137.5–138.8° (757 mm.), n_D^{20} 1.4371, was obtained. These properties check those in the literature (3).

Methyl tiglate was also prepared by the addition of 2 l. (50 moles) of methanol and 90 ml. (5 moles) of water instead of 720 ml. of water to the cyanohydrin-sulfuric acid mixture obtained during a 10-mole preparation of tiglic acid. The methanol solution was boiled under reflux for 24 hours. All the volatile material was distilled and methyl tiglate was separated from the distillate. More crude methyl tiglate was obtained from the residue on dilution with water. Fractionation yielded 470 g. (41% based on 2-butanone) of methyl tiglate, b.p. 138–140° (760 mm.), n_D^{20} 1.4351. Saponification of 2.0 g. (0.018 mole) of this methyl tiglate yielded 1.5 g. (83%) of tiglic acid, m.p. 61–63°.

Methyl angelate. A mixture of 10.0 g. (0.10 mole) of angelic acid, 8.0 g. (0.058 mole) of anhydrous potassium carbonate, and 150 ml. of methanol was heated until the vigorous effervescence subsided. The solution was cooled somewhat and 12 ml. (21.4 g., 0.15 mole) of methyl iodide was added. The mixture was boiled gently under reflux for 28 hours, and carefully distilled until 100 ml. of methanol had been removed. Two ml. of methyl iodide was added to the residue which was heated gently for one hour. The solution was then treated with 100 ml. of water, and the ester layer was separated. The water layer was extracted with ether. The combined ether and ester solution was washed with 2% aqueous sodium bisulfite and then with a dilute silver nitrate solution. After the silver nitrate solution had been thoroughly shaken with the ether solution to remove all of the iodide ion, an excess of sodium chloride was added. The ether solution was dried over potassium carbonate and fractionally distilled. A 7.2-g. (63%) yield of methyl angelate, b.p. 127.2–128.0° (745 mm.), n_D^{20} 1.4330, d_4^{20} 0.933, was obtained. The hold-up of the fractionating column was 0.8 g. (7%). There was no residue. The properties of the methyl angelate check those reported (3).

A 2.0-g. (0.018 mole) sample of methyl angelate was dissolved in 10 ml. of methanol, and 2.0 ml. of 40% aqueous sodium hydroxide was added. The solution was allowed to stand at room temperature overnight, and then to evaporate to dryness. About 10 ml. of water was added, and the mixture was acidified to Congo Red with concentrated hydrochloric acid. A 1.4-g. (80%) yield of angelic acid, m.p. 42–44° was isolated by filtration and ether-extraction of the filtrate.

SUMMARY

1. Tiglic acid free of isomeric acids has been synthesized in 40–53% yields from 10 moles of 2-butanone. Angelic acid free of appreciable amounts of isomeric acids has been synthesized from tiglic acid in 33% yield by a three-step process.

2. Pure methyl and ethyl tiglate have been prepared by direct esterification of tiglic acid. Methyl angelate of confirmed identity has been prepared by a replacement reaction of angelate ion with methyl iodide.

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THE PREPARATION OF MANNICH BASES RELATED TO GRAMINE

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Recent interest in the chemistry of Mannich bases derivable from indole (1, 2) and its derivatives (3, 4) prompts us to report on work done in this field some years ago. At that time it was deemed desirable to add the indole nucleus to the list of basically substituted heterocyclic systems under investigation as potential antimalarials.

The compounds studied were all tertiary amines prepared from indole, 2-methylindole, or ethyl indole-2-carboxylate by treatment with formaldehyde and a secondary amine in glacial acetic acid solution. This procedure was the same as that used by Kuhn and Stein (5) and Supniewski and Serafin-Gajewski (6) in the preparation of gramine and 2-methylgramine respectively.

Indole and 2-methylindole were reactive enough to require the cooling of their reaction mixtures to avoid the formation of insoluble polymeric gums. However the electronegativity of the carbethoxyl group sufficiently lowered the reactivity of the indole nucleus to allow heating the reaction mixtures during the preparation of derivatives of 2-carbethoxyindole.

EXPERIMENTAL

A. Materials. Save as otherwise described below all starting materials were commercial products.

Ethyl indole-2-carboxylate. *o*-Nitrophenylpyruvic acid was prepared by the condensation of ethyl oxalate and *o*-nitrotoluene according to the method of DiCarlo (7). Reduction of this material with sodium hydrosulfite gave indole-2-carboxylic acid as described by Cornforth and Robinson (8). Refluxing the acid in ethanol solution for several hours gave a 90% yield of crystalline (m.p. 119–120°) ethyl indole-2-carboxylate after cooling the mixture.

1-Diethylamino-4-n-propylaminopentane. Over a period of two hours 24 g. of propionaldehyde was added dropwise with stirring to 64 g. of Noval diamine (1-diethylamino-4-aminopentane) kept at 0° in an ice-salt bath. A small amount of solid potassium hydroxide was added to the clear solution, and after standing for one hour the aqueous layer was removed. The organic layer was dried over crushed potassium hydroxide in the refrigerator overnight. The dried aldimine was distilled from fresh pellets of alkali, b.p. 124–128°/34–35 mm. The freshly distilled, colorless Schiff base was dissolved in 100 cc. of ethanol and reduced with hydrogen at a pressure of 3 atm. over a 5% palladium-charcoal catalyst. After removing the ethanol *in vacuo* the product was distilled; yield, 54.4 g. (68%), b.p. 128–135°/30–32 mm. Before being used the product was redistilled at atmospheric pressure, b.p. 234–236°.

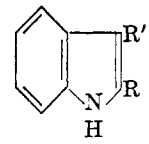
When dry hydrogen chloride gas was bubbled through a solution of this diamine in dry ether a solid *dihydrochloride* precipitated. After recrystallization from ethanol and isopropyl alcohol the slightly hygroscopic white crystals melted at 219.5–220.5°.

Anal. Calc'd for $C_{12}H_{30}Cl_2N_2$: N, 10.27; Found: N, 10.14.

B. The Mannich bases. A solution of the indole compound in glacial acetic acid (about 5 cc./0.01 mole) was treated with a slight excess (about 10% over the equimolecular quantity) of a secondary amine and then with 37% aqueous formaldehyde solution. In those cases where the reaction mixture was initially homogeneous, *i.e.* when indole (I) or 2-methylindole (II) was used, considerable heat was evolved and external cooling was applied. With 2-carbethoxyindole (III), insoluble in the reaction mixture described here, the mix-

CHART I

COMPOUNDS PREPARED



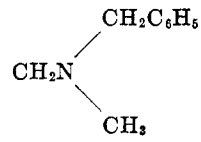
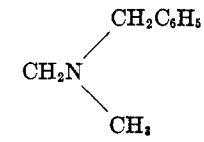
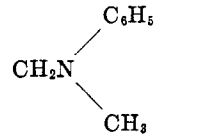
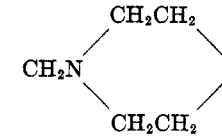
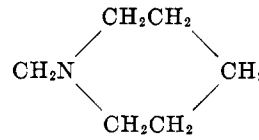
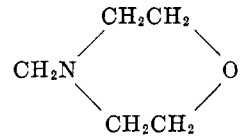
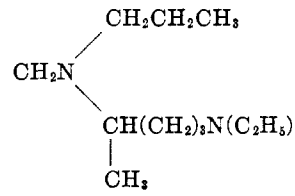
	R	R′		R	R′
I	H		VII	$COOC_2H_5$	
II	H		VIII	$COOC_2H_5$	
III	H	$CH_2N(CH_2CH{=}CH_2)_2$	IX	$COOC_2H_5$	$CH_2N(CH_2CH{=}CH_2)_2$
IV	CH_3		X	$COOC_2H_5$	$CH_2N(CH_2CH_2CH_3)_2$
V	CH_3		XI	$COOC_2H_5$	$CH_2N(CH_2CH_2OH)_2$
VI	$COOC_2H_5$		XII	$COOC_2H_5$	$CH_2N(CH_3)_2$

TABLE I

MANNICH BASES RELATED TO GRAMINE

COMPOUND NUMBER	EMPIRICAL FORMULA	M.P., °C.	YIELD, %	ANALYSIS N	
				Calc'd	Found
I	$C_{17}H_{18}N_2$	114	90	11.19	11.43, 10.95
II	$C_{16}H_{16}N_2$	126–127	7	11.86	11.97
III	$C_{15}H_{18}N_2$	77.5–78	60	12.38	12.47
IV	$C_{18}H_{20}N_2$	156–157	79	12.27	12.36
V	$C_{14}H_{18}N_2O$	175–176	92	12.17	12.37
VI	$C_{24}H_{39}N_3O_2$	78–79	80	10.47	10.19
VII	$C_{20}H_{22}N_2O_2$	104–105	93	8.69	8.77
VIII	$C_{16}H_{20}N_2O_2$	152–153	94	10.29	10.53
IX	$C_{18}H_{22}N_2O_2$	100–101	88	9.39	9.59
X	$C_{18}H_{26}N_2O_2$	78–79	94	9.26	9.46
XI	$C_{16}H_{22}N_2O_4$	105–107	70	9.15	9.31
XII	$C_{14}H_{18}N_2O_2$	86–87	83	11.38	11.28

ture was heated on the steam-bath for several hours until complete solution was attained. After dilution with an excess of water and removal of non-basic material by extraction with ether the solution was made basic with an excess of aqueous alkali. The precipitated product was then collected by filtration or extraction with ether and purified by crystallization from a suitable solvent. A summary of the properties of the compounds prepared in this manner is given in the accompanying table.

SUMMARY

A series of compounds resembling gramine have been prepared by the use of the Mannich reaction. The reagents employed were indole, 2-methylindole or 2-carbethoxyindole, formaldehyde, and various secondary amines.

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[CONTRIBUTION NO. 192 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. VIII. ENZYMATIC RESOLUTION OF RACEMIC β-2-THIENYLALANINE AND PREPARATION OF SOME SUBSTITUTED β-2-THIENYLALANINES[1]

BERNARD F. CROWE[2] AND F. F. NORD

Received January 16, 1950

Previous studies in this laboratory have demonstrated the applicability of the N-methylformanilide (1) and rhodanine (2) syntheses to reactions in the thiophene series. Among the compounds made available through these investigations was the amino acid analog of phenylalanine, *viz.*, β-2-thienylalanine, which has proved to be of interest in growth inhibition experiments both on microorganisms (3) and on the rat (4). Since different effects were noted in these metabolism studies with the racemic amino acid and its optical isomers, it was decided to use an enzymatic method (4a) for its resolution thus obviating the more tedious chemical resolution previously applied (3). For this purpose a carboxypeptidase preparation (5) was utilized because of its effectiveness in asymmetrically hydrolyzing chloroacetylphenylalanine (6). This investigation indicated some major differences between thienyl- and phenyl-alanine. It was found that while the enzyme did not attack chloroacetyl-D-thienylalanine, it completely hydrolyzed the L-isomer but only in the presence of a buffer. However no buffer was required for the enzymatic hydrolysis of chloroacetyl-L-phenylalanine (6). It was also noted that the chloroacetylated thienyl enantiomorphs were susceptible to racemization when hydrolyzed with 2 *N* HCl, followed by three successive evaporations to dryness. Substitution of 1 *N* HBr for 2 *N* HCl with one evaporation produced optically-pure amino acids. The results from the two methods are compared in more detail in the experimental section.

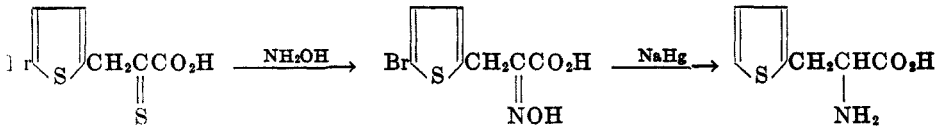
In view of the biological importance of β-2-thienylalanine the alkyl- and halogen-substituted thienylthiopyruvic acids, reported previously (2), were further reacted to obtain their corresponding thienyl amino acids. The preparation of the alkyl-substituted amino acids proceeded readily like that of the first member of the series, but the halogen-substituted acids presented some unforeseen results. When the 5-bromothienyloximino acid was reduced with 2% sodium amalgam, hydrogenolysis occurred yielding β-2-thienylalanine instead of the expected β-(5-bromo-2-thienyl)alanine (Chart I). This was proved conclusively by the analysis and melting point of the amino acid isolated and from the melting point of its phenylurea derivative. Prior investigations have demonstrated the removal of bromine from the thiophene ring with hydrogen in the presence of palladium on charcoal (7, 8).

[1] For Papers VI and VII of this series see *J. Org. Chem.*, **15**, 81, 89 (1950). This investigation was carried out under the auspices of the Office of Naval Research. For a preliminary communication see *Arch. Biochem.*, **25**, 460 (1950). The analyses were carried out by Dr. F. Bühler and A. A. Sirotenko of this Department.

[2] Abridged from a part of the dissertation presented to the Graduate School of Fordham University, 1950, in partial fulfillment of the requirements of the degree of Doctor of Philosophy.

The preparation of β-(5-chloro-2-thienyl)alanine was achieved in lower yields than the alkyl-substituted products and under anomalous conditions. In the other cases cited above, the free amino acid precipitated from solution after the reaction mixture had been cooled. The chloro compound failed to precipitate even after standing for one week in a refrigerator. However when the solution was diluted with water to twice the original volume and chilled, the amino acid

CHART I



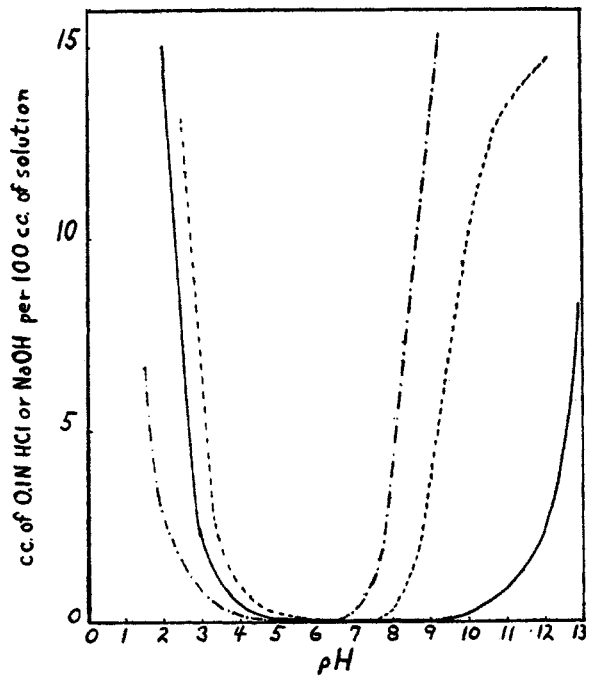


FIGURE 1. TITRATION CURVES OF β-2-THIENYLALANINE AND β-(5-CHLORO-2-THIENYL)-ALANINE. Water blank ————; β-2-Thienylalanine - - - -; β-(5-Chloro-2-thienyl)-alanine —·—·—·.

appeared. It may be noted that since small additions of lactic acid were used to keep the reduction media acidic, the *p*H of the solution at the end of the reaction was about 5.7, while the *p*H of the solution after dilution was 4.9, A marked difference between β-2-thienylalanine and β-(5-chloro-2-thienyl)alanine was shown by titrating them in an aqueous HCl solution with NaOH. These results are presented in Figure 1. These observations indicate that the presence of the chlorine atom has an appreciable effect on the properties of the resultant amino acid.

EXPERIMENTAL[3]

*Chloroacetyl-β-2-thienyl-*DL*-alanine.* Applying the method described for the chloroacetylation of L-phenylalanine (9), 9.5 g. (0.055 mole) of β-2-thienyl-DL-alanine was dissolved in 56 cc. of 1 *N* NaOH and placed in an ice-bath. To this solution was added, with shaking and in small portions, 83 cc. of 1 *N* NaOH and a solution of 8.8 g. of chloroacetyl chloride in ether. Dry hydrogen chloride gas was then passed into the alkaline mixture for 30 minutes, which precipitated the chloroacetylated compound as an oil. After standing overnight cold, the oil solidified giving a yield of 11.35 g. (82%). Recrystallization from hot water (Norit) gave 9.75 g. of white crystals (71%).

Carboxypeptidase preparation. The enzyme was obtained from 10 kilos of fresh-frozen beef pancreas (5), and stored with 480 cc. of water at −14°. One-eighth of this suspension was used for each enzymatic digestion. The amount of chloroacetylated compound used as substrate varied between 9.5 g. and 30 g.

TABLE I

SPECIFIC ROTATIONS OF OPTICAL ISOMERS OF β-2-THIENYLALANINE

COMPOUND	$[\alpha]_D^{21}$ OBSERVED		$[\alpha]_D^{21}$ LITERATURE	
	L-form	D-form	L-form	D-form
β-2-Thienylalanine	−31.4[a]	+31.4[b]	−31.7 (12)	+31.6 (12)
Chloroacetyl-β-2-thienylalanine	+46.5[c]	−47.2[d]	—	—

[a] 1.0834 g. in 50 cc. of water. [b] 0.2624 g. in 25 cc. of water. [c] 0.8468 g. in 50 cc. of absolute alcohol. [d] 0.9487 g. in 50 cc. of absolute alcohol.

Resolution procedure. Chloroacetyl-β-2-thienyl-DL-alanine (9.5 g., 0.038 mole) was suspended in water and dissolved by the cautious addition of 6 *N* LiOH with vigorous stirring. The enzyme was brought into solution by adjusting the suspension to *p*H 7.6 with 0.2 M LiOH. After the insoluble globulins were removed by filtration, 75 cc. of MacIlvaine buffer (*p*H 7.6) was added and the solution was mixed with the substrate, forming a total volume of about 300 cc. The digestion was carried out at 37° for 48 hours. The mixture was then acidified with glacial acetic acid to *p*H 5.0, and evaporated *in vacuo* to half of its original volume. The L-amino acid filtered off at this point amounted to 1.2 g. (36%) after washing with cold water and absolute alcohol. The filtrate was concentrated further *in vacuo*, layered with ethyl acetate, acidified to *p*H 2.0 with conc'd HCl, and extracted five times with ethyl acetate. The extract was dried with sodium sulfate and evaporated *in vacuo* to an oil which crystallized after washing with petroleum ether. Upon filtration there was obtained 3.2 g. (67%) of chloroacetyl-β-2-thienyl-D-alanine. This product, after recrystallization from hot water, had a specific rotation of $[\alpha]_D^{21}$ −47.2°, which is in agreement with its L-antipode obtained by chloroacetylation of the L-amino acid.

Chloroacetyl-β-2-thienyl-D-alanine (1.35 g., 0.055 mole) was refluxed for 70 minutes with 1 *N* HBr and evaporated to dryness *in vacuo*. The white residue was dissolved in absolute alcohol and adjusted to *p*H 5.2 with 4*N* LiOH whereupon 0.65 g. (69%) of the D-amino acid precipitated.

In a previous experiment no buffer was used during the enzymatic digestion and while some optically-pure L-amino acid was obtained, the chloroacetylated D-compound was evidently contaminated with unhydrolyzed chloroacetylated L-amino acid because it had the specific rotation $[\alpha]_D^{21}$ −31.1°. This mixture when hydrolyzed with 2 *N* HCl yielded a free amino acid with no optical activity.

[3] The authors wish to acknowledge the cooperation of Dr. J. V. Fiore and S. N. Timasheff.

Data relative to the four optically-active compounds described are recorded in Table I.

To verify the identity of the chloroacetylated racemic acid, used as the starting material in the resolution, it was converted to the unsaturated azlactone by treatment with acetic anhydride and pyridine (10). This product showed no depression in melting point when

TABLE II

ANALYTICAL AND MELTING-POINT DATA OF OPTICAL ISOMERS

COMPOUND	NITROGEN		M.P., °C.	
	Calc'd	Found	Observed	Literature
β-2-Thienyl-DL-alanine	8.18	8.27	273–275[c] 238–244[d]	274–275[c] (13) 243–245[d] (3)
β-2-Thienyl-D-alanine	8.18	8.38	273–276[c] 239–246[d]	239–244[d] (12)
β-2-Thienyl-L-alanine	8.18	8.25	272–274[c] 238–244[d]	239–244 (12)
Chloroacetyl-β-2-thienyl-DL-alanine	5.65	5.85	127–128	
Chloroacetyl-β-2-thienyl-D-alanine	5.65	5.90	119.5–120	
Chloroacetyl-β-2-thienyl-L-alanine	5.65	5.65	120.5–121.5	
2-Methyl-4-(2-thenal)-5-oxazolone[a]	7.26	7.34	131–132.5	
2-Methyl-4-(2-thenal)-5-oxazolone[b]	7.26	7.27	131.5–132.5	

[a] From chloroacetyl-β-2-thienyl-DL-alanine. [b] From 2-thenaldehyde. [c] Preheated oil-bath to 270°. [d] Oil-bath heated at rate of 8°/minute.

TABLE III

5-THIENYL-SUBSTITUTED 3-(2-THIENYL)-2-OXIMINOPROPIONIC ACIDS DERIVED THROUGH THE RHODANINE SYNTHESIS

5-THIENYL SUBSTITUENT	M.P.[a, f], °C.	YIELD[b], %	ANALYSES			
			Calc'd		Found	
			C	H	C	H
5-Methyl[c]	155–156	94	48.24	4.52	48.05	4.44
5-Ethyl[c]	152.5–153.5	94	50.70	5.16	50.90	5.23
5-Propyl[d]	143–144	93	52.90	5.72	53.20	5.33
5-Chloro[e]	153.5–154.5	95	38.26	2.73	38.29	2.73
5-Bromo[e]	156–157	90	31.81	2.27	31.78	2.44

[a] Oil-bath heated rapidly to within 7–8° of the recorded melting point. [b] Yields represent per cent conversion from the corresponding 2-thienylthiopyruvic acids. [c] Recrystallized from toluene. [d] Recrystallized from benzene. [e] Recrystallized from chloroform. [f] All melting points indicate decomposition.

mixed with an authentic sample prepared from 2-thenaldehyde by means of the Erlenmeyer azlactone synthesis (11).

The analyses and melting points of the isomeric amino acids and their chloroacetylated compounds are listed in Table II together with those of the azlactone.

Preparation of oximino propionic acids. The procedure employed was the same for all, as exemplified by the preparation of the 5-methyl compound. Benzene and chloroform were

TABLE IV

β-2-Thienylalanines Prepared by the Rhodanine Synthesis

Starting material	Amino acids									Phenylurea derivatives				
	Product	Yield, %	m.p.,[g] °C.	Analyses						M.p.,[g] °C.	Analyses			
				Calc'd			Found				Calc'd		Found	
				C	H	N	C	H	N		C	H	C	H
5-Methyl-2-thenaldehyde	β-(5-Methyl-2-thienyl)alanine	65	253[a]–255	51.89	5.94	7.56	52.10	6.14	7.70	162.5–163	59.21	5.26	59.49	4.99
5-Ethyl-2-thenaldehyde	β-(5-Ethyl-2-thienyl)alanine	62	235[a]–238	54.27	6.53	7.03	54.56	6.24	7.19	165.5–166.5	60.37	5.66	60.48	5.41
5-Propyl-2-thenaldehyde	β-(5-Propyl-2-thienyl)alanine	55	217[a]–220	56.34	7.04	6.57	56.74	6.93	6.72	158 –159	61.44	6.02	61.76	6.08
5-Chloro-2-thenaldehyde	β-(5-Chloro-2-thienyl)alanine	47	226[a]–228	40.87	3.89	6.81	40.97	3.85	6.82	163.5–164	51.77	4.00	51.58	4.12
5-Bromo-2-thenaldehyde	β-2-Thienylalanine	50	273[b,c]–275	33.60	3.20	5.60	49.00[d]	5.27[d]	8.22[d]	175[e,f]–176	—	—	—	—

[a] Oil-bath was heated at a rate of 6° per minute. [b] β-2-Thienylalanine has m.p. 274–275° (13). [c] Mixed m.p. with an authentic sample of β-2-thienylalanine showed no depression. [d] Calculated for β-2-thienylalanine: C, 49.12; H, 5.26; N, 8.18. [e] Phenylurea derivative of β-2-thienylalanine has m.p. 175–176° when the oil-bath is preheated to 165° (2). [f] Mixed m.p. with an authentic sample of the phenylurea derivative of β-2-thienylalanine showed no depression. [g] All melting points indicated decomposition.

substituted for toluene in the recrystallization of some of these products. These variations are indicated in Table III as well as other pertinent data relative to the compounds thus synthesized.

3-(5-*Methyl-2-thienyl*)-*2-oximinopropionic acid.* To a solution of 1.7 g. of sodium in 49 cc. of ethanol was added 5.16 g. of hydroxylamine hydrochloride. This solution after filtration was added to 4.6 g. (0.023 mole) of 5-methyl-2-thienylthiopyruvic acid and heated on a steam-bath for 30 minutes. After removal of the alcohol under a vacuum the residue was dissolved in 12 cc. of 5% NaOH and filtered. The cooled filtrate was carefully acidified under ether with 11 cc. of 10% HCl and the precipitated acid filtered off and dried *in vacuo* over potassium hydroxide. The water layer was removed in a separatory-funnel and extracted three times with ether. The combined ether extracts were dried over Drierite and evaporated to dryness. Total yield, 4.31 g. (94%).

Preparation of amino acids and their ureides. The preparation of β-(5-methyl-2-thienyl)-alanine described below was followed in all instances with the exception that the 5-chloro compound was precipitated by diluting the final reaction mixture with water to twice the original volume. All the amino acids prepared exhibited a positive ninhydrin reaction. The phenylurea derivatives were prepared in the usual manner with phenyl isocyanate. In Table IV are listed the compounds so obtained.

β-(5-*Methyl-2-thienyl*)*alanine.* 3-(5-Methyl-2-thienyl)-2-oximinopropionic acid (4.41 g., 0.022 mole) was dissolved in 60 cc. of absolute alcohol and 200 g. of 2% sodium amalgam was added in small portions with heating on a steam-bath. Small additions of lactic acid were made during the reduction to keep the solution acidic to litmus. When addition of the the amalgam was complete, the solution was decanted and left in the refrigerator overnight. Filtration afforded 2.85 g. of amino acid. By evaporation of the solution to a syrup and treatment with absolute alcohol a further 0.2 g. was obtained; total yield, 3.05 g. (74%).

The aqueous solutions of β-2-thienylalanine and β-(5-chloro-2-thienyl)alanine used for titration contained 0.2424 g. and 0.4443 g. of amino acid per 100 ml. of solution, respectively. A Fisher titrimeter was employed to obtain the data presented in Figure 1.

SUMMARY

Racemic β-2-thienylalanine was resolved into its optical isomers through the asymmetric hydrolysis of its chloroacetylated derivative using a purified beef pancreas carboxypeptidase preparation.

Four thienyl amino acids were prepared from 5-methyl-2-thenaldehyde, 5-ethyl-2-thenaldehyde, 5-propyl-2-thenaldehyde, and 5-chloro-2-thenaldehyde.

NEW YORK 58, N. Y.

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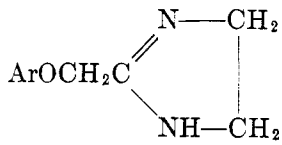
[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

2-(ARYLOXYMETHYL)THIAZOLINES AND PENTHIAZOLINES

CARL DJERASSI[1] AND CAESAR R. SCHOLZ

Received May 16, 1949

In continuation of earlier work (1, 2) on 2-(aryloxymethyl)imidazoline derivatives (I), we investigated the effect on pharmacological activity of replacing one of the nitrogen atoms by sulfur. The present report deals with the synthesis of such 2-(aryloxymethyl)thiazolines (II) and their six-membered homologs, the penthiazolines (dihydrothiazines) (III); the pharmacological evaluation of these compounds will be reported elsewhere by Dr. B. N. Craver and colleagues from our Division of Macrobiology.



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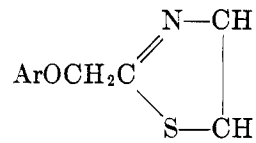

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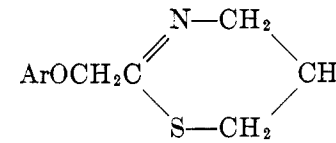

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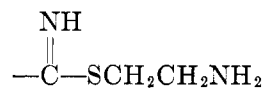
METHOD A

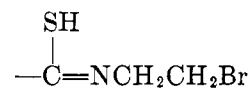
The aryloxyacetonitriles (IV) described previously (1) were converted in high yield to the corresponding acetothioamides (V) (Table I) in the usual manner (3) with ammonia and hydrogen sulfide in alcohol solution. Fusion of the thioamides with 2-bromoethyl- or 3-bromopropyl-amine hydrobromide according to the procedure of Gabriel and Hirsch (4) led to the respective thiazoline (II) (Table IV) and penthiazoline derivatives (III) (Table V). In most instances, higher yields were obtained in the penthiazoline series. All compounds were isolated and characterized as their picrates. For biological testing, the picrates were converted to the free bases and thence to the water-soluble hydrochlorides.

$$\underset{\text{IV}}{ArOCH_2CN} \rightarrow \underset{\text{V}}{ArOCH_2CSNH_2} \xrightarrow[n = 2 \text{ or } 3]{Br(CH_2)_nNH_2 \cdot HBr} \text{II or III}$$

The reaction presumably involves as an intermediate (A) or (B) (5) rather than (C), since the latter would give rise to the imidazoline (I) by the Forssel reaction (6).



(A)



(B)

(C)

METHOD B

As an alternate route to the desired heterocyclics, 2-bromoethyl- (VII) (Table II) or 3-bromopropyl-aryloxyacetamides (VIII) (Table III) were refluxed in

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TABLE I

ARYLOXYACETOTHIOAMIDES $ArOCH_2CSNH_2$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		S	
				Calc'd	Found	Calc'd	Found
Phenoxy[a]	112–113	96	C_8H_9NOS	8.38	8.44	19.17	19.16
o-Toloxy	131–132	91	$C_9H_{11}NOS$	7.73	7.84	17.69	18.26
p-Toloxy	118–120	93	$C_9H_{11}NOS$	7.73	7.73	17.69	17.22
2,5-Dimethylphenoxy	148–150	86	$C_{10}H_{13}NOS$	7.17	6.97	16.42	16.45
o-Isopropylphenoxy	120–121	82	$C_{11}H_{15}NOS$	6.69	7.09	15.32	15.20
Thymoxy	134–135	74	$C_{12}H_{17}NOS$	6.27	6.63	14.36	14.37
Carvacryloxy	82–84	79	$C_{12}H_{17}NOS$	6.27	6.80	14.36	14.58
p-Chlorophenoxy	105–107	93	C_8H_8ClNOS	6.96	6.88	15.90	15.55
m-Chlorophenoxy	124–125	93	C_8H_8ClNOS	6.96	6.84	15.90	16.24
p-Diphenyloxy	186–188	95	$C_{14}H_{13}NOS$	5.76	5.73	13.18	12.93

[a] Fritzsche, *J. prakt. Chem.* [N.F.] **20**, 267 (1879), reported m.p. 111°.

TABLE II

2-BROMOETHYLARYLOXYACETAMIDES $ArOCH_2CONHCH_2CH_2Br$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		Br	
				Calc'd	Found	Calc'd	Found
Phenoxy	75–77	52	$C_{10}H_{12}BrNO_2$	5.43	5.31	30.96	30.71
m-Toloxy	81–83	90	$C_{11}H_{14}BrNO_2$	5.15	4.78	29.37	29.06
2,5-Dimethylphenoxy	99–101	94	$C_{12}H_{16}BrNO_2$	4.90	4.82	27.93	27.99
Thymoxy	56–58	43	$C_{14}H_{20}BrNO_2$	4.46	4.47	25.43	25.47
Carvacryloxy	83–84	68	$C_{14}H_{20}BrNO_2$	4.46	4.74	25.43	25.54
p-Chlorothymoxy[a]	72–74	83	$C_{14}H_{19}BrClNO_2$	4.02	3.82		
2,4-Dichlorophenoxy[b]	115–117	89	$C_{10}H_{10}BrCl_2NO_2$	4.28	4.60		

[a] Calc'd: C, 48.22; H, 5.49. Found: C, 48.53; H, 5.61. [b] Calc'd: C, 36.72; H, 3.08. Found: C, 37.16; H, 3.36.

TABLE III

3-BROMOPROPYLARYLOXYACETAMIDES $ArOCH_2CONH(CH_2)_3Br$

ArO	M.P., °C.	YIELD, %	FORMULA	ANALYSIS			
				N		Br	
				Calc'd	Found	Calc'd	Found
Phenoxy	67–69	75	$C_{11}H_{14}BrNO_2$	5.15	5.19	29.37	29.77
m-Toloxy	61–63	80	$C_{12}H_{16}BrNO_2$	4.90	4.66	27.93	27.82
2,5-Dimethylphenoxy	85.5–87.5	79	$C_{13}H_{18}BrNO_2$	4.67	5.08	26.62	26.56
Thymoxy	62–64	64	$C_{15}H_{22}BrNO_2$	4.27	4.20	24.35	24.29
Carvacryloxy	oil	73	$C_{15}H_{22}BrNO_2$	4.27	3.95	24.35	24.05
p-Chlorothymoxy[a]	66–68	81	$C_{15}H_{21}BrClNO_2$	3.86	3.85		
2,4-Dichlorophenoxy[b]	89–91	82	$C_{11}H_{12}BrCl_2NO_2$	4.11	3.84		

[a] Calc'd: C, 49.67; H, 5.84. Found: C, 50.13; H, 5.81. [b] Calc'd: C, 38.74; H, 3.55. Found: C, 38.98; H, 3.68.

TABLE IV

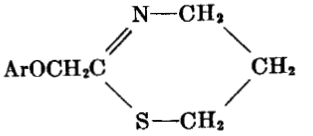
2-(ARYLOXYMETHYL)THIAZOLINES $ArOCH_2C$(=N—CH_2—S—CH_2)

ArO	PICRATES							HYDROCHLORIDES			
	M.P., °C. (dec.)	Procedure and Yield	Formula	ANALYSIS N Calc'd	N Found	S Calc'd	S Found	M. p., °C.[a]	Formula	Analysis[b] Cl Calc'd	Cl Found
Phenoxy	177–179	A (20 min., 110°), 32%; B, 9%; C, 8%	$C_{16}H_{14}N_4O_8S$	13.27	13.11	7.59	7.95	147–149	$C_{10}H_{12}ClNOS$	15.43	15.34
o-Toloxy	166–168	A (5 min., 160°), 30%	$C_{17}H_{16}N_4O_8S$	12.84	13.33	7.35	7.59	160–163	$C_{11}H_{14}ClNOS$	14.55	14.01
m-Toloxy	188–190	B, 36%	$C_{17}H_{16}N_4O_8S$	12.84	12.73	7.35	7.49	158–160	$C_{11}H_{14}ClNOS$	14.55	14.71
p-Toloxy	174–176	A (8 min., 140°), 49%	$C_{17}H_{16}N_4O_8S$	12.84	12.98	7.35	6.83	165–168	$C_{11}H_{14}ClNOS$	14.55	14.85
2,5-Dimethylphenoxy	176–178	A (5 min., 160°), 26%; B, 24%	$C_{18}H_{18}N_4O_8S$	12.44	11.88	7.12	7.27	176–180	$C_{12}H_{16}ClNOS$	13.76	13.95
o-Isopropylphenoxy	165–167	A (15 min., 130°), 25%	$C_{19}H_{20}N_4O_8S$	12.06	12.25	6.90	7.17	180–181	$C_{13}H_{18}ClNOS$	13.05	13.19
Thymoxy	167–168	A (20 min., 140°), 42%; B, 8%	$C_{20}H_{22}N_4O_8S$	11.71	11.28	6.70	7.16	149–151	$C_{14}H_{20}ClNOS$	12.41	12.45
Carvacryloxy	167–169	A (10 min., 150°), 20%; B, 9%	$C_{20}H_{22}N_4O_8S$	11.71	11.75	6.70	6.96				
m-Chlorophenoxy	185–187	A (15 min., 135°), 63%	$C_{16}H_{13}ClN_4O_8S$	12.27	12.65	7.02	6.89	172–174	$C_{10}H_{11}ClNOS$	26.84	26.43
p-Chlorophenoxy	168–169	A (20 min., 140°), 32%	$C_{16}H_{13}ClN_4O_8S$	12.27	12.28	7.02	6.69	179–181	$C_{10}H_{11}ClNOS$	26.84	26.26
2,4-Dichlorophenoxy	185–187	B, 20%	$C_{16}H_{12}Cl_2N_4O_8S$	11.40	11.80	6.53	6.64				
p-Diphenyloxy	183–185	A (10 min., 160°), 43%	$C_{22}H_{18}N_4O_8S$	11.24	10.99	6.43	6.71	150–154	$C_{16}H_{16}ClNOS$	11.60	11.99

[a] All melting points were determined in sealed capillaries. [b] These values were obtained by combustion analyses, since many of the compounds appear to give soluble complexes with silver nitrate or mercuric nitrate.

TABLE V

2-(ARYLOXYMETHYL)PENTHIAZOLINES



ArO	PICRATES							HYDROCHLORIDES			
	M.p., °C. (dec.)	Procedure and Yield	Formula	ANALYSIS N Calc'd	ANALYSIS N Found	ANALYSIS S Calc'd	ANALYSIS S Found	M.p., °C.	Formula	Analysis Cl Calc'd	Analysis Cl Found
Phenoxy	177–179	A (10 min., 170°), 58%; B, 37%; C, 10%	$C_{17}H_{16}N_4O_8S$	12.84	12.65	7.35	6.79	162–164	$C_{11}H_{14}ClNOS$	14.55[a]	14.73
o-Toloxy	158–160	A (5 min., 160°), 69%	$C_{18}H_{18}N_4O_8S$	12.44	12.62	7.12	7.46	186–187	$C_{12}H_{16}ClNOS$	13.75[a]	13.93
m-Toloxy	168–170	B, 48%	$C_{18}H_{18}N_4O_8S$	12.44	12.07	7.12	7.31	146–147	$C_{12}H_{16}ClNOS$	13.75	13.72
p-Toloxy	151–153	A (10 min., 150°), 64%	$C_{18}H_{18}N_4O_8S$	12.44	12.53	7.12	7.06	175–177	$C_{12}H_{16}ClNOS$	13.75	14.16
2,5-Dimethylphenoxy	175–176	A (5 min., 160°), 67%; B, 51%	$C_{19}H_{20}N_4O_8S$	12.07	11.61	6.90	7.13	172–173	$C_{13}H_{18}ClNOS$	13.05[a]	13.39
o-Isopropylphenoxy	155–157	A (20 min., 135°), 62%	$C_{20}H_{22}N_4O_8S$	11.71	12.06	6.70	7.12	193–195	$C_{14}H_{20}ClNOS$	12.40	12.20
Thymoxy	183–185	A (10 min., 140°), 68%; B, 64%	$C_{21}H_{24}N_4O_8S$	11.38	11.45	6.51	6.02	166–170	$C_{15}H_{22}ClNOS$	11.82[a]	12.08
Carvacryloxy	167–169	A (15 min., 120°), 20%; B, 52%	$C_{21}H_{24}N_4O_8S$	11.38	11.01	6.51	6.38	102–106	$C_{15}H_{22}ClNOS$	11.82	12.25
m-Chlorophenoxy	180–181	A (15 min., 130°), 54%	$C_{17}H_{15}ClN_4O_8S$	11.90	12.08	6.81	7.14	148–150	$C_{11}H_{13}Cl_2NOS$	12.74[a]	13.07
p-Chlorophenoxy	179–180	A (10 min., 160°), 57%	$C_{17}H_{15}ClN_4O_8S$	11.90	12.33	6.81	7.09	205–207	$C_{11}H_{13}Cl_2NOS$	25.49	25.33
2,4-Dichlorophenoxy	191–192	B, 40%	$C_{17}H_{14}Cl_2N_4O_8S$	11.09	11.29	6.35	6.65	166–168	$C_{11}H_{12}Cl_3NOS$	34.02	33.79
p-Chlorothymoxy	191–193	B, 57%	$C_{21}H_{23}ClN_4O_8S$	10.63	11.14	6.08	5.70	180–181	$C_{15}H_{21}Cl_2NOS$	10.61[a]	11.08
p-Diphenyloxy	174–176	A (10 min., 160°), 84%	$C_{23}H_{20}N_4O_8S$	10.93	10.50	6.26	6.48	189–190	$C_{17}H_{18}ClNOS$	11.09[a]	11.47

[a] These analyses were determined by titration with mercuric nitrate, while the remaining ones were carried out by combustion.

toluene solution with phosphorus pentasulfide by a modification of Salomon's synthesis (7). In a few instances [*e.g.*, 2-(carvacryloxymethyl)penthiazoline] this method was superior to A. The required amides were prepared (8) *via* the corresponding aryloxyacetyl chlorides (VI).

$$\underset{\text{VI}}{ArOCH_2COCl} \longrightarrow \underset{\substack{\text{VII } n = 2\\ \text{VIII } n = 3}}{ArOCH_2CONH(CH_2)_nBr} \xrightarrow{P_2S_5} \text{II or III.}$$

METHOD C

$$\underset{\text{V}}{ArOCH_2CSNH_2} + \underset{\substack{n = 2 \text{ or } 3\\ X = Br, Cl}}{Br(CH_2)_nX} \longrightarrow \text{II or III}$$

The synthesis was first published by Gabriel (9) and proved to be inferior to the other methods (A and B) when tested with phenoxyacetothioamide.

EXPERIMENTAL[2]

Aryloxyacetothioamides (V). The following procedure (3) gave excellent results: Ammonia was passed through 20 cc. of methanol in a pressure bottle cooled in ice, until 2 g. had been absorbed, followed by hydrogen sulfide until an additional gain in weight of 4 g. was observed. Four grams of aryloxyacetonitrile (IV) (1) was added, the bottle closed and then heated at 70–80° for one hour. The thioamides usually crystallized on cooling, but water was added in every instance to ensure complete precipitation of the product. Recrystallization was effected from ethanol. The physical constants and yields are summarized in Table I.

2-Bromoethylaryloxyacetamides (VII). Essentially the method of Leffler and Adams (8) for benzamides was used, a typical example being described below. The physical constants of the various derivatives are given in Table II.

A solution of 10.2 g. (0.05 mole) of 2-bromoethylamine hydrobromide in 75 cc. of water was placed in a flask equipped with a dropping-funnel and an efficient Hershberg stirrer, and cooled to 15° with running water. A solution of 0.055 mole of the aryloxyacetyl chloride [prepared from the corresponding acid with thionyl chloride in the absence of a solvent (10)] in 25 cc. of benzene was added, the stirrer was started, and 4.6 g. (0.115 mole) of sodium hydroxide in 95 cc. of water was dropped in over a period of five minutes. After stirring for one hour at 15° and an additional hour at room temperature, ether was added, the organic layer was washed with sodium carbonate and water, dried and evaporated. The crystalline residue was triturated with hexane and filtered. The material thus obtained was usually of nearly analytical purity.

3-Bromopropylaryloxyacetamides (VIII). These were prepared exactly as above except that 10.95 g. (0.05 mole) of 3-bromopropylamine hydrobromide was used. The pertinent information regarding these compounds is given in Table III.

2-(Aryloxymethyl)thiazolines (II) and penthiazolines (III). Method A. The optimum conditions for the fusion of 0.03 mole of thioamide and 0.025 mole of bromoalkylamine hydrobromide (without solvent) had to be determined for each case and are listed in the appropriate columns in Tables IV and V. With few exceptions (*e.g.*, the 2-diphenyloxymethyl derivatives, where the melt was directly dissolved in ethanol and picric acid added), the mixture

[2] All melting points are corrected. The microanalyses were carried out by Mr. George L. Stragand, Microchemical Laboratory, University of Pittsburgh. Thanks are due to the Misses Edwina Leathem and Frances Hoffmann for technical assistance.

was partitioned between ether and hydrochloric acid, the latter made alkaline with ammonia and re-extracted. In particularly dark colored runs, this procedure was repeated. The desired product was always crystallized as the picrate from ethanol solution.

Method B. Salomon's synthesis (7), which involved melting an amide with phosphorus pentasulfide, was improved by the introduction of toluene as solvent. The reaction was carried out by refluxing 0.002 mole of bromoalkyl aryloxyacetamide (VII or VIII) with 90 mg. of phosphorus pentasulfide in 10–15 cc. of dry toluene for four hours. After dilution with ether, the product was isolated as in A.

Preparation of hydrochlorides. The picrates were converted into the free bases using lithium hydroxide (11) and either ether or chloroform. The heterocyclic amine was dissolved in anhydrous ether (the solution filtered if necessary) and treated with the calculated amount of 7 *N* ethanolic hydrogen chloride, whereupon the hydrochlorides precipitated. None of the samples were recrystallized in order to avoid any possible ring opening (7). The melting points and analyses are reported in Tables IV and V.

SUMMARY

A series of 2-(aryloxymethyl)thiazolines and penthiazolines have been synthesized by (A) fusion of the appropriate thioamide with a bromoalkylamine hydrobromide or (B) reaction of a bromoalkyl aryloxyacetamide with phosphorus pentasulfide.

SUMMIT, NEW JERSEY

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[CONTRIBUTION FROM THE DIVISION OF CHEMISTRY, RESEARCH DEPARTMENT, CIBA PHARMACEUTICAL PRODUCTS, INC.]

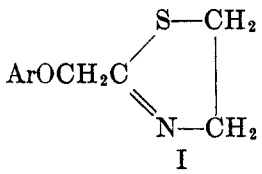
2-SUBSTITUTED-4-(2-DIALKYLAMINOETHYL)THIAZOLES

CARL DJERASSI[1], R. H. MIZZONI, AND C. R. SCHOLZ

Received February 3, 1950

In an earlier article (1) there was described a series of 2-(aryloxymethyl)-thiazolines (I), which were subjected to pharmacological screening and proved to be rather nontoxic. It was of interest to extend the biological investigation to analogous thiazole derivatives, which should be much more stable in aqueous solution than the thiazolines. The present paper describes the chemical portion of this research; the bacteriological and pharmacological results will be published elsewhere.

Since a series of aryloxyacetothioamides (II) was available from the thiazoline work (1), the conventional thiazole synthesis involving condensation of a thioamide with an α-haloketone was employed. Brominated "Mannich bases" have recently been used (2) with success in the preparation of thiazoles, and several readily available 1-bromo-4-dialkylaminobutan-2-one hydrobromides (III) were selected as the haloketone components.



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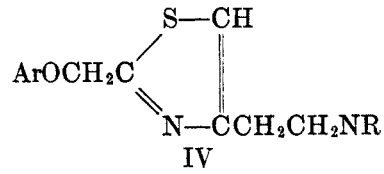

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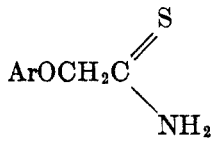

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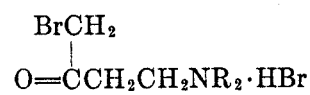

III

Most of the "Mannich bases" were synthesized by the Mannich reaction (3), though occasionally the condensation of a secondary amine with methyl vinyl ketone proved superior. Bromination with elementary bromine or pyridine hydrobromide perbromide (4) in hydrogen bromide—acetic acid solution (2, 5) yielded the brominated "Mannich bases" (III) (Table I), which on short warming with an equimolar amount of thioamide (II) (1) led to the desired 2-(aryloxymethyl)-4-(2-dialkylaminoethyl)thiazoles (IV) (Table II). In general, the thiazoles (IV) proved to be much more toxic than the corresponding thiazolines (I) (1).

In addition to 2-aryloxymethyl substituents, a number of 2-unsubstituted-4-(2-dialkylaminoethyl)thiazoles (V, R′ = H) (Table III) were synthesized from

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TABLE I

1-BROMO-4-DIALKYLAMINOBUTAN-2-ONE HYDROBROMIDES $RCH_2CH_2COCH_2Br \cdot HBr$

R	M.P., C°.	YIELD, %	FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	Br	C	H	Br
$(CH_3)_2N$[a]	84–85	16	$C_6H_{13}Br_2NO \cdot H_2O$		4.80 (N)	27.37[b]		4.78 (N)	27.25
$(C_2H_5)_2N$	82–83	36	$C_8H_{17}Br_2NO$		4.62 (N)	52.74		4.79 (N)	52.40
$(n\text{-}C_3H_7)_2N$	114.5–115.5	38	$C_{10}H_{21}Br_2NO$	36.27	6.39	48.27	36.54	5.99	47.96
$(iso\text{-}C_3H_7)_2N$	143–143.5	42	$C_{10}H_{21}Br_2NO$	36.27	6.39		36.10	6.43	
$(n\text{-}C_4H_9)_2N$	126.5–127.5	61	$C_{12}H_{25}Br_2NO$	40.13	7.02	3.90 (N)	40.02	6.83	3.78 (N)
$C_5H_{10}N$[c]	157–158	55							
C_4H_8NO	164–165	68	$C_8H_{15}Br_2NO_2$		4.42 (N)	25.18[b]		4.68 (N)	25.44

[a] Mannich (5) reported m.p. 103° for the anhydrous material. [b] Ionic halogen. [c] See ref. (2) and (4).

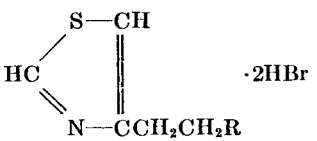
TABLE II

2-ARYLOXYMETHYL-4-(2-DIALKYLAMINOETHYL)THIAZOLE DIHYDROBROMIDES $ArOCH_2C$(S—CH, N–CCH_2CH_2R) · 2HBr

ArO	R	M.P., C°.	YIELD, %	FORMULA	ANALYSES					
					Calc'd			Found		
					C	H	Br	C	H	Br
Phenoxy	Morpholino	205–207	60	$C_{16}H_{22}Br_2N_2O_2S$	41.21	4.76	34.28	41.52	5.08	33.77
p-Toloxy	"	193–195	71	$C_{17}H_{24}Br_2N_2O_2S$	42.51	5.04	33.28	41.99	5.45	33.26
2,5-Dimethylphenoxy	"	208–210	38	$C_{18}H_{26}Br_2N_2O_2S$	43.73	5.30	32.34	43.96	5.71	32.44
o-Isopropylphenoxy	"	207–209	38	$C_{19}H_{28}Br_2N_2O_2S$	44.89	5.55	31.44	44.80	5.75	31.66
Thymoxy	"	199–200	47	$C_{20}H_{30}Br_2N_2O_2S$	45.98	5.79	30.60	45.55	5.74	30.01
p-Diphenyloxy[a]	"	193–194	57	$C_{22}H_{25}BrN_2O_2S$	57.26	5.46	17.32	57.44	5.16	16.80
m-Chlorophenoxy	"	193–195	57	$C_{16}H_{21}Br_2ClN_2O_2S$	38.38	4.23	31.92	37.95	4.44	31.90
p-Chlorophenoxy	"	222–224	68	$C_{16}H_{21}Br_2ClN_2O_2S$	38.38	4.23	31.92	38.72	4.47	32.03
p-Chlorophenoxy	Piperidino	232–234	67	$C_{17}H_{23}Br_2ClN_2OS$	40.94	4.65	32.05	41.36	4.82	31.68
Phenoxy	Diethylamino	173–174	73	$C_{16}H_{24}Br_2N_2OS$	42.48	5.35	35.34	42.59	5.42	34.89
p-Toloxy	"	182–184	69	$C_{17}H_{26}Br_2N_2OS$	43.78	5.62	34.28	44.07	5.60	33.84
2,5-Dimethylphenoxy	"	172–174	73	$C_{18}H_{28}Br_2N_2OS$	45.01	5.88	33.28	44.67	6.14	33.63
o-Isopropylphenoxy	"	184–186	36	$C_{19}H_{30}Br_2N_2OS$	46.16	6.12	32.33	46.01	5.78	31.83
Thymoxy	"	202–204	76	$C_{20}H_{32}Br_2N_2OS$	47.25	6.35	31.44	47.66	6.04	31.71
m-Chlorophenoxy	"	188–190	73	$C_{16}H_{23}Br_2ClN_2OS$	39.48	4.76	32.84	39.47	4.59	32.42
p-Chlorophenoxy	"	196–197	73	$C_{16}H_{23}Br_2ClN_2OS$	39.48	4.76	32.84	39.73	4.63	32.36
p-Diphenyloxy	Diethylamino	183–185	43	$C_{22}H_{28}Br_2N_2OS$	50.00	5.34	30.26	49.93	5.04	29.86
Phenoxy	Di-*n*-propylamino	172–173	69	$C_{18}H_{28}Br_2N_2OS$	45.00	5.88	33.27	45.32	6.09	33.38
p-Toloxy	"	166–168	66	$C_{19}H_{30}Br_2N_2OS$	46.15	6.12	32.33	45.73	6.08	32.09
2,5-Dimethylphenoxy	"	152–154	68	$C_{20}H_{32}Br_2N_2OS$	47.24	6.35	31.44	47.03	6.61	31.70
o-Isopropylphenoxy	"	164–166	62	$C_{21}H_{34}Br_2N_2OS$	48.28	6.56	30.60	48.58	6.41	30.96
Thymoxy	"	159–161	51	$C_{22}H_{36}Br_2N_2OS$	49.26	6.77	29.84	49.62	6.76	29.65
p-Diphenyloxy[a]	"	157–159	33	$C_{24}H_{31}BrN_2OS$	60.62	6.57	16.81	60.67	6.73	16.31
m-Chlorophenoxy	"	125–127	62	$C_{18}H_{27}Br_2ClN_2OS$	42.00	5.29		41.60	5.54	
p-Chlorophenoxy	"	137–138 and 182–184	91	$C_{18}H_{27}Br_2ClN_2OS$	42.00	5.29	31.05	41.95	5.56	30.77
Phenoxy	Di-*n*-butylamino	173–175	48	$C_{20}H_{32}Br_2N_2OS$	47.25	6.35	31.44	46.83	6.58	31.86
p-Chlorophenoxy	Di-*n*-butylamino	105–107	74	$C_{20}H_{31}Br_2ClN_2OS$	44.25	5.76	29.45	43.71	5.91	29.28

[a] Monohydrobromide.

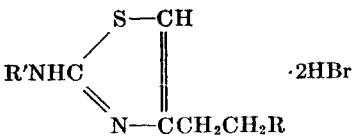
TABLE III

4-(2-DIALKYLAMINOETHYL)THIAZOLE DIHYDROBROMIDES  ·2HBr

R	M.P., C°.	YIELD, %	FORMULA	ANALYSIS					
				Calc'd			Found		
				C	H	Br	C	H	Br
Morpholino	252–254	32	$C_9H_{16}Br_2N_2OS$	30.01	4.48	7.78 (N)	30.29	5.13	7.54 (N)
Piperidino	271–272	38	$C_{10}H_{18}Br_2N_2S$		7.82 (N)	44.63		7.97 (N)	45.18
Dimethylamino	235–237	37	$C_7H_{14}Br_2N_2S$	26.43	4.43	8.81 (N)	26.56	4.47	8.45 (N)
Diethylamino	253–254	29	$C_9H_{18}Br_2N_2S$	31.23	5.24	46.18	31.14	5.26	46.20
Di-*n*-propylamino	196.5–197	47	$C_{11}H_{22}Br_2N_2S$		7.49 (N)	42.71		7.81 (N)	42.50
Di-isopropylamino	238–239	69	$C_{11}H_{22}Br_2N_2S$		7.49 (N)	42.71		7.67 (N)	42.34

TABLE IV

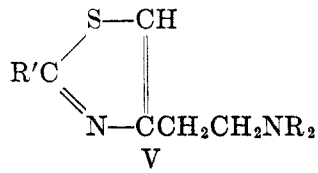
2-(N-ALKYLAMINO)-4-(2-DIALKYLAMINOETHYL)THIAZOLE DIHYDROBROMIDES



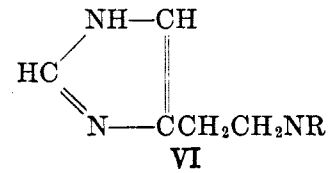
R'	R	M.P., C°.	YIELD, %	FORMULA	ANALYSIS					
					Calc'd			Found		
					C	H	N	C	H	N
Allyl	Morpholino	185.5–186.5	75	$C_{12}H_{21}Br_2N_3OS$	34.71	5.10	10.12	34.66	4.73	9.82
Anilino	"	204–205	70	$C_{15}H_{21}Br_2N_3OS$	39.93	4.69		39.38	4.72	
Benzyl	"	193.5–195.5	91	$C_{16}H_{23}Br_2N_3OS$	41.30	4.98	9.03	41.08	5.49	8.88
Anilino	Piperidino	208–210	78	$C_{16}H_{23}Br_2N_3S$	42.77	5.16	9.35	42.71	5.07	9.44
Benzyl	"	206.5–208	67	$C_{17}H_{25}Br_2N_3S$	44.07	5.44		44.11	5.60	
Allyl	Diethylamino	190–191	61	$C_{12}H_{23}Cl_2N_3S$[a]	46.15	7.42	13.45	46.56	7.22	12.95
Anilino	"	176.5–177	75	$C_{15}H_{23}Br_2N_3S$	41.20	5.30	9.61	41.22	5.38	9.72
Allyl	Di-*n*-propylamino	192.5–193	55	$C_{14}H_{27}Br_2N_3S$	39.17	6.34	9.81	39.37	6.16	9.52
Anilino	"	136–138	70	$C_{17}H_{27}Br_2N_3S$	43.88	5.85	9.03	44.83	6.04	9.00
Benzyl	"	185–187	45	$C_{18}H_{29}Br_2N_3S$	45.10	6.10	8.77	45.06	6.20	8.73
Allyl	Di-isopropylamino	177–178	87	$C_{14}H_{27}Br_2N_3S$		7.47 (S)	9.79		7.45 (S)	9.63
Anilino	"	159–160	60	$C_{17}H_{27}Br_2N_3S$		34.35 (Br)	9.03		34.16 (Br)	9.17
Allyl	Di-*n*-butylamino	175.5–177	46	$C_{16}H_{31}Br_2N_3S$	42.02	6.83	9.19	42.61	6.32	9.29

[a] Dihydrochloride.

thioformamide and III, in order to be compared with the corresponding imidazoles (VI), which have recently been prepared in this laboratory (6). Finally, several N-substituted thioureas (allyl, phenyl, benzyl) were condensed with the brominated "Mannich bases" (III) thus affording a series of N-substituted 2-amino-4-(2-dialkylaminoethyl)thiazoles (V, R′ = NHR″) (Table IV).



V



VI

EXPERIMENTAL[2]

4-Dialkylaminobutan-2-ones (*"Mannich Bases"*) $R_2NCH_2CH_2COCH_3$, R = CH_3 (7), C_2H_5 (7, 8), *n*-C_3H_7 (7), *n*-C_4H_9 (7), piperidine (R_2N) (9), and morpholine (R_2N) (10), were prepared by the Mannich reaction (3) from the amine hydrochloride, formalin solution, and acetone. The use of methyl vinyl ketone is illustrated with diisopropylamine:

A mixture of 38 g. of methyl vinyl ketone (85% azeotrope) and 50.5 g. of diisopropylamine was heated for six hours on the steam-bath and the upper layer was separated and distilled; 39.6 g. (46%) of 4-diisopropylaminobutan-2-one, b.p. 95–99° at 12 mm. was obtained.

Anal. Calc'd for $C_{10}H_{21}NO$: Neut. equiv., 171.3. Found: Neut. equiv., 175.2.

1-Bromo-4-dialkylaminobutan-2-one hydrobromides (III). The bromination of the "Mannich bases" was conducted in 35–40% hydrogen bromide-acetic acid solution (2, 5) except that the reaction mixture was cooled rather than warmed (2). Such a procedure or the use of pyridine hydrobromide perbromide (4) invariably led to colorless material. The pertinent information is summarized in Table I.

Preparation of thiazoles. The following procedure is typical: To a hot solution of 20.2 g. of phenoxyacetothioamide (1) in ethanol was added in one portion 40 g. of 1-bromo-4-di-*n*-propylaminobutan-2-one hydrobromide and the mixture was shaken while warm until all the hydrobromide was dissolved. After gradual cooling to room temperature, the product was partially precipitated by the addition of *ca.* one-fifth the volume of anhydrous ether. The crude material (42.1 g., m.p. 170–173° with previous sintering) was recrystallized from ethanol-ether and afforded 40 g. (69%) of colorless crystals of 2-phenoxymethyl-4-(2-di-*n*-propylaminoethyl)thiazole dihydrobromide (Table II) melting at 172–173°. In a few instances (Table IV), the dihydrobromide was oily, whereupon it was converted to the free base and thence the hydrochloride. In the preparation of 2-unsubstituted thiazoles (Table III), the thioformamide represented a 1:1 mixture of formamide and thioformamide (11) and hence a proportionately larger amount had to be used. The formamide presented no complication in the isolation procedure since it remained in solution.

Acknowledgment: The authors are indebted to the Misses Frances Hofmann, Edwina Leathem, and Verda Powell for their capable assistance.

SUMMARY

1-Bromo-4-dialkylaminobutan-2-one hydrobromides, obtainable from the corresponding "Mannich bases", were condensed with (a) aryloxyacetothioamides to yield a series of 2-(aryloxymethyl)-4-(2-dialkylaminoethyl)thiazole dihydro-

[2] The microanalyses were performed by G. L. Stragand, Microchemical Laboratory, University of Pittsburgh.

bromides; (b) thioformamide, to give the corresponding 2-unsubstituted thiazole derivatives; and (c) N-alkylated thioureas, to provide the N-monosubstituted 2-amino-4-(2-dialkylaminoethyl)thiazole dihydrobromides.

SUMMIT, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, COLUMBIA UNIVERSITY]

CASHEW NUT SHELL LIQUID. VII. THE HIGHER OLEFINIC COMPONENTS OF CARDANOL[1]

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Cardanol,[3] the monophenolic component of commercial cashew nut shell liquid, is the decarboxylation product of anacardic acid, an olefinic phenolic acid possessing the carbon skeleton and unsaturation of a pentadecadienylsalicylic acid. Recent investigations in this laboratory have revealed, however, that the unsaturation of cardanol (2) and of anacardic acid (3) represent an average of a complex mixture of mono-, di-, and poly-olefins. Consequently, the loss in unsaturation observed during the distillation of cardanol[4] can best be explained in terms of polymerization reactions involving selectively the more highly unsaturated components.

By the action of Prévost's reagent (silver iodobenzoate) on cardanol methyl ether containing 1.56 double bonds, Sletzinger and Dawson (2) isolated an iodinated monoglycol in which the OH groups were attached to the 8 and 9 positions of the 15-carbon side chain, thereby establishing the structure of the corresponding monoölefin as 3-(8′-pentadecenyl)anisole. An iodinated diglycol was also obtained in quantities too small to investigate.

The object of the present work, accordingly, was to develop a method for obtaining the diglycol in greater quantities in order that the structure of the corresponding diolefinic component might be established. For this purpose a cardanol methyl ether containing 1.76 double bonds was used.

Hydroxylation of the cardanol methyl ether with Prévost's reagent did not prove to be a feasible method for obtaining the diglycol in pure form. After removal of the monoglycol fraction (30–40% yield) the residual glycols proved to be very resistant to separation by fractional precipitation and by chromatographic adsorption techniques. The best product, obtained in low yield, appeared to be an associated compound composed of diglycol and triglycol in a 1:1 ratio. Incidentally, the oxidation of the monoglycol with periodate yielded not only heptaldehyde, as previously reported (2), but also a compound analyzing correctly for 2-iodo-5-methoxyphenylcaprylic acid—the aromatic fragment to be anticipated from previous studies in this laboratory (2).

As described elsewhere (3), hydroxylation by the 30% hydrogen peroxide-formic acid reagent of Swern and co-workers (4) produces glycols which can be

[1] Previous paper, Izzo and Dawson, *J. Org. Chem.*, **14**, 1039 (1949).

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[3] The monophenol has also been termed "anacardol." The reasons for preferring the name "cardanol" have been presented elsewhere (1).

[4] A rapid, single distillation at 1.5 mm. usually yields a nearly colorless monophenolic fraction having an olefinic unsaturation value of about 1.9 double bonds, while a longer distillation at a higher temperature and 5 mm. may yield a monophenolic product containing as low as 1.26 double bonds.

partially separated by molecular distillation. Experience with the hydroxylated products of anacardic acid (methyl ether ester) indicated that the mono- and di-glycols were distillable whereas the triglycolic material was not. When this method was applied to the methyl ether of cardanol possessing 1.76 double bonds the hydroxylation reaction resulted in excellent yields of total glycolic material, and by molecular distillation it was possible to obtain a product analyzing correctly for a diglycol. This product along with monoglycolic material was found in the distillable fractions (usually about 75%) of the glycol mixture. No distillable fraction was ever obtained which gave analytical values for a triglycol; the latter apparently decomposed in the molecular still to a hard black residue.

It was not found possible to obtain a pure sample of the diglycolic material by a single molecular distillation. A preliminary rough separation into crude monoglycol and diglycol fractions (see Table I-A) proved to be a necessary first step. Subsequent redistillation of the crude diglycolic material at 10^{-5} mm. gave a fraction between 150–175° (in 27% yield) which analyzed correctly for the diglycol of methylcardanol.

Cleavage of the diglycol with periodic acid yielded formaldehyde which was characterized as its methone derivative. No other water-soluble aldehydes were detected, and the ether-soluble aldehydes could not be obtained in sufficient quantity for identification. Likewise, no success was had in attempts to isolate and identify the aromatic fragments of the molecule remaining after the cleavage. Formaldehyde was also identified as a lead tetraacetate cleavage product of the higher-boiling glycolic material (Fraction III, Table I-B).

The identification of formaldehyde as a cleavage product of the diglycol definitely establishes the presence of a terminal glycol structure, and consequently establishes the presence of a terminal olefinic double bond in the diolefinic component (or components) of cardanol. The yields of formaldehyde obtained, however, were so low (usually about 10%) that it raises a question as to the homogeneity of the diglycolic material. It appears probable that there is more than one isomeric diglycol in the diglycol fraction and some of the diglycols (possibly most of them) do not possess a terminal glycol grouping.

Formaldehyde was recovered in only about 50% yield when model compounds such as ethylene glycol and phenylpropylene glycol were cleaved with $Pb(OAc)_4$ or with HIO_4 under the same conditions as used above. It made little difference which oxidizing agent was employed. Judging from these model experiments one might expect to obtain formaldehyde in about a 50% yield on cleavage of a homogeneous diglycol. Furthermore, a homogeneous diglycol would be expected to produce a recognizable dialdehyde fragment as one of the other cleavage products.

Particular attention was paid to the possibility that the diglycolic material might have the structure of 3-(8′,9′,14′,15′-tetrahydroxypentadecyl)methoxybenzene, for it will be recalled that the monoglycol structure was established as that of 3-(8′,9′-dihydroxypentadecyl)methoxybenzene. The cleavage of a

homogeneous diglycol having the 8′,9′,14′,15′-tetrahydroxy structure would yield formaldehyde and adipic aldehyde as the aliphatic fragments. Model experiments with adipic aldehyde established that no difficulty would be expected

TABLE I

FRACTIONATION OF THE METHYL CARDANOL GLYCOLS INTO MONO- AND DI-GLYCOL COMPONENTS BY MOLECULAR DISTILLATION AT 10^{-5} MM.

A. FIRST STEP: Rough Fractionation of 20 grams of Crude Glycol Mixture in Three Separate Batches

BATCH NO.	CRUDE GLYCOL, GRAMS	FRACTION	TEMP. RANGE, °C.	HOURS	APPEARANCE OF DISTILLATE	DISTILLATE	
						Grams	%
1	7.5	I	126–170	10	White solid	3.5	47
		II	170–250	15	Reddish liquid	1.8	24
						5.3	71
2	8.2	I	126–160	14	White solid	4.2	51
		II	160–250	14	Reddish liquid	1.9	23
						6.1	74
3	4.3	I	126–165	8	White solid	2.5	60
		II	165–240	8	Reddish liquid	1.0	23
						3.5	83
Totals and Summary	20	I	Crude Monoglycol Fraction[a]			10.2	52
		II	Crude Diglycol Fraction[b]			4.7	23

B. SECOND STEP: Redistillation of 4.4 g. of the Above Crude Diglycol Fraction (II)

FRACTION	TEMP. RANGE, °C.	HOURS	APPEARANCE OF DISTILLATE	ANALYSIS[c]		AMOUNT	
				C	H	Grams	%
I	126–150	7	Yellow oil	73.03	9.86	2.0	45
II[d]	150–175	7	Yellowish semi-solid	69.26	9.86	1.2	27
III	175–245	8	Reddish glassy liquid	70.05	9.83	0.7	16
Residue	Undistillable		Black tar			0.5	12

[a] Main part distilled in the vicinity of 146°. [b] Main part distilled in the vicinity of 225°. [c] Samples taken for analysis directly from distillation without further purification. Calc'd for monoglycol, $C_{22}H_{38}O_3$: C, 75.38; H, 10.93. Calc'd for diglycol, $C_{22}H_{38}O_5$: C, 69.07; H, 10.01. [d] Solidified on cold-finger.

in isolating and identifying it as a cleavage reaction product. However, all attempts to isolate adipic aldehyde or any other dialdehyde were without success.

Although such arguments are far from conclusive, and are not intended as such, they do lend some support to the view that the diglycolic material result-

ing from the hydroxylation of cardanol is not a single, homogeneous diglycol possessing a terminal glycol grouping, but is more likely a mixture of isomeric diglycols with one or more of the isomers possessing the terminal glycol grouping.

It is of interest to note that the first step in the fractionation of the crude methyl cardanol glycol mixture (see Table I-A) showed about 75% of the glycolic material to be distillable. About 50% was obtained as monoglycol fraction and 25% as a diglycol fraction. Further distillation of the diglycol fraction (Table I-B) resulted in the separation (Fraction I) of more monoglycolic material. Starting with 20 g. of the crude hydroxylated material, the distillation results (shown in Table I) may be broken down about as follows:

Monoglycol—12 g. (60%)—Combined from first and second steps.

Diglycol—2 g. (10%)—Fractions II and III of second step.

Polyglycol—6 g. (30%)—(By difference) non-distillable.

These percentages are representative of the relative amounts of mono-, di-, and poly-olefinic components present in the original methylcardanol mixture. A simple calculation, assuming the polyglycol to be essentially triglycol, reveals that such a proportion of olefinic components corresponds in striking fashion to the degree of unsaturation of the starting cardanol (1.76 double bonds).

EXPERIMENTAL

Distillation of raw commercial cashew nut shell liquid. In order to shorten the heating period and minimize polymerization reactions, a 550-ml. sample of commercial cashew nut shell liquid was simultaneously decarboxylated and distilled *in vacuo*, rather than in separate stages as previously reported from this laboratory (2, 5). The dark brown liquid was placed in a two-liter flask fitted with an electrically-heated modified Claisen still-head and was rapidly heated. The distillation was carried out rapidly at a pressure of about 2 mm., during which carbon dioxide was continuously bubbled through the capillary. The process was marked by much foaming and vaporous spraying as decarboxylation occurred simultaneously with distillation. The main fraction distilled at 218–224° and was obtained as a clear, pale, yellow oil. From a total of 1100 ml. of raw oil, distilled in two charges of 550 ml. each, 600 ml. of the above fraction was obtained, leaving in the flask about 400 ml. of a black dense liquid residue which on standing soon set to a hard, tacky mass.

The distilled cardanol darkened slightly on standing in air, but this change in color did not significantly change its degree of unsaturation, for after standing one year, though its color had turned almost black, the unsaturation decreased but slightly. The freshly-distilled oil possessed 1.91 olefinic bonds as revealed by quantitative hydrogenation using ethyl acetate as solvent and 5% palladium-on-carbon as catalyst.

Methyl cardanol. A 360-gram sample of the above monophenol (1.2 mole) was methylated using dimethyl sulfate (6). After distilling off about one-half of the methanol solvent, one liter of water was added. The oil was separated and the solution was extracted twice with 200-ml. portions of benzene and dried over magnesium sulfate. During the extraction, troublesome emulsions were formed.

After removing the benzene under diminished pressure the oil was treated with 200 ml. of Claisen solution (50% aqueous KOH in an equal volume of methanol) to remove unmethylated cardanol. The mixture was shaken vigorously, and on standing three well-defined layers appeared: the bottom of a light yellow color, the middle a dark brown, and the top, amber. The top layer was separated and shaken again with Claisen solution, but the second time, no middle layer appeared. The top layer was separated, dissolved in 100 ml. of benzene, and dried over magnesium sulfate. The benzene was removed *in vacuo* and

the 400 ml. of amber-colored oil remaining (crude cardanol methyl ether) was fractionated at 1.5 mm. using a 19-inch electrically-heated Fenske column under an atmosphere of CO_2. The distillation data are summarized as follows:

FRACTION	DISTILLATION TEMP., °C.	VOLUME, ML. APPEARANCE
I	133–147°	25 Light yellow
II	147–151°	300 Colorless oil
Residue	—	75 Amber-colored oil

The main fraction (II) weighed 280 g. (73% yield on the methylation). It gave a negative test for a free phenolic hydroxyl group when tested with phosphorus pentachloride. A quantitative hydrogenation showed an unsaturation equivalent to 1.76 olefinic bonds. This material, used in all the investigations to be described, remained a clear, colorless oil without any significant change in the degree of unsaturation during a period of over 1½ years when stored in a glass-stoppered, brown bottle at room temperature.

Hydroxylation of methyl cardanol with the Prévost reagent(2,7). The methyl ether, iodine, and silver benzoate were used in the ratio of 1:2:3. The iodine (28 g., 0.112 mole) was dissolved in 300 ml. of hot, anhydrous thiophene-free benzene, and to this was added 38 g. (0.167 mole) of silver benzoate. An immediate yellow precipitate appeared. The mixture was stirred and 10 g. (0.031 mole; 0.055 mole of double bonds) of methyl cardanol was added at 60°. Heat was evolved and the reaction became vigorous. After shaking until most of the iodine color had disappeared, the mixture was refluxed for three hours, cooled, and filtered from the insoluble silver iodide. The slight excess of iodine was removed by shaking the benzene solution with saturated sodium bisulfite, followed by washing with saturated sodium bicarbonate until neutral, and then twice with water.

After removing the benzene at reduced pressure, the brown oil was taken up in a solution of 25 g. of potassium hydroxide in 250 ml. of ethanol and refluxed on the steam-bath for one hour with occasional stirring. About 150 ml. of ethanol was then distilled off, and the precipitated potassium benzoate was separated. The clear solution was diluted with 200 ml. of water, extracted several times with benzene, and dried over magnesium sulfate. Evaporation left a residue of 12 g.(75%) of crude glycol mixture (brown oil).

This material was dissolved in 150 ml. of methanol, treated with 3 g. of Darco, refluxed and filtered. The resulting light brown solution on standing in the refrigerator for a few hours precipitated 4 grams of a white amorphous-appearing material (m.p. 71–74°). After three recrystallizations from methanol, it had m.p. 87–89° and analyzed for an iodinated monoglycol.

Anal. Calc'd for $C_{22}H_{37}IO_3$: C, 55.46; H, 7.77.
Found: C, 55.33; H, 7.94.

The methanol mother liquor from the first crystallization was evaporated. The residual brown oil was then treated with hot benzene which dissolved the major portion. The benzene-insoluble material was filtered off and recrystallized three times from methanol to yield finally 100 mg. (0.6%) of white crystals containing iodine and melting at 102–107°. The benzene-soluble material was precipitated as a gummy semi-solid by Skellysolve D as described by Sletzinger and Dawson (2) but no success was had in obtaining high-melting crystals on recrystallization from methanol. For this reason, subsequent efforts were concentrated on the benzene-insoluble fraction.

A series of Prévost reactions like the one described above was carried out on batches of 10 g. and 20 g. Altogether 100 g. of methyl cardanol was hydroxylated, which theoretically should yield 160 g. of glycolic material. From the total hydroxylated material 1.7 g. (about 1%) of glycols melting at 100–106° were finally obtained as described above. This combined yield was recrystallized from methanol, and a white powdery material was obtained, m.p. 106–108°.

Anal. Calc'd for $C_{22}H_{37}IO_5$ (diglycol): C, 51.96; H, 7.28.
Found: C, 49.27; H, 7.00.

Another methanol recrystallization gave m.p. 106–108°.

Anal. Found: C, 50.18; H, 6.83.

A recrystallization from carbon tetrachloride (in which the material was soluble with great difficulty at refluxing temperature) did not significantly change the melting point nor the analytical data.

Anal. Found: C, 50.31; H, 6.82.

An ebulliometric molecular weight determination in trichloroethane gave a value of 552. This substance was finally placed in a micro-Soxhlet and washed with hot carbon tetrachloride for one hour. The substance now melted at 109–111°.

Anal. Found:[5] C, 50.47, 50.54; H, 6.84, 6.82.

Cleavage of the monoglycol with periodic acid (8); *2-iodo-5-methoxyphenylcaprylic acid.* The monoglycol of m.p. 87–89° (1.0 g., 0.0021 mole) was cleaved with 0.5 g. of paraperiodic acid (equivalent to 0.0022 mole HIO_4) (2, 3) in the usual way. *n*-Heptaldehyde was recovered from the reaction mixture by steam-distillation and identified as its 2,4-dinitrophenylhydrazone (9). The residue left in the flask from the steam-distillation was extracted with ether. The ether was evaporated and the residue was oxidized with 3% hydrogen peroxide in alkaline medium (9). After acidification, extraction with ether and evaporation of the ether, an oily residue was left which was recrystallized from aqueous alcohol; m.p. 69–71°. The white crystalline material analyzed for 2-iodo-5-methoxyphenylcaprylic acid.

Anal. Calc'd for $C_{15}H_{21}IO_3$: C, 47.88; H, 5.63.
Found: C, 48.15; H, 5.82.

Cleavage of the crude iodinated glycols with lead tetraacetate (8, 10); *isolation of 2-iodo-5-methoxyphenylcaprylic acid and formaldehyde.* The above caprylic acid was also obtained when the mixture of crude glycols, obtained after a preliminary crystallization from methanol to remove excess of monoglycol, was cleaved with lead tetraacetate. A one-gram sample of the crude glycols was dissolved in 50 ml. of glacial acetic acid and 1.7 g. of lead tetraacetate was added. The mixture was shaken until all was in solution. After standing at room temperature for two hours, the solution was diluted with water until addition of ether no longer produced a homogeneous solution. The aldehydes were extracted with ether, the ether evaporated, and the residue oxidized with 3% hydrogen peroxide as described above. The mixture of acids was steam-distilled to remove the steam-volatile aliphatic acids.[6] The residue left in the flask from the distillation was extracted with ether, the ether evaporated, and the residue recrystallized from aqueous ethanol. A colorless crystalline acid, m.p. 71–73° was obtained.

Anal. Calc'd for $C_{15}H_{21}IO_3$: C, 47.88; H, 5.63.
Found: C, 47.72; H, 5.51.

The aqueous acetic acid solution remaining after extracting the ether-soluble aldehydes was steam-distilled directly into an alcoholic solution of methone (9) and a small amount of the formaldehyde methone derivative crystallized; m.p. 183–186° without further purification.

Anal. Calc'd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27.
Found: C, 69.88; H, 8.25.

Hydroxylation with 30% hydrogen peroxide in formic acid (4). A 20-g. sample (0.062 mole) of methyl cardanol (0.11 mole of double bonds) was mixed with 85 ml. of 93–100% formic acid (m.p. 8°) and 14 g. of 29–30% hydrogen peroxide (0.12 mole). The mixture was vigorously stirred for four hours at 40°. An initial heat effect was observed after a time lag of 5–10 minutes, the temperature reaching 70° and the mixture turning dark brown. Thereafter

[5] Calc'd for triglycol, $C_{22}H_{37}IO_7$: C, 48.89; H, 6.90.
Calc'd for associated compound (di-tri-glycol, 1:1): C, 50.38; H, 7.11.

[6] The pungent odor of the steam-distillate indicated the presence of small amounts of fatty acids; however, it was not feasible to attempt their separation.

temperature was maintained at 40° by means of a warm-water bath. At the end of four hours, the excess formic acid was distilled off *in vacuo* and the amber oil residue was taken up in a solution of 3 *N* NaOH in 70% ethanol, and refluxed for one hour. About 50 ml. of alcohol was then distilled off and 100 ml. of water was added, followed by acidification to *p*H 2 with dilute sulfuric acid. The black sticky suspension was extracted several times with ethyl acetate, until the extracts were only faintly colored yellow. The ethyl-acetate extracts were combined and the solvent removed *in vacuo*. The dense residue was dissolved in 50 ml. of benzene and slowly distilled until the distillate ran clear. The solution was then filtered and evaporated *in vacuo* leaving a very viscous, black, glycol mixture weighing 22.5 g. (95% yield).

Molecular distillation of the methyl cardanol glycols. In three separate batches (see Table I-A) a total of 20 g. of the above material was fractionated using a large molecular still of the type used previously for anacardic acid glycols (3). Previously a single fractionation had revealed that collecting the various fractions over short temperature intervals did not lead to good separation of the higher glycol fractions.

The first fraction (126–160° or 170°) obtained as a white waxy solid was recrystallized once from aqueous ethanol. The white crystalline product melted at 53–54° and analyzed for the monoglycol.

Anal. Calc'd for $C_{22}H_{38}O_3$: C, 75.38; H, 10.93.
Found: C, 75.36; H, 11.06.

The combined second fractions (160–250°) obtained from three distillations (see Table I-A) were refractionated into three fractions (Table I-B) collected at 25°-intervals. Fraction II from this distillation which solidified entirely on the cold finger, was a semi-solid resembling petroleum jelly and analyzed for a diglycol.

Anal. Calc'd for $C_{22}H_{38}O_5$: C, 69.07; H, 10.01.
Found: C, 69.26; H, 9.86.

Fraction III of this distillation was a clear, reddish, glassy liquid analyzing 1% higher in carbon than the theory for diglycol.

Cleavage of diglycol fractions. A 1-g. sample of fraction II (Table I-B) (0.0026 mole) was dissolved in 75 ml. of aldehyde-free ethanol and 1.2 g. of paraperiodic acid (equivalent to 0.0052 mole of HIO_4) was added in 19 ml. of water. The solution immediately turned red, but no test for liberated iodine could be obtained. After standing for four hours the solution was diluted with twice its volume of water and worked up as usual [see cleavages of anacardic acid glycols (3)]. From the water extract 30 mg. (10%) of formaldehyde methone derivative was obtained. After one recrystallization from aqueous ethanol, the crystals melted at 183–185°. Mixed melting points with an authentic sample of *formaldehyde methone derivative* showed no depression.

Anal. Calc'd for $C_{17}H_{24}O_4$: C, 69.83; H, 8.27.
Found: C, 69.76; H, 8.28.

The ether-soluble aldehydes were steam-distilled directly into a methone solution which became cloudy. On centrifuging, after long standing, a small amount of non-crystalline oily residue was deposited. Repeated attempts to crystallize this material were without success.

A 1-g. sample of fraction III (Table I-B) was dissolved in 50 ml. of anhydrous, thiophene-free benzene and 1.8 g. of lead tetraacetate (0.0047 mole) was added. The reddish-brown solution became turbid due to the separation of lead acetate, but this turbidity disappeared on adding 10 ml. of glacial acetic acid. The reddish-brown color, however, persisted throughout the cleavage reaction. After five-hours standing at room temperature, the benzene solution was extracted repeatedly with small portions of water and the water extracts were steam-distilled directly into a methone solution. Formaldehyde methone derivative was obtained, m.p. 182–183° without recrystallization (35 mg.).

The benzene solution was evaporated to a small volume and steam-distilled directly into a methone solution. No crystalline material could be recovered, although the solution developed a cloudiness almost immediately.

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SUMMARY

The mono- and di-olefinic components of commercial cardanol have been separated by means of their glycol derivatives. The monophenolic fraction obtained by distillation of the commercial cashew nut shell liquid was methylated and then hydroxylated in good yield with a 30% hydrogen peroxide-formic acid mixture. The resulting glycols were "fractionated" in a molecular still.

The monoglycol was obtained in crystalline form and on periodate cleavage gave rise to *n*-heptaldehyde, thereby confirming the identity of the corresponding monoölefin as 3-(8′-pentadecenyl)anisole.

The diglycol, obtained as a semi-solid, gave small amounts of formaldehyde as the sole identifiable cleavage fragment, thereby establishing the presence of a terminal glycol structure in some of the diglycolic material.

The evidence is interpreted as supporting the view that the "diglycol" is probably a mixture of isomeric diglycols rather than a homogeneous diglycol.

A cardanol sample possessing an unsaturation equivalent to 1.76 olefinic bonds has been shown to have approximately the following olefinic composition: Monoölefin, 60%; diolefin, 10%; and tri- and poly-olefins 30%.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF MOUNT HOLYOKE COLLEGE]

THE CHLORINATION OF DIETHYL ETHER AT LOW TEMPERATURES[1, 2]

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A study of the properties, especially the ultraviolet absorption spectra, of nitrogen and oxygen compounds due to the unshared pair of electrons on the nitrogen or oxygen atom is being conducted in this laboratory. Unsaturated ethers of the type RCH=CHOCH=CHR are of interest in view of the conjugation of the two olefinic bonds with the oxygen electron-pairs. A possible general synthesis of these unsaturated ethers would be the dehydrohalogenation of α,α'-dihalo derivatives of aliphatic ethers or oxygen-containing heterocycles. This type of synthesis has been reported by Smedley (1) for the preparation of dioxadiene from 2,5-dichloro-1,4-dioxane.

This paper is a report of the initial investigation of a new preparation of the required α,α'-dihalo ethers. The only previously reported method for the preparation of these dihalo ethers is the treatment of an aldehyde with hydrogen chloride in the cold (2).

$$2\ RCHO + 2\ HCl \rightarrow RCHClOCHClR + H_2O$$

This method is limited to the availability of the aldehyde. It does not seem practical to attempt the preparation of the dichlorides of unsymmetrical ethers by this method, nor has the method been shown to be applicable to the preparation of dichloro cyclic ethers.

In the search for a more general method of preparation of α,α'-dichloro ethers, the mechanism proposed by Summerbell and Bauer (3) to account for the predominant formation of 2,3-dichloro-1,4-dioxane in the chlorination of 1,4-dioxane at room temperature or above suggested that low-temperature chlorination might be a feasible means of approach. They suggest that the unstable monochlorodioxane first formed loses a molecule of hydrogen chloride to form 1,4-dioxene, which then adds a molecule of chlorine to give 2,3-dichloro-1,4-dioxane. The present investigators consider this sequence to be applicable also to the chlorination of diethyl ether. At ordinary temperatures the products formed by successive substitution of four chlorine atoms (4, 5) are α-chloroethyl, α,β-dichloroethyl, α,β,β-trichloroethyl, and α,β,β,β-tetrachloroethyl ethyl ether. The introduction of the chlorine atoms in the β-position may be formulated as occurring by the repeated loss of hydrogen chloride and addition of chlorine to the resultant double bond, the chlorine of the hydrogen chloride coming in each case from the labile α-position. The lability of a chlorine atom in the α-position of an ether and the olefin-like behavior of such an ether is emphasized by the work of Shostakovskiĭ and Bogdanova (6).

[1] Abstracted from the Master's thesis of Florence M. Ubertini, Mount Holyoke College, June 1949.

[2] This work was carried out under contract with the Office of Naval Research.

Chlorination of chloromethyl ethyl ether gives α-chloroethyl chloromethyl ether (7), indicating that an entering chlorine atom will attack a new α-position in preference to an α-position already substituted. This suggests that if the loss of hydrogen chloride from α-chloro ethers could be avoided, as by operating at a low temperature, the second atom of chlorine would enter the second alkyl group to form, in the case of diethyl ether, α,α′-dichlorodiethyl ether. In agreement with this postulate, Smedley (1) has obtained 2,5-dichloro-1,4-dioxane by chlorinating dioxane at low temperatures. Pendleton (8) in this laboratory has been able to confirm this reaction and to increase the yields with decreased reaction time by irradiating the reaction mixture with light of short wave length.

In this investigation it has been found that α,α′-dichlorodiethyl ether could be prepared without difficulty by the chlorination of either diethyl ether or α-chloroethyl ethyl ether at −20° or lower. It is essential to conduct the reaction at a low temperature to avoid the formation of β-chloro products. In contrast to the 57% yield of α,α′-dichlorodiethyl ether at −20° to −30°, a chlorination at +5° to −5° gave a mixture of approximately equal parts of α-chloroethyl ethyl ether, α,β-dichloroethyl ethyl ether, and α,α′-dichlorodiethyl ether. While these results are in agreement with the reaction route suggested above, no attempt has been made to study the electronic mechanism of the chlorination.

Monochlorination at low temperatures is also a convenient method of preparation of α-chloroethyl ethyl ether. The more common method, originated by Henry (9), is the reaction of acetaldehyde, ethanol, and hydrogen chloride. This method suffers from the disadvantage that water is one of the products and α-chloro ethers are sensitive to hydrolysis. If the direct chlorination of diethyl ether at low temperatures is stopped when the gain in weight is equivalent to a one-mole portion of chlorine, the monochloro ether is the chief product. The separation of α-chloroethyl ethyl ether prepared by chlorination from the more highly chlorinated products in the reaction mixture is easier, because of the greater difference in boiling points, than is the separation of the chloro ether from the by-products, such as acetal, formed in Henry's method.

An attempt to substitute a third chlorine atom at low temperatures was unsuccessful. In one experiment the passage of chlorine into the reaction mixture at −20° to −30° was continued for eight hours after the mixture had gained the weight calculated for the substitution of two chlorine atoms. A loss of weight occurred during this period, indicating that the chlorine was acting merely as an inert gas to flush hydrogen chloride out of the solution. No trichloro ether could be isolated.

It has been essential in this work to determine the identity of the various chlorination products. There is a paucity of reports of derivatives of the chloro ethers suitable for their characterization (17). No solid derivative of α-chloroethyl ethyl ether has been reported. In view of Houben's (10) identification of α,β-dichloroethyl ethyl ether by its reaction with urethane in the presence of water to form β-chloroethylidene diurethane, a similar method was applied to α-chloroethyl ethyl ether to give ethylidene diurethane. However, this reaction would give the same product from α,α′-dichlorodiethyl ether as from the mono

α-chloro ether. For a specific, although non-solid, derivative of the monochloro compound, it was treated with sodium ethoxide to give diethyl acetal.

Geuther (11) has reported a solid formed on treatment of α,α′-dichlorodiethyl ether with sodium benzoate but gave no melting point. The use of this procedure by the present investigators gave only benzoic acid. Treatment of the dichloro ether with phenyl- or α-naphthyl-magnesium bromide gave oils which could not be crystallized. An attempt to prepare the S-alkylisothiourea picrate (12) was unsuccessful. However, treatment of the dichloro ether with potassium phthalimide did give a nicely crystalline derivative.

The extension of this reaction to other ethers and an investigation of the use of α,α′-dichloro ethers in synthesis is in progress.

EXPERIMENTAL [3, 4]

Chlorination procedure. The general method of chlorination was to pass dry chlorine into the ether contained in a 500-ml. three-neck flask equipped with an alcohol thermometer and a mechanical stirrer and protected by a drying-tube. The flask used in all cases except the chlorination of α-chloroethyl ethyl ether was of Vycor brand no. 791 glass. This high silica content glass has a guaranteed transmission of 70% at 254 mμ for a thickness of 2 mm. (13). The reaction flask was cooled in a Dry Ice-acetone bath and irradiated with light from a carbon arc.

In the early runs the addition of the chlorine was interrupted whenever the solution became deep yellow and was not resumed until it had again become nearly colorless. This was done because it was feared, in view of the experience of early investigators (14, 15) at higher temperatures, that the reaction might become violent if the chlorine concentration became too great. In later runs the chlorine was added continuously with a corresponding decrease in the time necessary to accomplish the chlorination. No difficulty was encountered if, after the chlorine addition had been stopped, the irradiation was continued until the remaining chlorine had reacted. Otherwise, as the reaction mixture warmed up the excess chlorine reacted vigorously and exothermically forming β-chloro products. Pendleton (8) noted the same effect in the low-temperature chlorination of 1,4-dioxane in carbon tetrachloride, the reaction being sufficiently violent in larger runs to eject a large part of the liquid from the flask.

α-Chloroethyl ethyl ether. Chlorine was passed into 150 g. (2.02 moles) of anhydrous diethyl ether at −25° to −30° during 4 hours until the reaction mixture had gained 144 g. (equivalent to 2.01 moles chlorine). The product was distilled through a Vigreux column. The fraction boiling at 98–100° [reported b.p., 93–94° at 735 mm. (16) and 97.5° at 750 mm. (17)] weighed 94.0 g. (42%). The α-chloroethyl ethyl ether reacted vigorously with dry sodium ethoxide to give diethyl acetal, identified by its boiling point and its characteristic odor.

α,α′-Dichlorodiethyl ether. Anhydrous diethyl ether (82 g., 1.1 moles) was placed in the Vycor flask and cooled to −25°. Chlorine was passed into the ether at −20° to −30° during 15 hours. The addition was interrupted whenever the solution became deep yellow and was resumed when the solution had become colorless or nearly so. The reaction mixture gained 85 g., 9% in excess of that calculated for the substitution of two chlorine atoms. Distillation of one-half of the product at 761 mm. gave a dark, tarry residue and the following fractions: 70–111°, 9.3 g.; 111–115°, 44.7 g.; 115–122°, 13.2 g.; 122–132°, 5.5 g. The second fraction represents a 57% yield of α,α′-dichlorodiethyl ether. It is probable that the yield could be increased by better fractionation of the third fraction. Redistillation gave a colorless liquid

[3] All experimentally determined melting points are corrected for stem exposure.

[4] Analyses by Clark Microanalytical Laboratory, Urbana, Illinois.

with a sharp, irritating odor boiling at 113–114° (corr.), n_D^{24} 1.4183 [reported (18) b.p. 112.5-114°; n_D^{25} 1.4186].

α,α′-Diphthalimidodiethyl ether. Two grams (0.014 mole) of α,α′-dichlorodiethyl ether was refluxed with 5.5 g. (0.029 mole) of dry potassium phthalimide (19) in 100 ml. of dioxane for 1.5 hours. The salts were filtered out and water added to precipitate the phthalimido derivative. The product was crystallized three times from absolute alcohol to constant melting point to give fine, colorless needles; m.p. 270.5–271°. Material prepared from α,α′-dichlorodiethyl ether obtained by chlorination had properties identical with those of a sample prepared from known α,α′-dichlorodiethyl ether obtained by the treatment of acetaldehyde with dry hydrogen chloride (20). A mixed melting point showed no depression.

Anal. Calc'd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.40; N, 7.69.

Found: C, 65.99, 65.71; H, 4.32, 4.46; N, 7.69, 7.63.

Urethane derivatives from α-chloro ethers. A small amount of solid urethane was placed in a beaker moistened with water. Enough α-chloro ether was added to wet the solid. The mixture was stirred vigoruosly until it became thick, at which point water was immediately added to prevent polymerization. The residual solid was recrystallized from water. The results are shown in Table I.

TABLE I

URETHANE DERIVATIVES FROM α-CHLORO ETHERS

ETHER	DERIVATIVE	M.P., °C.	
		Observed	Reported (Ref.)
α-Chloroethyl ethyl	Ethylidene diurethane	125.2–126	126 (21)
α,α′-Dichlorodiethyl	Ethylidene diurethane	124.5–125.6	126 (21)
α,β-Dichloroethyl ethyl	β-Chloroethylidene diurethane	148.5–149	148–149 (10)

SUMMARY

1. Direct chlorination at −20° and below has been employed to prepare α,α′-dichlorodiethyl ether from diethyl ether and from α-chloroethyl ethyl ether and to prepare α-chloroethyl ethyl ether from diethyl ether.

2. Derivatives to characterize these chlorinated ethers are described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF IOWA STATE COLLEGE AND MUHLENBERG COLLEGE]

STERIC HINDRANCE IN HIGHLY-SUBSTITUTED ORGANOSILICON COMPOUNDS. I. THE REACTION OF ARYLLITHIUM COMPOUNDS WITH SOME CHLOROSILANES, ETHOXYSILANES, AND RELATED COMPOUNDS

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From time to time reference has been made to the effects of steric hindrance in connection with the preparation and reactions of certain organosilicon compounds. Cusa and Kipping (1) were unable to prepare *sym*-tetracyclohexyldiphenyldisiloxane from dicyclohexylphenylsilanol and they attributed this failure to steric factors. Schumb and Saffer (2) showed that in the reaction of silicon tetrachloride with *p*-, *m*-, and *o*-tolylmagnesium bromides, the yields of the corresponding tetratolylsilanes were 35%, 8%, and 0%, respectively. They were also unsuccessful in their attempts to prepare tetra-*o*-tolylsilane by a Wurtz reaction involving silicon tetrachloride, *o*-bromotoluene, and sodium. The negative results here were also attributed to steric factors. Gilman and Clark (3) have shown that when silicon tetrachloride (or ethyl silicate) is treated with excess isopropyllithium at moderate temperatures only three chlorine atoms are replaced by isopropyl groups. Again, while triisopropylphenylsilane could be prepared, triisopropyl-*o*-tolylsilane could not. Tyler, Sommer, and Whitmore (4) were able to prepare *tert*-butyltrichlorosilane by treating silicon tetrachloride with *tert*-butyllithium at the boiling point of *n*-pentane. A second *tert*-butyl group was readily attached to the silicon by the use of somewhat higher temperatures but neither tri-*tert*-butylchlorosilane nor tetra-*tert*-butylsilane could be prepared. These data may be interpreted in terms of steric hindrance.

The experiments reported in this paper indicate that steric factors are of prime importance in the case of *o*-tolyl- and mesityl-silanes. In *o*-methoxyphenylsilanes these factors appear to be less important. These conclusions are in accord with the findings of Adams and co-workers (5) who have demonstrated that the steric effect of the methoxyl group is much less than that of the methyl group. These investigators found, for example, that active β-chloro-β-(2-*methoxy*-4,6-dimethyl-5-chlorophenyl)acrylic acid could be easily racemized, the half-life being nine minutes in butanol at 20°; active β-chloro-β-(2-*methyl*-4,6-dimethyl-5-bromophenyl)acrylic acid had a half-life of 200 minutes in boiling butanol.

As might be predicted on the basis of atomic volume and position in the Periodic Table, steric factors are of greater importance in organosilicon compounds than in the corresponding derivatives of germanium, tin, and lead. Johnson and Nebergall encountered steric factors while preparing highly substituted germanes from germanium tetrachloride and organolithium compounds (6) but tetra-*o*-tolylgermane (7), tetra-*o*-tolyltin (8), and tetraisopropyllead (9) have all been prepared using less drastic conditions than appear necessary for the preparation of tetraisopropyl- and tetra-*o*-tolyl-silanes. On the other hand, steric

factors appear to be less important in organosilicon compounds than in the corresponding methane derivatives. Tetraisopropylmethane, tetra-*o*-tolylmethane, and similar compounds have not been reported although both tri-*o*-tolylmethane (10) and triisopropylmethane (11) are known. The preparation of tris-2,5-dimethylphenylboron (12) is noteworthy. Here, however, the boron to carbon bonds may well be all in one plane [as they are in trimethylboron (13)] so that steric hindrance would be diminished as compared with the tetrahedral fourth-group elements.

Our attempts to prepare tetra-*o*-tolylsilane by the action of excess *o*-tolyllithium on silicon tetrachloride, silicochloroform, or ethyl silicate at the temperature of refluxing diethyl ether were without success, the tri-*o*-tolyl derivative being formed in each case:[1]

$$3\ RLi + SiCl_4 \xrightarrow{35^\circ} R_3SiCl + 3\ LiCl \qquad 1.$$

$$3\ RLi + HSiCl_3 \xrightarrow{35^\circ} R_3SiH + 3\ LiCl \qquad 2.$$

$$3\ RLi + Si(OC_2H_5)_4 \xrightarrow{35^\circ} R_3SiOC_2H_5 + 3\ LiOC_2H_5 \qquad 3.$$

where R = *o*-$CH_3C_6H_4$—.

Tri-*o*-tolylchlorosilane, the most reactive of these derivatives (see Table II), did not react with *o*-tolyllithium or with *o*-methoxyphenyllithium at 35°, but with phenyllithium and *p*-methoxyphenyllithium the corresponding tetraarylsilanes formed readily:

$$R_3SiCl + R'Li \xrightarrow{35^\circ} R_3SiR' + LiCl \qquad 4.$$

where R = *o*-$CH_3C_6H_4$- and R′ = C_6H_5- or *p*-$CH_3OC_6H_4$—.

Di-*o*-tolyldichlorosilane did not react with mesityllithium even at elevated temperatures, but with phenyllithium in refluxing ether di-*o*-tolyldiphenylsilane was produced in excellent yield:

$$R_2SiCl_2 + 2\ R'Li \xrightarrow{35^\circ} R_2SiR'_2 + 2\ LiCl \qquad 5.$$

where R = *o*-$CH_3C_6H_4$—, R′ = C_6H_5—.

When hexachlorodisilane was treated with excess *o*-tolyllithium, *sym*-tetra-*o*-tolyldihydroxydisilane (I) was isolated after hydrolysis instead of the expected hexa-*o*-tolyldisilane:

[1] We subsequently isolated tetra-*o*-tolylsilane (m.p. 230°) following reaction of *o*-tolyllithium with tri-*o*-tolylchlorosilane at 170°. Furthermore, when ethyl silicate or tri-*o*-tolylethoxysilane is refluxed with a large excess of *o*-tolyllithium in ether for a prolonged period of time a trace of highly insoluble material separates out (m.p. *ca.* 340°). Preliminary examination and analysis indicate that this may also be tetra-*o*-tolylsilane. We are considering the possibility that these two substances are geometrical isomers. This work and its extension will be described in a later report.

$$4\ o\text{-}CH_3C_6H_4Li + Cl_3Si{-}SiCl_3 \xrightarrow[\text{then water}]{35^\circ,\ \text{in ether}} (o\text{-}CH_3C_6H_4)_2Si(HO){-}Si(OH)(o\text{-}CH_3C_6H_4)_2 + 4\ LiCl + 2\ HCl \qquad 6.$$

I

The reaction of excess mesityllithium with ethyl silicate at 35° gave dimesityldiethoxysilane in fair yield:

$$2\ RLi + Si(OC_2H_5)_4 \xrightarrow{35^\circ} R_2Si(OC_2H_5)_2 + 2\ LiOC_2H_5 \qquad 7.$$

where R = 2,4,6-$(CH_3)_3C_6H_2$—.

This compound resisted the further replacement of ethoxy groups with mesityls and did not react with phenyllithium at 35°. With silicochloroform excess mesitylmagnesium bromide apparently gave mono- and di-substituted mesitylsilanes at 35°, but at elevated temperatures three mesityl groups may have been introduced. Tetra-*o*-methoxyphenylsilane may be readily prepared at 35° by the action of *o*-methoxyphenyllithium on silicon tetrachloride (equation 8, R = *o*-$CH_3OC_6H_4$—) or tri-*o*-methoxyphenylchlorosilane (equation 4, R = R′ = *o*-$CH_3OC_6H_4$—).

$$4\ RLi + SiCl_4 \xrightarrow{35^\circ} R_4Si + 4\ LiCl \qquad 8.$$

When tri-*o*-methoxyphenylethoxysilane was treated with *o*-tolyllithium at 35°, tri-*o*-methoxyphenyl-*o*-tolylsilane was produced in excellent yield:

$$R_3SiOC_2H_5 + R'Li \xrightarrow{35^\circ} R_3SiR' + LiOC_2H_5 \qquad 9.$$

where R = *o*-$CH_3OC_6H_4$— and R′ = *o*-$CH_3C_6H_4$—.

It is an important commentary on the nature and magnitude of steric hindrance in these compounds that tri-*o*-methoxyphenyl-*o*-tolylsilane formed so readily, while tri-*o*-tolyl-*o*-methoxyphenylsilane could not be prepared although more drastic conditions were used.

We had been concerned about the structure of those compounds designated as *o*-methoxyphenylsilanes. The ease of formation of tetra-*o*-methoxyphenylsilane was disturbing when contrasted with the non-formation of tetra-*o*-tolylsilane under similar conditions, even when allowance was made for the difference in steric effects of the methoxy and methyl groups. Furthermore, some *o*-methoxyphenylsilane derivatives were stable to a warm solution containing equal volumes of glacial acetic and concentrated sulfuric acids. This acetic-sulfuric reagent apparently attacks all phenyl-, *o*-tolyl-, *m*-tolyl-, *p*-tolyl-, and mesityl-silanes with the production of colloidal silica (about 20 compounds were tested). And again, tri-*o*-methoxyphenylchlorosilane[2] is abnormally insoluble and has a very high melting point when compared with the corresponding triphenyl, tri-*o*-tolyl, and tri-*p*-tolyl compounds. The abnormality in melting point is shown in Table I.

[2] This compound was prepared by Mr. H. Melvin.

Several hypotheses were advanced to account for the anomalous behaviors, but these could not be supported by experiment. One explanation supposed that the so-called tetra-*o*-methoxyphenylsilane was actually tri-*o*-methoxyphenyl-*p*-methoxyphenylsilane. Gilman and Edwards (19) showed by carbonation experiments that *p*-methoxyphenyllithium can metalate itself in the *ortho* position, giving appreciable quantities of *o*-methoxyphenyllithium after prolonged periods of time. If *o*-methoxyphenyllithium can undergo an opposite [though unlikely (20)] rearrangement, then *p*-methoxyphenyllithium would be formed. This substance would then be expected to react with tri-*o*-methoxyphenylchlorosilane (formed early in the reaction from *o*-methoxyphenyllithium and silicon tetrachloride) to give tri-*o*-methoxyphenyl-*p*-methoxyphenylsilane. This could account for the ease of formation of the tetraarylsilane which was actually isolated. However, tri-*o*-methoxyphenyl-*p*-methoxyphenylsilane was made from pure tri-*o*-methoxyphenylethoxysilane and freshly prepared *p*-methoxyphenyllithium (equation 9, R = *o*-$CH_3OC_6H_4$— and R′ = *p*-$CH_3OC_6H_4$—) and was found to be different from the so-called tetra-*o*-methoxyphenylsilane. A second hypothesis entertained

TABLE I

THE MELTING POINTS OF SOME TETRAARYLSILANES AND TRIARYLCHLOROSILANES

R	R_4Si M.P., °C.	R_3SiCl M.P., °C.
C_6H_5—	233 (14)	111 (15)
o-$CH_3C_6H_4$—	230 (16)	116 (16)
p-$CH_3C_6H_4$—	228 (14)	116 (17)
o-$CH_3OC_6H_4$—	224.5 (16)	203 (18)

the possibility that *o*-methoxyphenyllithium can metalate itself on the methyl carbon giving phenoxymethyllithium. With silicon tetrachloride this reagent would give tetraphenoxymethylsilane or, more probably, mixed phenoxymethyl-*o*-methoxyphenylsilanes. This hypothesis would account for the ease of formation of the tetraarylsilane and, since alkylsilanes resist the action of hot acetic acid-sulfuric acid solution, might account for the stability to this reagent. However, when the mixture resulting from reaction of *o*-bromoanisole with lithium in diethyl ether was aged and subsequently carbonated, *o*-methoxybenzoic acid (m.p. 99–100°) was produced but neither phenoxyacetic acid (m.p. 99–100°) nor anisic acid (m.p. 184°) was isolated.

On the basis of this work, then, it appears that the various *o*-methoxyphenylsilane structures postulated for our reaction products are correct and that an explanation for the abnormal properties must be sought elsewhere. Further reference is made to the acid stability of these materials in the experimental section dealing with qualitative tests for silicon.

Incidental to the main studies evidence has been obtained to indicate that, in the tri-*o*-tolylsilyl series at least, a chlorosilane is more reactive than a silicon hydride which in turn is more reactive than an ethoxysilane in the reaction of such compounds with phenyllithium and *p*-methoxyphenyllithium. Table II sum-

marizes the results of experiments in which the tri-*o*-tolylsilyl derivatives were separately treated with an RLi compound under controlled conditions. The reactions are represented by equations 4, 9, and 10, where R = *o*-$CH_3C_6H_4$— and R′ = C_6H_5— or *p*-$CH_3OC_6H_4$—.

$$R_3SiH + R'Li \xrightarrow{35°} R_3SiR' + LiH \qquad 10.$$

The results are in general agreement with others derived from simple rate studies: Color Test I (21) indicated that in a given run silicon tetrachloride reacted completely with 2.4 moles of *o*-tolyllithium (per mole of silicon tetrachloride) in less than ten minutes, while under identical conditions ethyl silicate consumed this amount only in about 30 minutes.[3] Further supporting evidence was obtained from reactions leading to the formation of triphenylsilyl and tri-*o*-tolylsilyl ethers and sulfides. This latter work will be discussed in a later report.

EXPERIMENTAL[4]

Preparation and purification of reagents. The organolithium compounds and Grignard reagents used in these researches were prepared for immediate use according to standard directions (23). These preparations were at all times protected by an atmosphere of dry nitrogen. Starting materials were carefully dried before use. The yield of organometallic compound was determined by direct titration (24), unless otherwise noted, and in every case this approximated the yield reported earlier.

Ethyl orthosilicate[5] was purified by distillation and the fraction boiling at 164.8–165.2°/752 mm. was used. Silicon tetrachloride was always distilled immediately before use; the fraction boiling at 55.5–56.5°/750 mm. was used. Hexachlorodisilane[6] and silicochloroform[7] were used without purification. Diethyl ether was thoroughly dried over fresh sodium. Bromobenzene, the bromotoluenes, and the bromoanisoles were Eastman Kodak White Label products; these were dried over phosphoric anhydride and distilled before use. Bromomesitylene was prepared[8] according to the directions of Smith (25). *p*-Bromodimethylaniline was dried and purified by distillation, and the *o*- and *p*-bromophenols by distilling in the presence of a little benzene (water removed as a low-boiling azeotrope).

Silicon analysis. About 0.25 g. of sample was weighed into a tared platinum crucible and treated with 1 ml. of concentrated sulfuric acid. The mixture in the covered crucible

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[3] A curious inversion was observed when more than three moles of *o*-tolyllithium was added. Although there is no evidence that appreciable reaction takes place between *o*-tolyllithium and tri-*o*-tolylchlorosilane or tri-*o*-tolylethoxysilane at the temperature of refluxing ether, nevertheless, the organolithium compound is slowly consumed (presumably in a side reaction). The rate of disappearance of the "excess" *o*-tolyllithium was markedly greater when ethyl silicate rather than silicon tetrachloride was used as the starting substance. We suggest that the by-product lithium ethoxide (equation 3) catalyses the ether cleavage reaction of the organolithium compound (see Ref. 22).

[4] Melting points were determined by use of a flame-heated copper block. Values are uncorrected.

[5] We acknowledge the generous gift of this compound from the Carbide and Carbon Chemicals Corporation.

[6] The authors are grateful to Dr. Walter C. Schumb, Massachusetts Institute of Technology, for this compound.

[7] We acknowledge the generous gift of this compound from the Dow Chemical Company.

[8] This material was prepared by Mr. R. C. Wiley.

was heated with a small ring burner at a level about 2 cm. above the sulfuric acid. The acid is best evaporated and the carbon burned off using a low flame. The white residue was then heated briefly with the full force of a Fisher burner. The silica residue was weighed and calculated as percent silicon.

Silicon tests. The decomposition of organosilicon compounds on heating with acetic acid-sulfuric acid solution was first observed during an attempt to hydrolyze tri-*o*-tolylethoxysilane. Finely divided silica (or some closely related substance) was produced. Similar results were obtained when we attempted to rearrange *sym*-tetra-*o*-tolyldihydroxydisilane (I) to the unsymmetrical isomer using this reagent. These preliminary observations were extended, and treatment with the acetic-sulfuric solution was found to constitute a useful test for the presence of silicon in organic compounds or mixtures.[9,10]

A small crystal or microdrop of the test compound in a 75-mm. test tube was dissolved in a minimum amount of glacial acetic acid (2–5 drops in most cases). The mixture was heated to achieve complete solution in the case of sparingly soluble substances. An equal volume of concentrated sulfuric acid was carefully added. If silicon was present a white cloud appeared at the interface between the two acids. Heat was generated at the interface

TABLE II

THE REACTION OF TRI-*o*-TOLYSILYL DERIVATIVES (R_3Si—) WITH ORGANOLITHIUM COMPOUNDS (R'Li)

ORGANOSILICON COMPOUND (R = *o*-$CH_3C_6H_4$—)	R'Li	MOLES R'Li / G.-ATOM Si	REACTION TIME, HOURS	PRODUCT R_3SiR' MOLE-%	RECOVERED R_3Si— MOLE-%
R_3SiCl	C_6H_5Li	2.5	50	80	0
R_3SiH	C_6H_5Li	2.1	50	80	0
$R_3SiOC_2H_5$	C_6H_5Li	2.5	50	<20[a]	>20[a]
R_3SiCl	*p*-$CH_3OC_6H_4Li$	5.0	36	65	0
R_3SiH	*p*-$CH_3OC_6H_4Li$	2.2	15	0	70

[a] The separation of tri-*o*-tolylphenylsilane and tri-*o*-tolylethoxysilane is difficult in view of similar solubility characteristics; only a partial separation of the crude mixture was achieved.

and additional heating was not required. An alternate procedure involved complete mixing of the acetic acid solution with the sulfuric acid. Here the liquid became turbid within 10–30 seconds; heating was not necessary, although it did accelerate the reaction. The two procedures were used interchangeably and are together designated as Silicon Test I.

Positive results were obtained with the following compounds: triphenylsilane, tetraphenylsilane, triphenylsilanol, di-*o*-tolyldiphenylsilane, tri-*o*-tolylsilane, tri-*o*-tolylphenylsilane, tri-*o*-tolylsilanol,[11] tri-*o*-tolylethoxysilane, tri-*o*-tolylchlorosilane, tri-*o*-tolyldi-*n*-butylaminosilane,[11] *sym*-tetra-*o*-tolyldihydroxydisilane, tetra-*m*-tolylsilane, tetra-*p*-tolylsilane, and tri-*o*-tolyl-*p*-methoxyphenylsilane. Dimesityldiethoxysilane gave the precipitate when sulfuric was added but, in addition, a beautiful cyclamen color was produced. This color faded on dilution with water but was restored by the addition of concentrated sulfuric or strong phosphoric acid (but not strong nitric acid or acetic anhydride). Alkali had the same effe t as dilution. A crude syrup believed to be largely trimesitylsilane gave an orange-brown color along with the precipitate in Silicon Test I.

[9] The authors are grateful to Mr. B. Hofferth for assistance.

[10] The ignition of silicon-containing organic compounds generally gives an ash but this test may be unsatisfactory if the sample volatilizes on heating.

[11] The preparation of these compounds will be described in a later report.

Tetra-*o*-methoxyphenylsilane and tri-*o*-methoxyphenylethoxysilane did not give a precipitate under the above conditions. On long standing a pink color was produced in each case. When the acetic-sulfuric solution was heated to the boiling point for a few minutes a gel deposited on the wall of the test tube. Negative results under the standard conditions of the test may be attributable, in part, to the low solubility of the test substances; when a larger amount of the *o*-methoxyphenylsilane was held in solution by the use of benzene along with the other reagents, silica deposited more readily although the character of the deposit differed from that obtained in the standard test. Crude materials thought to contain hexa-*o*-tolyldisiloxane and di-*o*-tolyl "Silicones" responded to Test I. But other crudes formed in the reaction of *p*-dimethylaminophenyllithium with silicon tetrachloride gave negative results even though the test material was readily soluble in acetic acid and unquestionably had *p*-dimethylaminophenyl groups in direct combination with silicon.

We have considered the possibility that sulfuric acid merely acts as a precipitant for the organosilicon compound in Test I and that the suspended solid was the starting material rather than silica. This hypothesis finds support in the fact that *o*-methoxyphenylsilanes and *p*-dimethylaminophenylsilanes (sulfuric-soluble materials) apparently do not respond to the standard test. However, one gram of tetraphenylsilane was treated with acetic and sulfuric acids under conditions approximating those of the standard test, the precipitate was separated in 80% yield (as SiO_2) and was found to be non-organic in character. It was insoluble in the common organic solvents at the boiling point and in water, dilute acid, and dilute alkali. It was unaffected by concentrated sulfuric acid at 200° but it dissolved readily in hydrofluoric acid and in hot 30% alkali. The material powdered on a spatula, but did not char, burn or melt. While the precipitate seems to be silica, the possibility should not be overlooked that in certain cases only partial degradation occurs with the formation of insoluble siliconic acid polymers. Since sulfuric-soluble substances do not appear to give silica it may be supposed that these (or intermediate degradation products) are stabilized by salt formation.

A method was devised for testing compounds which did not respond to Silicon Test I. Here the test sample was dissolved in a few drops of concentrated sulfuric acid in a 75-mm. test tube. A drop of 70% nitric acid was added and the solution heated until nitrous fumes were no longer evolved because of the exhaustion of either the nitric acid or the organic material. If the nitric acid was used up first, another drop was added to the cooled mixture and heating was resumed until the oxidation was complete. The clear solution was then poured off and the test tube washed with water. If silicon was present in the test sample the inside of the test tube was coated with a gel. This procedure (Silicon Test II) gave positive results with all of the test materials mentioned earlier, including those which did not give a positive reaction in Silicon Test I.

Arylation of silicon compounds (General procedure). Silicon tetrachloride, ethyl orthosilicate, trichlorosilane, hexachlorodisilane, a triarylchlorosilane, a triarylethoxysilane, a triarylsilane, or a diaryldichlorosilane was measured into a 3-necked flask equipped with a sealed stirrer, graduated funnel, and reflux condenser. The sample was diluted with 5–10 volumes of anhydrous ether and a calculated amount of an aryllithium or an arylmagnesium bromide in 1–2-molar ether solution was added. In general the reaction mixture was cooled during the addition period and, without exception, the reactions were carried out under a positive pressure of dry nitrogen.[12] The mixture was then stirred for a certain period at room temperature (20°), at the temperature of refluxing ether, or at a more elevated temperature.

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[12] Good quality nitrogen was used and was further purified by passage through a train consisting of alkaline pyrogallol, sulfuric acid, and soda lime. Although every reasonable precaution was observed it must be pointed out that "absolute" protection was not afforded. When reactions were carried out over a period of many days, the RLi was slowly consumed and phenolic materials were produced.

Depending on the properties of the product the run was worked up in one of three different ways. Water-stable substances were generally isolated following hydrolysis of the reaction mixture with water, ice, or dilute acid. If a solid was present at this point it was filtered. The ether layer was then separated, dried, and the solvent evaporated. The syrupy or solid residue was treated with cold petroleum ether[13] and any resulting crystalline material was separated and further purified. This purification was almost invariably effected by recrystallization from petroleum ether, alcohol, benzene, or some combination of these solvents. In those cases where crystals could not be obtained from the crude syrup by treatment with petroleum ether, other common solvents were tried. The preliminary removal of by-products by evacuation, steam-distillation, or adsorption on alumina often proved beneficial. Seeding techniques were used in the resolution of certain syrupy mixtures. In several cases unisolable arylchlorosilanes were treated with boiling ethanol in the presence of hydrogen chloride in an effort to produce the corresponding isolable arylethoxysilanes. For convenient reference in the tables this general method for recovering the product is designated as Method X.

If crystallization could not be effected by other means, the syrup obtained after hydrolysis was distilled at reduced pressures and the individual fractions were examined and, if possible, crystallized. In certain cases recovery by distillation was found to be superior to Method X even where the crudes could be crystallized. Distillation used in conjunction with crystallization afforded the means of obtaining excellent yields of good-quality products. This procedure is called Method Y.

Water-unstable substances were recovered by distillation under nitrogen without prior hydrolysis. Here the ether solution was siphoned away from the precipitated salts and distilled or, alternately, the ether and volatile product were removed from the reaction flask directly by distillation. (The concentration of reagents and heat-treatment characteristic of this method sometimes served to drive otherwise-reluctant reactions to completion.) In either case, separation was best effected by a preliminary rapid distillation followed by redistillation under more auspicious conditions. Further redistillation or crystallization gave good-quality products. This method is referred to as Method Z.

The results of this investigation are presented in the following manner. Table III records the analyses and chief physical properties of nineteen new aromatic organosilicon compounds.[14] The experimental conditions governing the preparation (and reactions of some) of these compounds are given in Tables IV to IX along with information on other runs which either failed to yield isolable products or which resulted in the formation of significant by-products. Considered together these results furnish a comprehensive picture of the nature of steric hindrance in highly-substituted organosilicon compounds. Tables IV, V, and VI survey those runs in which silicon tetrachloride, ethyl silicate, silicochloroform, or hexachlorodisilane was treated with a given aromatic organolithium compound or Grignard reagent. The runs in Table VII were characterized by the two-stage addition of two differing organolithium compounds to ethyl silicate. Tables VIII and IX summarize those runs in which a triarylchlorosilane, triarylethoxysilane, triarylsilane, or di-*o*-tolyldichlorosilane was treated with a given aromatic organolithium compound. This report also includes a detailed description of six runs, selected to illustrate as widely as possible the techniques which were used.

Tetra-o-methoxyphenylsilane (Table IV, run 9). To a solution of 9 g. (0.053 mole) of silicon tetrachloride in 100 ml. of ether was added 153 ml. of an ether solution containing an estimated 0.210 mole of *o*-methoxyphenyllithium (mole ratio 1:3.8). The first three equivalents were consumed very rapidly [as indicated by Color Test I (21)], but the fourth reacted so slowly that after 36 hours reflux Color Test I was still positive. The reaction

[13] Petroleum ether in this report refers to the hydrocarbon fraction, b.p. 60–68°.

[14] The chemical properties of some of these compounds will be further discussed in a later report.

TABLE III

THE PROPERTIES OF SOME AROMATIC ORGANOSILICON COMPOUNDS

FORMULA	M.P., °C.	B.P., °C.	SOLUBILITY	Si	
				Calc'd	Found
$(C_6H_5)_3Si(o\text{-}CH_3C_6H_4)$	186.5–187.5	—	s.B; vss.P, EA	8.01	8.17
$(C_6H_5)_2Si(o\text{-}CH_3C_6H_4)_2$	174.0–174.2	—	s.B; vss.P, EA	7.70	7.66
$(o\text{-}CH_3C_6H_4)_3SiH$	89–90	190–192/2 mm.	vs.B, P, EA	9.28	9.08
$(o\text{-}CH_3C_6H_4)_3Si(C_6H_5)$	195.5–195.9	—	s.B; ss.P, EA	7.41	7.32
$(o\text{-}CH_3OC_6H_4)_3Si(o\text{-}CH_3C_6H_4)$	193.5–194.0	—	s.B; ss.P, EA	6.37	6.53
$(o\text{-}CH_3OC_6H_4)_4Si$	224.0–224.5	—	s.B; vss.EA, EE	6.14	6.27
$(o\text{-}CH_3C_6H_4)_3Si(p\text{-}CH_3OC_6H_4)$	179–180	—	vs.B; ss.P, EA	6.88	6.80
$(o\text{-}CH_3OC_6H_4)_3Si(p\text{-}CH_3OC_6H_4)$	178–180	—	vs.B; ss.P, EA	6.14	6.01
$(o\text{-}CH_3C_6H_4)_3SiCl$	115.5–116.0	*ca.* 250/19 mm.	vs.B; s.P; ss.EA(d.)	8.33[a]	8.34
$(o\text{-}CH_3C_6H_4)_3SiOC_2H_5$	144.5–145.0	—	vs.B; ss.P, EA	8.10	8.02
$(o\text{-}CH_3C_6H_4)_3SiOC_6H_4CH_3\text{-}(o)$	153–154	*ca.* 225/2 mm.	vs.c.B, c.C, h.P, h.EA	6.88[b]	7.03
$(o\text{-}CH_3OC_6H_4)_3SiOC_2H_5$	102–104	—	vs.B; ss.P, EA; s.h.EA	7.11	7.03
$(o\text{-}CH_3C_6H_4)_2Si(OH)_2$	135.5–136.5	—	vs.A; s.h.P; ss.c.P	11.48[c]	11.56
$(o\text{-}CH_3C_6H_4)_2SiCl_2$	74–75	138–140/1 mm.	vs.A, h.P; ss.c.P; d.EA	10.00[d]	9.90
$(o\text{-}CH_3C_6H_4)_2Si(OC_2H_5)_2$	57.0–58.5	185–190/18 mm.	vs.B; s.c.P, h.M, h.EA	9.34	9.37
$[2,4,6\text{-}(CH_3)_3C_6H_2]_2Si(OC_2H_5)_2$	63.5–64.0	138–140/0.2 mm.	vs.B; s.P, EA	7.87	7.98
$[p\text{-}(CH_3)_2NC_6H_4]_2Si(OC_2H_5)_2$	—[e]	229–231/3 mm.	vs.; s.dil.acid (d.)	7.82[f]	7.76
$[p\text{-}(CH_3)_2NC_6H_4]Si(OC_2H_5)_3$	—[g]	144–146/2 mm.	vs.; s.dil.acid (d.)	9.90[h]	9.70
$[(o\text{-}CH_3C_6H_4)_2SiOH]_2$	158.0–158.5	—	s.B, EE, h.P; vss.c.P	12.35[i]	12.03

A = acetone; B = benzene; C = carbon tetrachloride; EA = ethyl alcohol; EE = ethyl ether; M = methyl alcohol; P = petroleum ether; vs. = very soluble; s. = soluble; ss. = slightly soluble; vss. = very slightly soluble; h. = hot; c. = cold; d. = decomposed.

[a] Calc'd for $C_{21}H_{21}ClSi$: Cl, 10.52. Found: Cl, 10.47. [b] Calc'd for $C_{28}H_{28}OSi$: C, 82.30; H, 6.92. Found: C, 81.78; H, 7.25. [c] Calc'd for $C_{14}H_{16}O_2Si$: Active hydrogens, 2.00. Found: Active hydrogens, 1.94, 2.10. (Zerewitinoff determinations by Mr. J. S. Ahmann). [d] Calc'd for $C_{14}H_{14}Cl_2Si$: Cl, 25.20. Found: Cl, 25.15. [e] d_4^{25} 1.102; n_D^{25} 1.5765. (The density may be in error). [f] Calc'd for $C_{20}H_{30}N_2O_2Si$: Neut. equiv., 179.3; MR_D^{25} 106.84. Found: Neut. equiv. 179.6; MR_D^{25} 107.76. [g] d_4^{25} 1.012; n_D^{25} 1.5012. (The density may be in error). [h] Calc'd for $C_{14}H_{23}NO_3Si$: MR_D^{25} 79.34. Found: MR_D^{25} 82.55. [i] Calc'd for $C_{28}H_{30}O_2Si_2$: Active hydrogens, 2.00. Found: Active hydrogens, 2.06. (Zerewitinoff determination by Mr. J. S. Ahmann).

TABLE IV

THE REACTION OF SILICON TETRACHLORIDE WITH RM COMPOUNDS; SEE EQUATIONS 1, 8, AND 14 (ALSO 11–13, 15–22)

NO.	MOLES $SiCl_4$	MOLES RM / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[a], %	M.P., °C.
1[b]	0.400	2.1 *o*-$CH_3C_6H_4MgBr$	10 hr./35[c] —/dist.[d]	R_2SiCl_2[e, f]	Z (dist.) (2) P P (2)	45 35 12	65–69[g] 71.0–72.5[g] 74–75[g]
2	.018	5.0 *o*-$CH_3C_6H_4MgBr$	72 hr./170	—[h]	X and Y		
3	.274	2.9 *o*-$CH_3C_6H_4Li$	15 hr./20 0.3 hr./35[d]	R_3SiCl[i]	Y (dist.)[j] P	65 55[k]	110–114
4[b]	.350	3.0 *o*-$CH_3C_6H_4Li$	20 hr./20 1 hr./35[c]	R_3SiCl[e] $R_3SiOC_2H_5$[i, l]	Y EE, (dist.) P (dist.) P (3)	96 75 3 1	107–116 115.5–116.0 130–136 153–154
5	.012	4.9 *o*-$CH_3C_6H_4Li$	172 hr./35[c]	$R_3SiOC_2H_5$[i]	Y[m] P EA	10 5	137–139 143–144
6	.040	5.2 *o*-$CH_3C_6H_4Li$	18 hr./35[c]	R_3SiCl[i]	X[n] EE P	90 70	95–114 113–116
7	.022	4.5 *m*-$CH_3C_6H_4Li$	2 hr./35	R_4Si[o]	X EA EA	27 14	135–150 152.5–153.5
8	.045	4.4 *p*-$CH_3C_6H_4Li$	2 hr./20	R_4Si[p, q]	X EE B-EA	82 48	156–225 227.5–228.5
9[b]	.053	3.8 *o*-$CH_3OC_6H_4Li$	36 hr./35[c, r]	R_4Si-R_3SiCl[p, s] R_4Si[s]	X EE EE, B, B-P, B-EA	97 50	175–205 224.0–224.5
10	.007	4.2 *p*-$CH_3OC_6H_4Li$	10 hr./35	—[s]	X		
11	.013	11.0 *p*-$CH_3OC_6H_4Li$	48 hr./35	—[s]	X		
12[b]	.080	2.0 *p*-$(CH_3)_2NC_6H_4Li$	1 hr./20	R_2SiCl_2 (?)	Z (dist.)	3	140–155

Consult Table III on the use of abbreviations.

X, Y, and Z refer to the method of product recovery as described in the text of this report.

[a] Yields are calculated on the $SiCl_4$ basis. [b] This run is described in detail in the text of this report. [c] Color Test I was positive at this stage (See Ref. 21). [d] Color Test I was negative at this stage. [e] The product was characterized by analysis. [f] The by-product $RSiCl_3$ was not isolated in the pure state, but it apparently boils at about 230°/745 mm. [g] The analysis improved as the purification proceeded. Calc'd for $C_{14}H_{14}Cl_2Si$: Cl, 25.20; Si, 10.00. Found (after successive purifications): Cl, 21.85, 24.05, and 25.15; Si, 9.30, 9.90, and 9.90. [h] Crystalline products could not be obtained. This run confirms the earlier work of Schumb and Saffer (See Ref. 2). [i] The product was characterized by mixed melting point with an analyzed sample. [j] The fraction b.p. 245–265°/19 mm. was recrystallized. [k] When 2.8 moles RLi was used 45% R_3SiCl and 7% crude $R_3SiOC_2H_5$ were isolated. [l] The preparation of this compound by another method will be described in a later report. [m] No crystalline products could be isolated by the ordinary means. The $R_3SiOC_2H_5$ was isolated after a fraction boiling 165–175°/0.1 mm. was allowed to stand in contact with cold petroleum ether for three months. The result was confirmed by another run where $SiCl_4$ was added to 4.3 moles RLi. [n] No R_4Si could be found in a careful search. [o] Schumb and Saffer (Ref. 2) prepared this material in 8% yield by the action of *m*-$CH_3C_6H_4MgBr$ on $SiCl_4$ at 175°. Reported m.p. 150.8°. [p] The product was insoluble in ether and was filtered directly from the reaction liquor. [q] Schumb and Saffer (Ref. 2) prepared this material in 35% yield by the action of *p*-$CH_3C_6H_4MgBr$ on $SiCl_4$ at 175°. Reported m.p. 228°. [r] Note the reluctance with which the fourth *o*-anisyl group goes into the silicon. [s] No crystalline products could be obtained.

mixture was poured into water; 20 g. of solid material was filtered off. Since an additional 3.5 g. of crude solid was isolated after evaporation of the ether solution the conversion of silicon tetrachloride to solid anisylsilanes must have been near-quantitative (theoretical R_4Si, 24.2 g.). The crude product (m.p. 175–205°) was apparently a mixture of R_4Si and R_3SiCl and the separation of these materials proved difficult. Ether extraction followed by six wasteful crystallizations from benzene, benzene-petroleum ether, and benzene-alcohol gave 5 g. (20%) of tetra-*o*-methoxyphenylsilane, m.p. 224.0–224.5°. When the crude residues were refluxed for a prolonged period of time with a mixture of benzene and alcohol, the tri-*o*-methoxyphenylchlorosilane was apparently converted to the more soluble ethoxysilane

$$R_3SiCl + C_2H_5OH \xrightarrow[Na,\ or\ Li]{aq.\ HCl,} R_3SiOC_2H_5 + HCl \qquad 11.$$

(where R = *o*-$CH_3OC_6H_4-$) and additional tetra-*o*-methoxyphenylsilane (total 50%) was readily isolated. Tri-*o*-methoxyphenylchlorosilane could not be isolated in the pure state (although it was later prepared by the action of three moles of *o*-methoxyphenyllithium on silicon tetrachloride[2]), but a eutectic mixture containing 70 mole-percent of the chlorosilane and 30 mole-percent of the tetraarylsilane separated out. This material melted in the range 186–189° without previous shrinking and could be recrystallized from benzene-petroleum ether or from benzene-ethyl ether without changing its melting point.

Anal. Calc'd for 70 mole-% $C_{21}H_{21}ClO_3Si$ and 30 mole-% $C_{28}H_{28}O_4Si$: Si, 6.91; Cl, 6.12. Found: Si, 6.71; Cl, 6.15.

That the mixture had this composition is supported by the fact that 4.4 g. of the eutectic after treatment with ethanol and benzene gave 1.4 g. of R_4Si. The ethoxysilane was not isolated here.

The formation of the R_3SiCl and R_4Si in the arylation reaction is represented by equations 1 and 8 where R = *o*-$CH_3OC_6H_4-$. The technique of product recovery is illustrative of Method X.

Sym-tetra-o-tolyldihydroxydisilane (I) (Table VI, run 5). To a solution of 3.16 g. (0.0118 mole) of hexachlorodisilane in 50 ml. ether was added 70 ml. of an ether solution containing an estimated 0.085 mole of *o*-tolyllithium (mole ratio 1:7.2). After refluxing for 26 hours Color Test I was still positive. Water was added to the reaction mixture and after standing for 36 hours, the ether layer was separated, washed, and dried. Subsequent to evaporation of the solvent and treatment of the residual syrup with petroleum ether, there was obtained 2.7 g. of a white crystalline solid, m.p. 156–158°, and 1.4 g. of less pure material, m.p. 147–153°. The total crude yield was 75%. One recrystallization from solution in benzene-petroleum ether (1:10) gave an over-all yield of 55% of pure I, m.p. 158.0–158.5°. This product contained no chlorine. The results of another run (Table VI, run 4) indicate that *sym*-tetra-*o*-tolyldichlorodisilane is the compound that is formed in the arylation reaction, I being produced only after prolonged standing with water. The over-all reaction is represented by equation 6 and the technique of product recovery is once again illustrative of Method X.

The properties of this interesting compound will be discussed in greater detail in a subsequent report. We favor the symmetrical over the unsymmetrical formula in view of the general instability of *gem*-diols among monosilanes and the high reactivity of diaryldichlorosilanes.

Tri-o-tolylchlorosilane (Table IV, run 4). To a cooled solution of 59.5 g. (0.350 mole) silicon tetrachloride in 220 ml. ether was slowly added 1136 ml. of 0.935 *M* *o*-tolyllithium in ether (mole ratio 1:3.0). The reaction mixture was stirred at room temperature for 20 hours and at 35° for one hour. Color Test I was still positive. The mixture was then poured onto 1000 g. of iced-water. The ether layer was separated and dried. During evaporation of the ether two crops of crystalline tri-*o*-tolylchlorosilane were filtered off: 71 g., m.p. 115–116°, and 28.5 g., m.p. 111–113°. The syrupy residue was distilled under reduced pressure. The fraction of b.p. 185–195°/2 mm. gave 13.6 g. of crude tri-*o*-tolylchlorosilane (m.p.

TABLE V

THE REACTION OF ETHYL SILICATE WITH RM COMPOUNDS; SEE EQUATIONS 3 AND 7

NO.	MOLES $Si(OC_2H_5)_4$	MOLES RM / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[a], %	M.P., °C.
1	0.018	4.0 *o*-$CH_3C_6H_4MgBr$	240 hr./35[b]	—[c]	X		
2[g]	.310	3.0 *o*-$CH_3C_6H_4Li$	3 hr./35[d]	$R_3SiOC_2H_5$[e]	Y P	57	139–145
			100 hr./20	$R_2Si(OC_2H_5)_2$[f]	(dist.)	30	36–41
					EA, M	18	57.0–58.5
3	.200	8.4 *o*-$CH_3C_6H_4Li$	48 hr./35[d, h]	$R_3SiOC_2H_5$[f, i]	X and Y B-EA	75	135–140
					B-P	50	143–144
				R_4Si (?)[k]	B-EA	2.3	290–330
					B-EA (2)	1.0	342–344
4	.020	12.7 *sym*-$(CH_3)_3C_6H_3Li$	120 hr./35[b]	$R_2Si(OC_2H_5)_2$[f]	Y (dist.)[p]	62	57–61
					EA (—20°)		63.5–64.0
5	.016	3.0 *o*-$CH_3OC_6H_4Li$	2 hr./35	$R_3SiOC_2H_5$[f]	X P	75	83–110
					EA (2)	35	102–104
6	.010	7.2 *o*-$LiOC_6H_4Li$[l, m]	10 hr./35[b]	—[n]	X M-H_2O	(1.7 g.)	50–90
	.030	1.8	30 hr./35[d]		From alk. with acid	(0.3 g.)	197–198
7	.025	4.8 *p*-$LiOC_6H_4Li$[l]	14 hr./35[d]	—[o]	X		
8	.013	2.0 *p*-$(CH_3)_2NC_6H_4Li$	19 hr./20[d]	$R_2Si(OC_2H_5)_2$[f]	Y[p] (dist.) (2)	37	—[q]
9[r]	.106	2.0 *p*-$(CH_3)_2NC_6H_4Li$	24 hr./20[d]	$R_2Si(OC_2H_5)_2$[s]	Z (dist.) (3)	55	—[u]
				$RSi(OC_2H_5)_3$[f, t]	(dist.) (2)	10	—[v]

[a] Yields are calculated on the $Si(OC_2H_5)_4$ basis. [b] Color Test I was positive. [c] Only syrupy products could be isolated. [d] Color Test I was negative. [e] This product was purified by recrystallization from petroleum ether and was identified by mixed melting point with an analyzed sample. [f] Characterized by analysis. [g] In a somewhat smaller run carried out under similar conditions the yield of crude $R_3SiOC_2H_5$ (m.p. 125–145°) was 61%. Recrystallisation from petroleum ether and from ethanol gave a 55% over-all yield of pure $R_3SiOC_2H_5$ (m.p. 144.5–145.0°). Dr. R. N. Clark of these laboratories observed the formation of a little R_3SiCl along with the $R_3SiOC_2H_5$ when 0.040 mole of $Si(OC_2H_5)_4$ was treated with four equivalents of *o*-tolyllithium. The identity of this by-product was established by mixed melting point and by analysis, but we have been unable to confirm the formation of this material in other runs. It is possible that the ethyl silicate was contaminated with a little chlorosilane. Otherwise the only source of chlorine was the dilute hydrochloric acid used for hydrolysis; however, neither R_3SiOH nor $R_3SiOC_2H_5$ is changed into R_3SiCl under these conditions. [h] After refluxing under nitrogen for a short time the reaction mixture turned intensely red-brown. [i] Characterized by mixed melting point with an analyzed sample. [j] Actually, the reaction mixture was divided into several portions: one part was treated with methyl iodide before hydrolysis, a second with absolute ethanol, and a third with carbon dioxide. In each case the intense color of the reaction mixture was immediately discharged and, on working up, no significant differences in yields were apparent. The values given are for that portion which was treated with ethanol prior to hydrolysis. [k] This material is identical with that isolated in run 9, Table VIII. It may be an isomer of that tetra-*o*-tolylsilane which melts at 230° (See footnote 1).

$$4\ RLi + Si(OC_2H_5)_4 \xrightarrow{35°} R_4Si + 4\ LiOC_2H_5$$

The properties of this material will be discussed in a later report. [l] These materials were prepared by treating *o*-or *p*-bromophenol with *n*-butyllithium:

$$HOC_6H_4Br + 2\ n\text{-}C_4H_9Li \rightarrow LiOC_6H_4Li + n\text{-}C_4H_9Br + n\text{-}C_4H_{10}$$

[m] Ethyl silicate (0.010 mole) was added to an estimated 7.2 equivalents of *o*-$LiOC_6H_4Li$ and the mixture was refluxed for ten hours. Since Color Test I was positive at this stage three additional 0.010-mole portions of ethyl silicate were added at intervals. When 0.040 mole had been added and the whole refluxed for 30 hours Color Test I was negative. The reaction mixture was hydrolyzed with dilute hydrochloric acid. [n] A small amount of solid was obtained from the syrupy reaction product by diluting a methanol solution with water. This material contained silicon and was alkali-soluble. Repeated precipitation from alkaline solution with acid gave a small amount of higher-melting material. This may have been a hydroxyphenylsilicon compound. [o] Some *p*-HOC_6H_4Br was recovered unchanged but besides this only syrupy products could be isolated. [p] Note the stability of the $R_2Si(OC_2H_5)_2$ to water. [q] Boiling range 222–224°/2 mm. [r] The results of this experiment were confirmed in all important details in another run. [s] Identified by comparison with an analyzed sample.

$$RLi + Si(OC_2H_5)_4 \xrightarrow{35°} RSi(OC_2H_5)_3 + LiOC_2H_5$$

[u] Boiling range 229–231°/3 mm. [v] Boiling range 144–146°/2 mm.

TABLE VI

THE REACTION OF TRICHLOROSILANE AND HEXACHLORODISILANE WITH RM COMPOUNDS; SEE EQUATIONS 2 AND 6

NO.	MOLES $HSiCl_3$ OR Si_2Cl_6	MOLES RM / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[a], %	M.P., °C.
1	0.250 $HSiCl_3$	4.7 *o*-$CH_3C_6H_4MgBr$	72 hr./35 48 hr./20[b]	R_3SiH[c]	Y (dist.)[d] (redist.)[d] EA, P (−20°)	65 50	75–80 85–90 89–90
2	.050 $HSiCl_3$	5.0 *o*-$CH_3C_6H_4Li$	14 hr./35[b]	R_3SiH[e, f]	X P EA (−20°)	50	85–90 89–90
3[g]	.350 $HSiCl_3$	5.0 *sym*-$(CH_3)_3C_6H_2Li$	120 hr./35[b, h]	—[i]	Y and Z		
4	.020 Si_2Cl_6[j]	1.9 *o*-$CH_3C_6H_4Li$ 0.3 *o*-$CH_3C_6H_4Li$	0.1 hr./35[k, l] 0.2 hr./35[h]	$(R_2SiOH)_2$[c, p]	X P B-P (3)	42 20	120–135 156.0–158.5
5[m]	.012 Si_2Cl_6	3.6 *o*-$CH_3C_6H_4Li$	26 hr./35[h]	$(R_2SiOH)_2$[f]	X P B-P	75 55	147–158 158.0–158.5
6	.002 Si_2Cl_6	12.5 *o*-$CH_3C_6H_4Li$	48 hr./135[m, h]	—[o]	X		

[a] Yields are calculated on the $HSiCl_3$ or Si_2Cl_6 basis. [b] No hydrogen was evolved on dilution. [c] Characterized by mixed melting point with an analyzed sample. [d] The crude reaction product was distilled. The R_3SiH came over in the range 185–195°/2 mm. and on redistillation in the range 190–192°/2 mm. Other syrupy products were isolated which gave proximate analyses for R_3SiOH and R_3SiCl but these could not be crystallized. The non-volatile residue (b.p. > 260°/2 mm.) analyzed for $(R_3Si)_2O$ but this too could not be crystallized. It is of interest that Taurke (26) has presented evidence that sodium, isoamyl chloride, and silicochloroform give hexaisoamyldisiloxane along with other products. [e] No tetra-*o*-tolylsilane could be found. [f] Characterized by analysis. [g] The run was carried out in collaboration with Mr. R. C. Wiley. [h] Color Test I was positive. [i] No crystalline products could be isolated. When distilled without prior hydrolysis 40% of the anticipated material boiled in the range 150–210°/0.5 mm. After redistillation a syrupy fraction (b.p. 165–175°/0.5 mm.) was obtained which gave a proximate silicon analysis for R_3SiH. However, this material discolored in air and contained appreciable amounts of chlorine. A portion of the original reaction liquor which was first hydrolyzed and then distilled gave only 10% of the anticipated material boiling in the range 150–210°/0.5 mm. Thus it appears that anhydrous distillation furthered the arylation reaction giving R_3SiH while hydrolysis stopped the arylation reaction and subsequent distillation resulted in decomposition of the lesser-substituted chloro- and hydroxy-silanes. [j] The hexachlorodisilane used in this run was of inferior quality. [k] Color Test I was negative. [l] The first four moles of RLi (per mole of Si_2Cl_6) reacted very rapidly, the next more slowly if at all. [m] This run is described in detail elsewhere in this report. [n] Xylene was added and the ether was removed by distillation. [o] The syrupy reaction products could not be crystallized. [p] The crude product was extensively contaminated with chlorine-containing compounds and was difficult to purify. This indicated that the *sym*-tetra-*o*-tolyldichlorodisilane was the intermediate product and tha this went over into the hydroxy compound on prolonged standing in contact with water. (In run 4 the hydrolysis time was 0.1 hour while in run 5 it was 100 hours.) When the crude chlorine-containing mixture was shaken with aqueous ammonia additional $(R_2SiOH)_2$ was isolated.

107–112°) after treatment with petroleum ether (total crude yield 96%). The fraction of b.p. 220–230°/2 mm. weighed 4.1 g.; this gave a crystalline solid, m.p. 130–136°, after treatment with petroleum ether. The tri-*o*-tolylchlorosilane was purified by recrystallization from petroleum ether and a 75% recovery of material was realized, m.p. 115.5–116.0°. The higher-melting solid was recrystallized from petroleum ether, benzene-alcohol, and several times from benzene-petroleum ether. The final product (yield 1%) had m.p. 153–154°. This compound, tri-*o*-tolyl-*o*-tolyloxysilane, was identical with that prepared directly from tri-*o*-tolylchlorosilane and sodium *o*-cresoxide, and on hydrolysis it gave tri-*o*-tolylsilanol and *o*-cresol.[15] The reactions which result in the formation of this compound may be the following:

$$o\text{-}CH_3C_6H_4Li + \tfrac{1}{2}O_2 \longrightarrow o\text{-}CH_3C_6H_4OLi \qquad 12.$$

$$(o\text{-}CH_3C_6H_4)_3SiCl + o\text{-}CH_3C_6H_4OLi \xrightarrow{\text{distilled}} (o\text{-}CH_3C_6H_4)_3SiOC_6H_4CH_3\text{-}(o) + LiCl \qquad 13.$$

The formation of tri-*o*-tolylchlorosilane in the arylation reaction is represented by equation 1 where R = *o*-$CH_3C_6H_4$—. The technique of product recovery used here is illustrative of Method Y.

In another (smaller) run where the product was isolated by Method X the yield of crude R_3SiCl was 85% and the formation of R_4SiOR was not noted. When 2.9 and 2.8 moles of RLi were used per mole of silicon tetrachloride the yields of R_3SiCl were substantially lower (66% and 45%, respectively). Excess RLi probably does not affect the yield adversely (see run 6) although in a pair of runs where 4.3 and 4.9 moles of RLi were used no R_3SiCl could be isolated. $R_3SiOC_2H_5$ was isolated in small yield from each of three different runs. This by-product may have resulted from the interaction of R_3SiCl with sodium or lithium ethoxide [from the sodium-dried ether or from an ether cleavage reaction (22)]; the reaction would be similar to that represented by equation 13. In those runs where RLi was used in excess there was no suggestion whatever that any R_4Si was formed.

Ethyl silicate with mesityllithium and phenyllithium (Table VII, run 4). To 1.25 g. (0.006 mole) of ethyl silicate in 25 ml. of ether was added 0.078 mole of mesityllithium in 50 ml. of ether (mole ratio 1:13.0). The mixture was refluxed for 120 hours; at the end of this time Color Test I was still positive. Two-thirds of the reaction mixture was separated and treated with 0.024 mole of phenyllithium (mole ratio 1:6.0) and the whole was refluxed for an additional 48 hours. After acid hydrolysis and evaporation of the ether no crystalline material could be obtained, but distillation gave 0.7 g. (50% yield) of crude dimesityldiethoxysilane b.p. 138–140°/0.2 mm., m.p. 57–63°. Three recrystallizations of this material from petroleum ether gave 0.24 g. of pure dimesityldiethoxysilane, m.p. 64.8–65.2°. Dimesityldiethoxysilane of similar quality was recovered in approximately the same yield from the one-third of the original reaction mixture which had been treated with mesityllithium alone. There was no evidence to suggest that mesitylphenylsilanes had formed.

The arylation reaction is represented by equation 7 where R = *sym*-$(CH_3)_3C_6H_2$—, and the technique of product recovery is illustrative of Method Y.

Di-o-tolyldichlorosilane (Table IV, run 1). To a solution of 68.0 g. (0.400 mole) of silicon tetrachloride in 200 ml. of ether was slowly added a solution of 0.823 mole of *o*-tolylmagnesium bromide in 350 ml. of ether (mole ratio 1:2.1). The addition was carried out at 0° and the mixture was then heated at 35° for 10 hours. Color Test I was still positive. The clear solution was siphoned from the precipitated salts. As the ether was removed from this solution by distillation further reaction took place with the consumption of the remaining Grignard reagent and the precipitation of additional salt. The siphoning and distilling operations were carried out under nitrogen. The volatile material boiling in the range 55°/760 mm. to 210°/10 mm. was collected and then redistilled. There was obtained

[15] This work will be described in a later report.

TABLE VII

THE TWO-STAGE REACTION OF ETHYL SILICATE WITH RM AND R'M; SEE EQUATIONS 3 AND 7

NO.	MOLES $Si(OC_2H_5)_4$	MOLES RM (R'M) / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[a], %	M.P., °C.
1	0.003	3.0 *o*-$CH_3C_6H_4Li$ 6.0 C_6H_5Li[b]	(R) 5 hr./20[c] (R') 48 hr./35[d, e]	—[f] $R_2SiR'_2$[g, i]	X(evap. EE) B-EA (4)	95 5	95–130 174.0–174.2
2	.003	3.0 *o*-$CH_3C_6H_4Li$ 2.0 *m*-$CH_3C_6H_4Li$	(R) 24 hr./20[c] (R') 28 hr./35[c]	$R_3SiOC_2H_5$[g]	X P P	50	135–140 143–144
3	.003	3.0 *o*-$CH_3C_6H_4Li$ 2.0 *sym*-$(CH_3)_3C_6H_2Li$	(R) 160 hr./20[c] (R') 120 hr./35[d]	$R_3SiOC_2H_5$[g]	X P P	50	130–140 143–144
4[h]	.004	13.0 *sym*-$(CH_3)_3C_6H_2Li$ 6.0 C_6H_5Li	(R) 120 hr./35[d] (R') 48 hr./35[d]	$R_2Si(OC_2H_5)_2$[i]	Y (dist.) P P (3)	50 20	57–63 64.8–65.2

[a] The yields are calculated on the $Si(OC_2H_5)_4$ basis. [b] The phenyllithium was of inferior quality. [c] Color Test I was negative. [d] Color Test I was positive. [e] During the second stage of the reaction the ether evaporated and a much higher temperature was attained. [f] The crude product was probably a mixture of the $R_2SiR'_2$, R_3SiR', and $R_2SiOC_2H_5$. [g] This product was characterized by mixed melting point with an analyzed sample. [h] This run is described in detail elsewhere in this report. [i] This product was characterized by analysis. [j] $2\ RLi + 2\ R'Li + Si(OC_2H_5)_4 \xrightarrow{35°} R_2SiR'_2 + 4\ LiOC_2H_5$.

54 g. (50% yield) of crude di-*o*-tolyldichlorosilane b.p. 155–165°/5 mm., m.p. 65–69°. This fraction was itself distilled giving a 90% recovery of material b.p. 138–140°/1 mm., m.p. 65–69°. Analysis showed that this product was impure (see footnote *g*, Table IV). One recrystallization from petroleum ether gave a 75% recovery of moderately pure product, m.p. 71.0–72.5° (analysis Table IV). One gram of this material was twice recrystallized from petroleum ether with the resulting 35% recovery of pure di-*o*-tolyldichlorosilane, m.p. 74–75°. The reaction is represented by equation 14 where R = *o*-$CH_3C_6H_4$– and M = – MgBr.

$$2\ RM + SiCl_4 \xrightarrow{35°} R_2SiCl_2 + 2\ MCl \qquad 14.$$

The technique of product recovery is illustrative of Method Z.

Silicon tetrachloride with p-dimethylaminophenyllithium[16] (Table IV, run 12). To a solution of 13.6 g. (0.080 mole) of silicon tetrachloride in 50 ml. of ether was added 0.160 mole of *p*-dimethylaminophenyllithium in 150 ml. of ether (mole ratio 1:2.0). The temperature was held at 0° during the addition period. At the beginning of the reaction an intense blue color was produced[17] and a white precipitate formed. After 90 minutes at 0° and one hour at 25° the mixture was filtered under nitrogen and the precipitated white and blue solids were separated from the clear brown solution. The filtrate further precipitated a small amount of the blue solid after contact with air. This was filtered off and the filtrate now gave no reaction on exposure to the atmosphere (the solid materials removed by filtration as described above were not studied). A syrupy residue was obtained after evaporation of the ether; its weight corresponded to only about 10–15% of the expected yield of organosilicon products. This residue was distilled and three grams of material, b.p. 100–200°/0.5 mm., was collected. The non-volatile residue was a highly-colored (blue, brown, and orange), vile-smelling solid. The volatile portion solidified in the receiver. On treating this with petroleum ether two crops of crystals were obtained: 1.0 g., m.p. 140–155° (*Product A*, white, slowly turns pink on standing in air); and 0.5 g., m.p. *ca.* 70° (white, quickly turns red). Both materials gave purple liquids on fusion. Both gave negative results with Silicon Test I (although very soluble in acetic acid), but positive results with Silicon Test II. Product A was insoluble in water and in the common neutral organic solvents, but it was soluble in both dilute acid and dilute alkali. A nitric acid solution of *A* gave a heavy precipitate of silver chloride on treatment with aqueous silver nitrate, but a neutral aqueous suspension of *A* gave no reaction. On neutralization of either the acid or alkaline solution of *A*, a white solid precipitated (m.p. *ca.* 155°). This material itself was soluble in both acid and alkali, but repeated precipitation of the same sample or prolonged standing in acid or alkaline solution gradually reduced the alkali solubility to zero. The unused portion of *Product A* was redistilled in an atmosphere of nitrogen and at reduced pressure but extensive decomposition took place. The volatile material (*Product B*) solidified in the receiver; it melted at about 70°. The odor of dimethylaniline was prominent. *B* was insoluble in water, in dilute alkali, and in the common neutral organic solvents. It dissolved readily in dilute acid but not dilute alkali. The non-volatile residue was insoluble in all solvents and charred on a spatula without melting. It did not contain any significant amount of chlorine. Silicon Test I was negative, but Silicon Test II was positive.

In view of the low yields, questionable purity, and lack of analytical data, the nature of the products cannot be defined with confidence. The arylation reaction is certainly abnormal and distinctly novel products might justifiably be expected. It seems fairly certain that *Product A* is a *p*-dimethylaminophenylsilicon derivative, but the alkali solubility is

[16] The observations reported here confirm and extend the earlier findings of Mr. R. C. Wiley.

[17] The blue color seems to be related directly to the reaction between silicon tetrachloride and the RLi compound since *p*-dimethylaminophenyllithium did not give the same reaction with anhydrous hydrogen chloride.

TABLE VIII

THE REACTION OF R_3SiCl, $R_3SiOC_2H_5$, AND R_3SiH COMPOUNDS WITH R'Li COMPOUNDS; SEE EQUATIONS 4, 9, AND 10

NO.	MOLES ORGANOSILICON COMPOUND	MOLES R'Li / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[a], %	M.P., °C.
1	0.005 (o-$CH_3C_6H_4$)$_3SiCl$	2.5 C_6H_5Li	50 hr./35	R_3SiR'[b]	X EE (evap.) B-EA	80	190–193 195–196
2	.007 (o-$CH_3C_6H_4$)$_3SiCl$	10.0 o-$CH_3C_6H_4Li$	240 hr./35[c]	—[d]	X and Y		
3	.008 (o-$CH_3C_6H_4$)$_3SiCl$	1.4 p-$CH_3C_6H_4Li$[e]	10 hr./35[f]	R_3SiCl[b]	X P	30	114–116
4	.006 (o-$CH_3C_6H_4$)$_3SiCl$	4.0 o-$CH_3OC_6H_4Li$	48 hr./35	R_3SiCl[b]	X P P	90 65	112–116 115–116
5	.010 (o-$CH_3C_6H_4$)$_3SiCl$	5.4 p-$CH_3OC_6H_4Li$	36 hr./35	R_3SiR'[g]	X EE (evap.) P	90 60	169–175 179–180
6	.004 (o-$CH_3OC_6H_4$)$_3SiCl$	5.0 o-$CH_3OC_6H_4Li$	48 hr./35	R_3SiR'[b] (= R_4Si)	X B-EA B-EA	95	215–221 223.5–224.0
7	.005 (o-$CH_3C_6H_4$)$_2SiOC_2H_5$	2.5 C_6H_5Li	50 hr./35	—[h] R_3SiR'[b] $R_3SiOC_2H_5$[b]	X EE (evap.) B-EA (2) B-EA (2)	80 <20 >20	140–160 193.5–195.0 142–143
8	.005 (o-$CH_3C_6H_4$)$_3SiOC_2H_5$	10.0 C_6H_5Li	15 hr./150	R_3SiR'[b, i]	X P P	43	187–195 195–196
9	.029 (o-$CH_3C_6H_4$)$_3SiOC_2H_5$	2.0 o-$CH_3C_6H_4Li$	168 hr./35[i, j]	$R_2SiOC_2H_5$[b] R_3SiR'(R_4Si)[k]	X P B-EA B-EA (2)	60 2.5	135–140 143–144 342–344

10	.001 (o-$CH_3OC_6H_4$)$_3SiOC_2H_5$	8.0 o-$CH_3C_6H_4Li$	15 hr./35	R_3SiR'[g]	X EE (evap.) P	85 75	180–188 193.5–194.0
11	.003 (o-$CH_3OC_6H_4$)$_3SiOC_2H_5$	1.1 p-$CH_3OC_6H_4Li$	24 hr./35[f]	R_3SiR'[g]	X EE (evap.) B-EA (2)	90 50	105–150 178–180
12	.012 $(C_6H_5)_3SiH$[l]	1.5 o-$CH_3C_6H_4Li$	48 hr./35[m]	R_3SiR'[g]	X B-P	62	186.5–187.5
13	.020 (o-$CH_3C_6H_4$)$_3SiH$	2.1 C_6H_5Li	50 hr./35[m,c]	R_3SiR'[g]	X EE (evap.) B-EA	80 66	193–195 195.5–195.9
14	.010 (o-$CH_3C_6H_4$)$_3SiH$	1.1 o-$CH_3OC_6H_4Li$	48 hr./35[c]	R_3SiH[b]	X EE (evap.)	80	84–87
15	.007 (o-$CH_3C_6H_4$)$_3SiH$	2.0 p-$CH_3OC_6H_4Li$	15 hr./35	R_3SiH[b]	X EE (evap.) EA (−20°)	95	78–87 87–88

[a] Yields are calculated on the R_3Si- basis. [b] Characterized by mixed melting point with an analyzed sample. [c] Color Test I was positive. [d] Many unsuccessful attempts were made to obtain a crystalline product: the crude syrup was treated with a variety of solvents and the solutions were seeded with R_3SiCl, R_3SiOH, $R_3SiOC_2H_5$, and R_4Si. Ultimately the syrup was distilled but little fractionation could be effected and no crystalline materials could be separated. [e] The p-tolyllithium was of questionable quality and the negative result should be accepted with reserve. [f] Color Test I was negative. [g] Characterized by analysis. [h] The separation of the $R_3SiOC_2H_5$ and R_3SiR' was difficult due to the similar solubility properties of the two substances; only a partial separation was achieved. [i] Additional R_3SiR' was obtained on reworking the syrupy residues. No $R_2SiR'_2$ could be found, however, indicating that the R-Si linkage is not cleaved by R'Li at elevated temperatures. [j] The anhydrous reaction mixture was an intense red-brown. This color was discharged instantly on dilution with water. [k] See Table V footnote k. [l] Prepared by Dr. R. A. Seibert from silicochloroform and phenyllithium. [m] A gas was evolved on hydrolysis. This was probably hydrogen from the by-product lithium hydride (see equation 10).

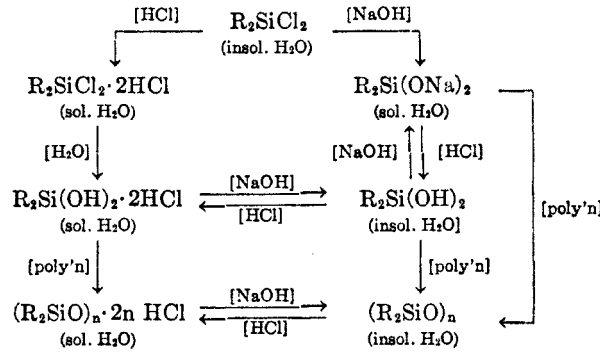
TABLE IX

THE REACTION OF DI-*o*-TOLYLDICHLOROSILANE (R_2SiCl_2) WITH R'M COMPOUNDS; SEE EQUATION 5

NO.	MOLES R_2SiCl_2[a]	MOLES R'M / G.-ATOM Si	REACTION CONDITIONS TIME/TEMP., °C.	PRODUCT	METHOD PRODUCT RECOVERY AND RECRYST. SOLVENT	YIELD[b], %	M.P., °C.
1	0.007	1.0 C_6H_5Li	10 hr./35[c]	—[d]	X		
2	.007	7.0 C_6H_5Li	15 hr./20 2 hr./35	$R_2SiR'_2$[e]	X EE B-EA	100 80	167–174 173.2–174.5
3	.006	3.5 *p*-$CH_3C_6H_4Li$[f]	10 hr./35[c]	—[d]	X		
4	.018	2.0 *sym*-$(CH_3)_3C_6H_2Li$	24 hr./35[g] 2 hr./100[g]	$R_2Si(OH)_2$[h]	X P (2)	50	135.5–136.5

[a] The R_2SiCl_2 used here melted in the range 71.0–72.5°; the pure material melted at 74–75°. [b] The yield is calculated on the R_2SiCl_2 basis. [c] Color Test I was negative. [d] The syrupy product which was obtained could not be crystallized. [e] This product was identified by analysis. [f] The *p*-tolyllithium was of poor quality and the run is of questionable value. [g] Color Test I was positive. [h] This product was identified by mixed melting point with an analyzed sample which had been prepared by direct hydrolysis of di-*o*-tolyldichlorosilane: $R_2SiCl_2 + 2\ H_2O \rightarrow R_2Si(OH)_2 + 2\ HCl$. (See subsequent report).

particularly disturbing. It suggests the presence of phenolic hydroxyls, perhaps derived from the RLi compound by oxidation or from a dimethylaminophenyl group by hydrolysis. We have considered and abandoned the possibility that one of the products might have been *p*-dimethylaminophenol (m.p. 78°). We suggest that *A* was impure bis-(*p*-dimethylaminophenyl)dichlorosilane, formed as indicated by equation 14 (where R = *p*-$(CH_3)_2NC_6H_4$- and M = Li). Its reactions could then be represented as follows:



15-22.

SUMMARY

1. Nineteen new aromatic organosilicon compounds have been prepared by reaction of organolithium compounds or Grignard reagents with some silicon chlorides, ethyl silicate, and related substances.

2. Tetra-*m*-tolylsilane and tetra-*p*-tolylsilane have been prepared in improved yields.

3. The failure of certain highly-substituted aromatic organosilicon compounds to form under the conditions of the arylation reaction appears to be related directly to steric factors.

4. It has been shown that tri-*o*-tolylchlorosilane is more reactive than tri-*o*-tolylsilane which, in turn, is more reactive than tri-*o*-tolylethoxysilane in the reaction of these substances with aryllithium compounds.

5 .Two useful tests for the presence of silicon in organic compounds are described.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, UNIVERSITY OF MARYLAND]

PEPTIDES *VIA* AMIDES OF α-BENZYLOXIMINO ACIDS[1a]

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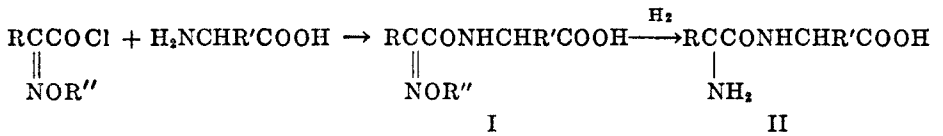
The convenient preparation of oximino acids in good yields and their ready hydrogenation to the corresponding amino acids (1, 2, 3) has led to the investigation of the possible use of these compounds as intermediates in the synthesis of peptides. Schemin and Herbst (4) were able to reduce the oximes of several oximino acid amides to the corresponding dipeptides. However, their route to the intermediates leaves much to be desired.

Waters and Hartung (5) found that the chlorides of oximino acids themselves are not directly accessible. The α-alkoximino acids, however, lend themselves admirably for the preparation of acid chlorides, from which amides may be synthesized. Amides of α-amino acids suggest the possibility for a new route to the synthesis of peptides, thus:



The O-alkyl ethers of oximes have received some study and, in particular, Adkins and Reeve (6) have shown that ethyl O-ethyloximinoacetoacetate was reduced by Raney nickel catalyst to the desired threonine. Hydrogenolysis of benzyl ethers proceeds at room temperature and lower pressures (7). Therefore, O-benzyl ethers of oximino acids (I) should be easily cleaved by hydrogenolytic procedures, with subsequent further reduction of the resulting oximino group to the amino group (II).

The benzylation of oximino acids has been reported by Waters and Hartung (5). In the course of the present work, it was observed that yields are improved if benzylation is conducted in an alcoholic medium rather than in aqueous acetone. Four α-oximino acids were benzylated in this way and their properties are given in Table I. They are low-melting, white crystals when obtained from ethanol and water.

Waters observed some difficulty in the preparation of the acid chlorides of the α-alkoximino acids using thionyl chloride. Even though redistilled purified thionyl chloride was refluxed with the acids, the reaction often did not go to completion. It is now found that with thionyl chloride and phosphorus pentachloride the acid chlorides are more consistently obtained in good yields than with either reagent alone. More than theoretical quantities of phosphorus pentachloride give a yellowish discoloration to the products.

[1a] Paper No. 9 on amino acids; for No. 8 see Barry, Mattocks, and Hartung, *J. Am. Chem. Soc.*, **70**, 693 (1948). [b] Present address: Medical College of Virginia, Richmond 19, Virginia. [c] Present address: University of North Carolina, Chapel Hill, North Carolina.

The benzyloximino acid chlorides, when pure, are colorless, rather high-boiling liquids. The acid chlorides of lower molecular weight possess peculiar, pungent, straw-like odors. They boil under reduced pressures without appreciable decomposition, but slowly turn dark on storage. Residues of the acid chlorides turned to red solids when stored for several months in glass-stoppered bottles. When the acid chlorides are poured into water they do not generate heat and react rather slowly. No attempt was made to analyse them, but they were characterized through their anilides.

The α-benzyloximino acid anilides were not prepared by the two-phase method, used with the amino acids, because of the availability of aniline to serve as a base

TABLE I

α-BENZYLOXIMINO ACIDS, ACID CHLORIDES, AND ANILIDES

$$\begin{matrix} RCCOR' \\ \| \\ NOCH_2C_6H_5 \end{matrix}$$

R	R′	YIELD, %	M.P., °C.[a]	B.P., °C./MM.	N, %[d]	
					Calc'd	Found
$C_6H_5CH_2$—	OH	66	78–79[b]			
CH_3—	OH	57	73–75		7.26	7.07
CH_3CH_2—	OH	45	86		6.79	6.92
$(CH_3)_2CHCH_2$—	OH	79	79–80		5.95	6.23
$C_6H_5CH_2$—	Cl	84		164/.7		
CH_3—	Cl	45		95–100/.75		
CH_3CH_2—	Cl	80		105–107/.3		
$(CH_3)_2CHCH_2$—	Cl	67		117–118/.85		
$C_6H_5CH_2$—	NHC_6H_5	81	72–73[c]			
CH_3—	NHC_6H_5	84	70–71		10.44	10.75
CH_3CH_2—	NHC_6H_5	84	71		9.93	10.33
$(CH_3)_2CHCH_2$—	NHC_6H_5	77	57		9.03	9.15

[a] Melting points on calibrated block. [b] Waters (5) reported 79–80°. [c] Waters (5) reported 73.5–74°. [d] Micro-analyses by Oakwold Laboratories, Alexandria, Virginia.

and of the ease of separation of aniline hydrochloride from the anilide produced. All the anilides are white solids melting below 100°. They are sometimes difficult to crystallize, cooling and stirring being necessary to induce crystallization.

Coupling amino acids with the α-benzyloximino acid chlorides was accomplished in a two-phase system of ether and aqueous alkali, similar to the procedure of McKie (8). Such a method saves valuable intermediates and allows easy isolation of the reaction product. Furthermore, acid sensitive substances such as tryptophane may be acylated.

The amides so obtained are white solids, usually melting around 100°. Often some difficulty is encountered in inducing crystallization; the products frequently separate as oils. The amides of lower molecular weight are slightly soluble in water, but the higher amides may be crystallized, as a rule, almost quantitatively from ethanol and water. The variation in the melting points of the amides

suggests the possible use of the acid chlorides as reagents for identification of amino acids. Constants for the anilides and amides of the amino acids are found in Tables I and II.

Reduction of the α-benzyloximino acid amides is expected to provide the desired dipeptides. In the course of this work, the reduction of β-phenyl-α-benzyloximinopropionylalanine was studied in an attempt to prepare phenylalanylalanine. Conventional procedures using palladium catalysts with the amide in 95% ethanol and added hydrochloric acid yield the diketopiperazine in small amounts.

TABLE II

α-BENZYLOXIMINO AMIDES RCCONHCHR'COOH
‖
NOCH$_2$C$_6$H$_5$

R	R'	YIELD, %	M.P., °C.[a]	N, %[b]	
				Calc'd	Found
$C_6H_5CH_2$—	H—	90–98	96.5–97	8.59	8.70
$C_6H_5CH_2$—	CH_3—	91	112	8.23	8.46
$C_6H_5CH_2$—	L-(+)$(CH_3)_2CHCH_2$—	77	86–87	7.33	7.10
$C_6H_5CH_2$—	$C_6H_5CH_2$—	85	140–141	6.73	6.97
$C_6H_5CH_2$—	L-(+)$HOOCCH_2CH_2$—	58	110	7.03	6.90
CH_3—	H—	60	127	11.20	11.39
CH_3—	CH_3—	54	118	10.14	10.43
$(CH_3)_2CHCH_2$—	H—	45	58–59	9.56	8.25
$(CH_3)_2CHCH_2$—	CH_3—	94	70	9.15	8.81
$(CH_3)_2CHCH_2$—	$C_6H_5CH_2$—	73	116–116.5	7.33	7.33
$(CH_3)_2CHCH_2$—	$(CH_3)_2CHCH_2$—	92	45–46	8.09	8.25
$(CH_3)_2CHCH_2$—	$C_5H_6NCH_2$—	86	90	9.97	10.43
$(CH_3)_2CHCH_2$—	L-(+)$HOOCCH_2CH_2$—	74	101	7.69	7.41
CH_3CH_2—	H—	90	106	10.60	10.64
CH_3CH_2—	CH_3—	84	94	10.06	10.31
CH_3CH_2—	$(CH_3)_2CHCH_2$—	77	87	8.75	8.39
CH_3CH_2—	$C_6H_5CH_2$—	82	89	7.91	8.17
CH_3CH_2—	L-(+)$HOOCCH_2CH_2$—	52	92–93	8.33	7.89

[a] Melting points on calibrated block. [b] Micro-analyses by Oakwold Laboratories, Alexandria, Va.

When a mixed palladium-platinum catalyst was used under similar conditions, significant amounts of diketopiperazine were isolated. Similar results were obtained with several other amides. Considerable alcohol-soluble material was found in the course of isolation of the reduction products. Consequently, the possibility of ester formation with subsequent cyclization to the diketopiperazine may be suspected, a well known mechanism for the formation of peptide anhydrides (9). Preliminary studies indicate that water added to the reduction mixture suppresses diketopiperazine formation and increases the yield of dipeptides. Further work is being carried out in an effort to complete this reduction to the dipeptide more successfully.

EXPERIMENTAL[2]

Reagents. Many of the chemicals used in this work were purchased from various sources and were used without further purification. Some of the malonic esters, glycine, DL-alanine, L-(−)-leucine, DL-leucine, and L-(−)-tryptophane were purchased from the Eastman Kodak Company. Thionyl chloride and benzyl chloride were redistilled. Ethyl benzylmalonate was prepared in 66–67% yields in a modification of Marvel's preparation (10) by using three moles of ethyl malonate to two moles of benzyl chloride instead of equal molar quantities.

The oximino acids were prepared by the alkaline nitrosation of the substituted malonic esters as reported by Barry (2), with some modifications. The following preparation is exemplary of the type.

β-Phenyl-α-oximinopropionic acid. Sodium (11.5 g., 0.5 mole) was added to 1 liter of absolute alcohol contained in a 2-liter, 3-necked, round-bottomed flask equipped with a condenser, drying tube, stirrer, and dropping-funnel. After solution of the sodium 125 g. (0.5 mole) of ethyl benzylmalonate was added to the hot mixture, which was then cooled to 0° in an ice-salt bath. Then 103 g. (1 mole) of butyl nitrite was added slowly beneath the surface of the mixture over a period of about one hour while keeping the temperature below 5°. The cooling bath was removed, the mixture was allowed to reach room temperature slowly (one hour), and then was heated to reflux. Suction was applied to remove the butanol and ethanol until a volume of about 200 ml. remained. Then 600 ml. of ice and water was added, the product was acidified with hydrochloric acid, and extracted with ether. The ether extract was extracted with 10% sodium hydroxide, which was then heated on the steam-bath for about one hour. After adding ice, the mixture was acidified with concentrated hydrochloric acid and the precipitate which formed was dried *in vacuo* over phosphorus pentoxide. Yield, 95% of light-tan solid melting at 160°. Barry reported 169° for the recrystallized product. Materials of the purity obtained here were adequate for further benzylation.

Benzylation. The preparation of β-phenyl-α-benzyloximinopropionic acid is illustrative of the most satisfactory method found.

In a 1-liter apparatus of the previous type was placed 500 ml. of commercial absolute alcohol and 11.5 g. (0.5 mole) of freshly cut sodium. After the sodium had reacted, 45 g. (0.25 mole) of finely divided β-phenyl-α-oximinopropionic acid was added. Then to the hot solution, 64 g. (0.5 mole) of benzyl chloride was added all at once and the mixture was refluxed for two hours, or until it became neutral. Then 100 ml. of 20% potassium hydroxide in 95% ethanol was added and about 400 ml. of alcohol was distilled out of the mixture. Water and enough hydrochloric acid to make the solution acid were added and the mixture was extracted with ether. The ether along with a good portion of the benzyl alcohol was removed *in vacuo*. The dry residue in the flask was then dissolved in ethanol and water and allowed to crystallize. Usually a quantitative yield of brown solid was obtained. When this material was recrystallized from ethanol-water and decolorized with Nuchar, the yield of solid was 43.5 g. (66%), melting at 78–79°. Waters (5) reported 79–80°.

The other benzylated oximino acids shown in Table I were prepared similarly and recrystallized from ethanol and water. This method was used in preference to Waters' original aqueous-acetone system. The latter method always yielded significant amounts of unreacted oxime which interfered with the isolation of the product. In addition, separation of the benzyl ether from the excess benzyl alcohol encountered in this preparation is not easy. Modifications of reaction temperatures, amount of alkali and benzyl chloride, and reflux times in the acetone-water system did not improve yields over Waters' adopted procedure. Benzylation with benzylphenyldimethylammonium chloride (11) was unsuccessful.

Acid chlorides. The acid chlorides were most economically prepared using a molar equivalent of phosphorus pentachloride with added thionyl chloride. The following preparation of β-phenyl-α-benzyloximinopropionyl chloride was general for these acid chlorides.

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[2] Experimental work carried out at the Naval Research Laboratory, Washington 25, D. C.

To 26.9 g. (0.1 mole) of β-phenyl-α-benzyloximinopropionic acid in 200 ml. of benzene was added 20.8 g. (0.1 mole) of phosphorus pentachloride, in several portions with agitation, and finally a few ml. of thionyl chloride. The mixture was then refluxed for one-half hour. On distillation, 24.1 g. (84%) of product boiling at 164°/0.7 mm. was obtained. The boiling points of the acid chlorides are given in Table I.

Anilides. The preparation of β-phenyl-α-benzyloximinopropionanilide, which follows, is general for this group.

To 1.9 g. (0.02 mole) of aniline and 20 ml. of dry benzene in a small beaker was added, with continuous stirring, 2.9 g. (0.01 mole) of β-phenyl-α-benzyloximinopropionyl chloride. During the addition, a light yellow precipitate formed and the contents of the beaker became warm. The mixture was allowed to stand several hours, the aniline hydrochloride was filtered off, and the benzene evaporated from the filtrate on the steam-bath. The yellow oil remaining was taken up in ethanol and water and allowed to cool. An oil separated which after further cooling crystallized. The crystals were dried *in vacuo* over phosphorus pentoxide. The anilide melted at 72–73°; yield, 2.8 g. (81%).

The properties of the various anilides are given in Table I.

Amides. The preparation of β-phenyl-α-benzyloximinopropionylglycine which follows is rather general for this group.

Glycine, 0.75 g. (0.01 mole), was dissolved in 4 ml. of 10% sodium hydroxide (0.01 mole) and 6 ml. of water, and the solution was overlayered with 10 ml. of ether. Then, while stirring, 2.9 g. (0.01 mole) of β-phenyl-α-benzyloximinopropionyl chloride in 10 ml. of absolute ether was added alternately with 4 ml. of 10% sodium hydroxide (0.01 mole) in 6 ml. of water. A little heat was developed in the reaction flask. The mixture was then allowed to stand in the refrigerator overnight. The lower alkaline layer was neutralized with a small amount of concentrated hydrochloric acid. The oil which separated crystallized on cooling. After drying *in vacuo* over phosphorus pentoxide, 2.95 g. (90%) of white solid was obtained. After recrystallization from ethanol and water, the product melted at 96.5–97°. In larger runs, the yields ranged up to 98%.

For all the glutamic acid derivatives, an extra equivalent of alkali was used. The glutamic acid derivatives were in general very much more soluble in water than those of the monocarboxylic acids.

The α-benzyloximinoisocaproamides were recrystallized from water or very dilute ethanol. In general, this series was very difficult to crystallize, and repeated stirring and cooling were necessary to induce crystal formation.

Several acid chlorides were allowed to react with L-(−)-tyrosine, but low analyses indicated that the pure desired monoacylated product was not obtained. In the preparation of the tryptophane derivative, care was taken to avoid excess acid chloride. This derivative had a tendency to fluff and gel which may account for the slightly high analysis shown in Table II. The amides from α-benzyloximinobutyryl chloride and the amino acids were characteristic in that they rarely separated from the crystallizing medium as oils.

Hydrogenation. The reductions of the acid amides, for the most part, were carried out at room temperature and 20 atmospheres pressure in a glass-lined vessel of such capacity that 0.01 mole of hydrogen gave approximately a 10–12 pound pressure drop, depending on the slight variations in amount of solvent used in the hydrogenations. The palladium catalyst was prepared by the method of Hartung (12) and the platinum catalyst was that of Adams (13).

β-Phenyl-α-benzyloximinopropionylalanine (0.15 mole) was dissolved in 100 ml. of 95% ethanol and 5 ml. of concentrated hydrochloric acid. After addition of 5 g. of palladium catalyst, another 0.5 g. of palladium chloride was added and the mixture was shaken at room temperature under 20 atmospheres of hydrogen. A definite odor of toluene was noted when the bomb was opened after hydrogen uptake was completed. The catalyst was filtered off, the filtrate was neutralized with sodium hydroxide, and then evaporated on the steam-bath. The residue was taken up in water, and alcohol added. A very small quantity of material melting at 268–270° precipitated. The diketopiperazine melts at 267–268° (14).

Anal. Calc'd for $C_{12}H_{14}N_2O_4$: C, 66.03; H, 6.47; N, 12.84.
Found: C, 65.78; H, 6.53; N, 12.86.

Use of an unfortified catalyst was unsuccessful and heating did not help in any way. Use of acetic acid, in place of hydrochloric acid, with an unfortified catalyst was also of no avail.

Since the fortified catalyst caused hydrogen to be taken up, a 40% palladium catalyst was used and the theoretical amount of hydrogen was absorbed. After removing the catalyst, the filtrate was dried *in vacuo* and ammonium hydroxide was added until neutrality was reached. After concentration, alcohol was added. Some of the precipitate which formed dissolved in water. The remainder was insoluble in alkali and acid, indicating anhydride formation.

When 0.015 mole of amide was reduced with 5 g. of 10% palladium catalyst and 0.15 g. of added platinum oxide in 95% ethanol and 5 ml. of concentrated hydrochloric acid, the theoretical amount of hydrogen was used. After neutralization with ammonium hydroxide, evaporation and washing with ethanol, a product was obtained which melted at 240°. The dipeptide melts at 241° (15). However, analyses showed impurities, probably due to diketopiperazine. The difficulties encountered here show how unreliable melting point information may be with products of this type.

In most of the reductions considerable alcohol-soluble material formed, indicating some product other than the diketopiperazine or the dipeptide.

When the amide was reduced in ethanol with added water and hydrochloric acid, considerable product, soluble in both acid and alkali was isolated, indicating more dipeptide formation than previously found. Addition of water, then, may aid in dipeptide formation at the expense of some other compound, possibly the ethyl ester of the amides.

The reductions did show that the benzyl group is readily removed by catalytic hydrogenation. However, the subsequent course of events and the influence of solvent require further study.

SUMMARY

1. An improved method for the preparation of certain α-benzyloximino acids is described.

2. The preparation of the acid chlorides of these acids has been carried out in good yield.

3. These acid chlorides may be condensed with a variety of amino acids, usually in good yield. The variation in melting point of the amides suggests possible use as amino acid derivatives for identification purposes.

4. A study of the reduction of these amides has shown that the benzyl group is readily removed by platinum-palladium catalysts at room temperatures and low pressures. The reaction products isolated indicate the oximes are reduced to the free amines in ethanol and aqueous ethanol with added hydrochloric acid. The isolation of diketopiperazines from these reduction mixtures suggests either the possible formation of ethyl esters or that an exceptionally easy method for anhydridization has been uncovered.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE CHEMISTRY OF HYDROPEROXIDES I. THE ACID-CATALYZED DECOMPOSITION OF α,α-DIMETHYLBENZYL (α-CUMYL) HYDROPEROXIDE[1]

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The decomposition of α-cumyl hydroperoxide, under a variety of conditions, has yielded the following compounds:

1. Phenol
2. Acetophenone
3. α,α-Dimethylbenzyl alcohol
4. Acetone
5. 2,4-Diphenyl-4-methyl-2-pentene
6. α-Cumyl peroxide (α,α-dimethylbenzyl peroxide)
7. Methane
8. Methanol
9. Oxygen
10. Water
11. Ethane
12. Hydrogen peroxide

Obviously such a diversity of products cannot be formed by a single mechanism. The purpose of this and of succeeding papers is to demonstrate that the chemistry of hydroperoxides can best be understood if it be assumed that they may undergo disintegration of any one of the three following independent types: (a) acid-catalyzed decomposition, which proceeds by an ionic mechanism; (b) free-radical decomposition; and (c) decomposition by a reagent which causes evolution of oxygen. Which course the reaction actually follows depends on the reagents used.

Failure to recognize these different mechanisms has hitherto made it impossible to interpret much of the experimental data recorded in the literature. For example, in many instances acid decomposition was carried out at an elevated temperature, and thus a free-radical reaction was superimposed upon the ionic reaction. A general method for carrying out exclusively ionic decompositions of hydroperoxides has now been perfected, and the products formed in many such reactions have been carefully determined.[2] The hydroperoxides were decomposed by dissolving them in glacial acetic acid and adding to the solution a small amount (0.01–0.2%, depending upon the hydroperoxide used) of perchloric acid. Under these conditions, *tertiary* hydroperoxides containing at least one aromatic group decompose rapidly at room temperature. Since these decompositions are exothermic, it is necessary, in some cases, to cool the reaction mixture. In the present paper, the decomposition of α-cumyl hydroperoxide is discussed.

DECOMPOSITION OF α-CUMYL HYDROPEROXIDE

The decomposition of α-cumyl hydroperoxide by strong acids is highly exothermic, and proceeds at an appreciable rate even at −80°. In order to minimize

[1] The authors wish to express their indebtedness to the Research Corporation for financial support which made this work possible.

[2] These will be reported in succeeding articles.

undesirable side-reactions, the decompositions here reported were carried out in acetic acid (in which the hydroperoxide is stable at room temperature) in the presence of 0.1 mole-per cent of perchloric acid.[3] Under these conditions, α-cumyl hydroperoxide decomposes quantitatively into phenol and acetone. The formation of these products is best accounted for by the following (perhaps oversimplified) chain-reaction mechanism.[4] In this scheme, "A" is an acid in the Lewis sense (1).

1. $C_6H_5(CH_3)_2C—OOH + A \rightarrow [C_6H_5(CH_3)_2CO]^+ + AOH^-$
2. $[C_6H_5(CH_3)_2CO]^+ \rightarrow [(CH_3)_2C—OC_6H_5]^+$
3. $C_6H_5(CH_3)_2C—OOH + [(CH_3)_2C—OC_6H_5]^+ \rightarrow [C_6H_5(CH_3)_2CO]^+ + (CH_3)_2CO + C_6H_5OH$

The validity of the idea that only (strong) acids in the Lewis sense cause decomposition of α-cumyl hydroperoxide is attested by the following facts: (a) hydrogen chloride, which is a weak acid in acetic acid, in acetic acid is a relatively ineffective agent for the decomposition;[5] (b) ferric chloride, which in alcohol is a weak acid, causes no decomposition of α-cumyl hydroperoxide in that solvent. However, ferric chloride in benzene is, in the Lewis sense, a relatively strong acid, and, in this solvent, it readily converts α-cumyl hydroperoxide into phenol and acetone. Similar results were obtained with other solvents (dioxane, benzene) and other acids (boron fluoride, aluminum chloride, sulfuric acid). This indicates the absence of a specific solvent or anion effect.

Furthermore, the decomposition of α-cumyl hydroperoxide can be substantially altered by introducing substances which compete for the acid "A." Thus, the addition to the acetic acid solution of varying amounts of α,α-dimethylbenzyl alcohol, or α-methylstyrene, followed by the addition of 70% perchloric acid to the extent of 0.1 mole per mole of the α-cumyl hydroperoxide used, causes the formation of correspondingly varying amounts of 2,4-diphenyl-4-methyl-2-pentene (α-methylstyrene dimer),[6] and correspondingly decreased amounts of phenol and acetone. When a large amount of α,α-dimethylbenzyl alcohol (2 or 3 moles per mole of hydroperoxide) is added to the α-cumyl hydroperoxide in the presence of the acid "A," the reaction which favors phenol and acetone formation (steps 1, 2, and 3) is completely suppressed; the dimer of α-methylstyrene and hydrogen peroxide are the sole products.[7] These data are interpreted upon

[3] As is well known, perchloric acid in acetic acid forms a "superacid solution" see, *e.g.*, Hall and Conant, *J. Am. Chem. Soc.*, **49**, 3047 (1927).

[4] The intermediate formation of a positively-charged oxygen atom in the oxidation of carbinols has been suggested by many investigators. The postulate that molecules containing a positive charge on the oxygen atom may undergo a rearrangement of the carbon skeleton was first emphasized by Criegee, *Ann.*, **560**, 127 (1948).

[5] Minute traces of hydrogen chloride in otherwise pure α-cumyl hydroperoxide induce a violent decomposition.

[6] This product wherever formed was identical with the dimer of α-methylstyrene prepared by the method of Bergmann, Taubadel, and Weiss, *Ber.*, **64**, 1493 (1931).

[7] α-Cumyl peroxide in acetic acid decomposes in the presence of small amounts of perchloric acid to give the dimer of α-methylstyrene, phenol, and acetone. However, here too, the addition of α,α-dimethylbenzyl alcohol suppresses completely the formation of phenol and acetone. The dimer of α-methylstyrene and hydrogen peroxide are the only reaction products.

the assumption that α,α-dimethylbenzyl alcohol is a stronger base than α-cumyl hydroperoxide; hence the reaction indicated in step 1 cannot take place.

On the other hand, when α,α-dimethylbenzyl alcohol, dissolved in glacial acetic acid, is treated, in the presence of acid, with a 3–5-mole excess of hydrogen peroxide, a quantitative yield of phenol and acetone is obtained. Similarly, when α-methylstyrene, dissolved in glacial acetic acid, is treated with hydrogen peroxide in the presence of concentrated hydrochloric acid (or any strong acid) a nearly quantitative yield of phenol is formed. These facts are not incompatible with the scheme postulated for the decomposition of α-cumyl hydroperoxide, for it must be remembered that under the conditions cited two of the equilibrium reactions are followed by further irreversible reactions (Chart I).

CHART I

4. $C_6H_5(CH_3)_2COH + A^a \rightleftharpoons C_6H_5(CH_3)_2C^+ + B + H_2O$
5. $C_6H_5(CH_3)_2C^+ + B \rightleftharpoons C_6H_5(CH_3)C{=}CH_2 + A$
6. $C_6H_5(CH_3)_2C^+ + H_2O_2 + B \rightleftharpoons C_6H_5(CH_3)_2C{-}OOH + A$
7. $C_6H_5(CH_3)_2C{-}OOH + A'^b \rightarrow C_6H_5(CH_3)_2C{-}O^+ + B' + H_2O$
8. $C_6H_5(CH_3)_2C^+ + C_6H_5(CH_3)C{=}CH_2 + B \rightarrow \text{Dimer}^c + A$

[a] A is an acid and B its conjugate base ($B + H^+ \rightleftharpoons A$). [b] In reactions 4 to 6 the acid A is a stronger acid than dimethylbenzyl alcohol, and in reaction 7 A′ is a stronger acid than the hydroperoxide. [c] Dimer of α-methylstyrene, namely, 2,4-diphenyl-4-methyl-2-pentene.

The final product depends, therefore, largely upon the experimental conditions used.[8] The observation of Hock and Lang (2) that α,α-dimethylbenzyl alcohol is formed when α-cumyl hydroperoxide is treated with dilute acids may readily be interpreted in accordance with the reaction scheme outlined above: namely, the carbinol arises by the hydrolytic attack of hydronium ion on the hydroperoxide with the simultaneous formation of hydrogen peroxide.[9]

Of considerable relevance to a general understanding of the reactions cited above is the observation that when α-methylstyrene, dissolved in acetic acid, is treated with hydrogen peroxide in the presence of catalytic quantities of perchloric acid, a different compound is obtained, namely α-phenyl-α-methylethylene glycol. The reactions of olefins with hydrogen peroxide to yield a variety of different products will be discussed in a future publication.

EXPERIMENTAL PART

Materials used. Commercial 72% α-cumyl hydroperoxide (Hercules Powder Company) was purified by the method of Hock and Lang (2). Extreme care was taken to insure com-

[8] These considerations made it possible to select various aryl tertiary alcohols to compare a number of aryl and other groups with respect to their tendency to migrate from carbon to oxygen. The results will be reported shortly.

[9] The decomposition of the hydroperoxide with 10% sulfuric acid according to the method of Hock and Lang was repeated. The water solution contained peroxidic material which was considerably more soluble in water than ether. When the neutralized aqueous solution was treated with potassium iodide, oxygen was liberated. The presence of hydrogen peroxide is thus demonstrated.

plete removal of acid during the purification. Under these conditions the final product is stable and may be distilled at pressures between 0.01–0.3 mm. The peroxide thus obtained had an iodometric titre of 98–99% of the calculated value. The glacial acetic acid used was reagent grade (99.5%) supplied by the General Chemical Company; this material was employed without further purification. α,α-Dimethylbenzyl alcohol was prepared by the reduction of α-cumyl hydroperoxide by the method of Hock (2). The compound was purified by crystallization from cold petroleum ether; the fraction used melted at 36°. In some instances, α-methylstyrene was prepared by dehydrating the carbinol with potassium bisulfate. In other instances, redistilled commercial α-methylstyrene (supplied by the Dow Chemical Company) was used. Commercial perchloric acid (70%) and hydrogen peroxide (Merck's 30% reagent grade) were used.

Decomposition of α-cumyl hydroperoxide in the presence of acetic acid and catalytic quantities of perchloric acid. α-Cumyl hydroperoxide (15.2 g., 0.1 mole), dissolved in 100 cc. of glacial acetic acid was treated with 0.1 cc. of a 5% solution of 70% perchloric acid in acetic acid. The temperature of the reaction mixture was kept below 22°. The peroxide titre of the mixture fell to zero after 5 minutes. *Phenol* (9 g., 95% yield) was isolated in crystalline form. *Acetone* was identified and estimated by means of its dinitrophenylhydrazone. An unidentified neutral oil (amounting to less than 3% of the starting material) was also obtained.

Similar results were obtained with dioxane or benzene as solvents, and with ferric chloride, boron fluoride, aluminum chloride, or sulfuric acid as acids. In the presence of traces of hydrogen sulfide, anhydrous ferrous salts or sulfur dioxide, violent decomposition to phenol and acetone occurred only after an induction period. During this period the catalysts were oxidized to their higher valence states, in which form they are stronger acids. With ceric sulfate a similar induction period was observed; here, however, the ceric sulfate is reduced to a lower valence state, thereby liberating sulfuric acid.

Acid decomposition of α-cumyl hydroperoxide in the presence of α,α-dimethylbenzyl alcohol. α-Cumyl hydroperoxide (15.2 g., 0.1 mole), and α,α-dimethylbenzyl alcohol (30 g.) were dissolved in 100 cc. of glacial acetic acid. To this solution was added 0.1 cc. of 5% perchloric acid in acetic acid. The temperature was maintained below 25°. The following fractions were isolated: phenol, less than 5%; α-methylstyrene, 12 g.; dimer of α-methylstyrene (b.p. 65°/0.001 mm., n_D^{20} 1.5790), 27 g.

Anal. Calc'd for $C_{18}H_{20}$: Mol wt., 236; C, 91.3; H, 8.7.

Found: Mol. wt., (cryoscopic, benzene), 225; C, 90.8; H, 8.7.

When 30 g. of the carbinol was similarly treated in acetic acid with perchloric acid, in the absence of α-cumyl hydroperoxide, the dimer of α-methylstyrene (12 g.) was obtained. When α-methylstyrene was used in place of the carbinol the results were similar.

Oxidation of α,α-dimethylbenzyl alcohol to acetone and phenol. α,α-Dimethylbenzyl alcohol (5 g.) in 75 cc. of glacial acetic acid was treated with 30% hydrogen peroxide (10 cc.) and 1 cc. of 70% perchloric acid. The reaction mixture was maintained below 30°. Phenol (3.3 g., 93%) was isolated in crystalline form.

Oxidation of α-methylstyrene. α-Methylstyrene 2.36 g. (0.02 mole), dissolved in glacial acetic acid (4.0 cc., 0.06 mole) was cooled to 5°. To this solution was added 1.72 cc. (0.02 mole) of concentrated hydrochloric acid. After 15 minutes, 30% hydrogen peroxide (2.5 cc., 0.023 mole) was added. The suspension was shaken, and the temperature of the reaction mixture was maintained below 50° by cooling until a homogeneous light-purple solution resulted. The reaction mixture was treated with 100 ml. of water, and the phenol was precipitated with bromine.

The melting point of this material was 93–95°. The yield of tribromophenol thus obtained was 90%, calculated upon the amount of α-methylstyrene used in the reaction.

SUMMARY

1. The variety of products obtained by the decompositions of α-cumyl hydroperoxide is due to the superimposition of different modes of decomposition.

2. It is shown that one mode of decomposition is that catalyzed by traces of strong acids (in the Lewis sense). With α-cumyl hydroperoxide the decomposition products are exclusively phenol and acetone.

3. In the presence of excess α-methylstyrene or α,α-dimethylbenzyl alcohol the acidic decomposition results in the exclusive formation of 2,4-diphenyl-4-methyl-2-pentene (α-methylstyrene dimer).

4. In the presence of a large excess of hydrogen peroxide 2,2-dimethylbenzyl alcohol gave exclusively phenol and acetone.

5. In the presence of equivalent amounts of concentrated hydrochloric acid, α-methylstyrene when treated with an equivalent amount of hydrogen peroxide gave 90 per cent phenol.

CHICAGO 37, ILLINOIS

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE CHEMISTRY OF HYDROPEROXIDES. II. THE PREPARATION AND PROPERTIES OF α,α-DIMETHYLBENZYL (α-CUMYL) PEROXIDE[1]

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α-Cumyl peroxide cannot be conveniently prepared by any of the methods ordinarily used for the preparation of tertiary aliphatic peroxides. *tert*-Butyl and *tert*-amyl peroxides, for example, are readily obtained by treating the corresponding hydroperoxides with the corresponding alcohols in the presence of a strong acid (1) (*e.g.*, 60–70% sulfuric). But for α-cumyl peroxide, because of the great sensitivity of α-cumyl hydroperoxide to acids (see preceding paper in this series), this method is not suitable. If α-cumyl hydroperoxide is treated with a strong acid, the reaction products, depending on experimental conditions, are either phenol and acetone, or the dimer of α-methylstyrene, or all three of these compounds.

α-Cumyl peroxide has now been prepared by four different thermal reactions.

1. $C_6H_5(CH_3)_2C{-}OOH \xrightarrow[95^\circ]{\text{Norit}} [C_6H_5(CH_3)_2CO{-}]_2$ (40%) + $CH_3COC_6H_5$ (10%) + $C_6H_5(CH_3)_2COH$ (16%) + C_6H_5OH (trace) + oil (unidentified) (30%) + O_2 (7%)
2. $C_6H_5(CH_3)_2C{-}OOH \xrightarrow[105^\circ]{CH_3COOH} [C_6H_5(CH_3)_2CO{-}]_2$ (20–35%) + $CH_3COC_6H_5 + CH_3OH + (CH_3)_2CO + C_6H_5OH$

The rate of decomposition of the hydroperoxide and the amount of α-cumyl peroxide formed vary in case 1 with the carbon used, and in case 2 with the dilution, temperature, and origin of the acetic acid. Thus, when the decomposition was conducted at 105° in "C.P." acetic acid (General Chemical Company) or in other acetic acid purified by crystallization, about 20% of α-cumyl peroxide was obtained. On the other hand, when the reaction was conducted in unpurified acetic acid purchased from the Niacet Chemical Company the yield of α-cumyl peroxide was consistently higher (often 35%, almost double the amount formed when recrystallized acetic acid was used). Many of the obvious impurities (water, anhydride, metallic salts) which might account for differences between acetic acids from various sources have been found to have little effect on the yield of the peroxide. The cause of the observed discrepancies is still unknown.

When equal weights of α-cumyl hydroperoxide and benzoic acid are heated to 105° for two hours, the yield of α-cumyl peroxide is 40%. The other principal

[1] The authors wish to express their appreciation to the Research Corporation for support which made this work possible.

products of the reaction are acetophenone (6%), phenol (30%), and α,α-dimethylbenzyl alcohol (12%).

3. $C_6H_5(CH_3)_2C—OOH \xrightarrow[95°]{C_6H_5(CH_3)_2COH} [C_6H_5(CH_3)_2CO—]_2$

This method is by far the best for preparing α-cumyl peroxide. The yield of the peroxide, on the basis of the hydroperoxide used (two moles of the hydroperoxide are converted into one mole of the peroxide), is almost quantitative. The extent of solvent participation is indicated by formation of 25% of acetophenone, about 7% of oxygen, and a small amount of methane.

When α-cumyl hydroperoxide was heated in tertiary aliphatic alcohols containing no aromatic group, traces of α-cumyl peroxide and mixed peroxide could be isolated. For example, the hydroperoxide decomposed when heated to 95° in *tert*-amyl alcohol, to give a small amount of methane, about 15% of oxygen, 26% of acetophenone, 39% of α,α-dimethylbenzyl alcohol, and 30% of an unidentified high-boiling material.

When α-cumyl hydroperoxide was heated to 95° in 1-phenylethanol, the reaction products were methane (about 2%), oxygen (15%), α,α-dimethylbenzyl alcohol (55%), and acetophenone (70%).

These products are well accounted for by assuming the following over-all reactions:

$$C_6H_5(CH_3)_2C—OOH \begin{cases} \xrightarrow{A} C_6H_5(CH_3)_2COH(30\%) + O_2(15\%) \\ \xrightarrow{B} CH_3COC_6H_5(45\%) + CH_3OH \\ \xrightarrow[CH_3(C_6H_5)CHOH]{C} CH_3COC_6H_5(25\%) + C_6H_5(CH_3)_2COH(25\%) \end{cases}$$

Reactions *A* and *B* are thermal decompositions of α-cumyl hydroperoxide in 1-phenylethanol. Reaction *C*, however, involves the oxidation of 1-phenylethanol to acetophenone, and the reduction of the hydroperoxide to α,α-dimethylbenzyl alcohol. It is noteworthy that α-cumyl hydroperoxide by itself, or in solution in inert solvents (*e.g.*, cumene or benzene) is stable at 100°. Studies on the effect of solvents on the thermal stability of the hydroperoxide will be reported in another paper.

4. $C_6H_5(CH_3)C—OOH$ (1.3 mole) + $(CH_3COO)_2$ (1 mole) $\xrightarrow[100°]{C_6H_5(CH_3)_2CH}$ $[C_6H_5(CH_3)_2CO—]_2$ (0.44 mole) + CH_4 (1.3 mole) + CO_2 (1.64 mole) + $C_6H_5(CH_3)_2COH$ (1.3 mole)

This rather bizarre reaction was attempted in the hope of elucidating the mechanism of formation of α-cumyl peroxide from α-cumyl hydroperoxide. It has been fairly well established that a tertiary aliphatic peroxide, when prepared from an aliphatic hydroperoxide and a tertiary aliphatic alcohol, is formed by a polar mechanism: that is, it is never necessary to assume that the peroxide is formed

by a combination of two free radicals, 2 RO· → RO:OR. α-Cumyl peroxide cannot be formed from the hyperperoxide and the alcohol in the presence of strong acids, but this fact does not preclude the possibility that, under carefully adjusted conditions, the peroxide might be formed from the hydroperoxide by a polar mechanism. The methods (1, 2, and 3) already mentioned involve thermal reactions, and, hence, do not furnish unequivocal proof in favor of either a polar or a free-radical mechanism. It was, therefore, desirable to demonstrate whether or not the free radical $C_6H_5(CH_3)_2CO\cdot$ is stable enough to dimerize to α-cumyl peroxide. The formation of α-cumyl peroxide (along with other reaction products) when acetyl peroxide (dissolved in cumene) is slowly added to a hot (100°) solu-

TABLE I

REACTION OF α-CUMYL HYDROPEROXIDE WITH ACETYL PEROXIDE (1 EQUIV.) IN THE PRESENCE OF SOLVENTS

REAGENTS (MOLES)	CUMENE		ETHYLBENZENE		1-PHENYL-ETHANOL
	75°	100°	75°	100°	85°
α-Cumyl hydroperoxide (initial)	1.5	1.9	1.12	1.68	2.5
α-Cumyl hydroperoxide (consumed)	0.84	1.29	0.68	0.9	None
PRODUCTS (MOLES)					
Methane[a]	1.07	1.32	1.4	1.2	1.0
Carbon dioxide	1.5	1.64	1.67	1.7	1.0
Acetophenone	0.03	Trace	0.11	0.7	1.0[b]
α,α-Dimethylbenzyl alcohol	.27	1.3	.15	.9	—
α-Cumyl peroxide	.44	0.44	—	—	—
High-boiling oil[c]	.17	.2	—	—	None
α-Phenethyl α-cumyl peroxide	—	—	0.55	None	—
1-Phenylethanol	—	—	None	None	—

[a] In all cases the gas was pure methane. [b] Acetic acid (0.7 mole) was also isolated. [c] Molecular weight, 300.

tion of α-cumyl hydroperoxide in cumene, may be accounted for by assuming the dimerization of free $C_6H_5(CH_3)_2CO\cdot$ radicals, formed from α-cumyl hydroperoxide. The reaction may be assumed to proceed as indicated in (*a*) and (*b*).

(*a*) $(CH_3COO—)_2 \rightarrow CH_3\cdot + CO_2 + CH_3COO\cdot$

(*b*) $C_6H_5(CH_3)_2CH + CH_3\cdot \rightarrow C_6H_5(CH_3)_2C\cdot + CH_4$

In the absence of α-cumyl hydroperoxide, the free radical thus formed would dimerize (quantitatively) to bi-α-cumyl (2,3-dimethyl-2,3-diphenylbutane). However, since no bi-α-cumyl is formed under these conditions, reactions (*c*) and (*d*) suggest themselves.

(*c*) $C_6H_5(CH_3)_2C\cdot + C_6H_5(CH_3)_2C—OOH \rightarrow C_6H_5(CH_3)_2COH + C_6H_5(CH_3)_2CO\cdot$

(*d*) $2\ C_6H_5(CH_3)_2CO\cdot \rightarrow [C_6H_5(CH_3)_2CO—]_2$

The quantitative relationships of the various reaction products (transformation of over 75% of the α-cumyl hydroperoxide to the peroxide; formation of two moles α,α-dimethylbenzyl alcohol per mole of α-cumyl peroxide, etc.), are consistent with this scheme.

However, a more thorough study of the reactions of acetyl peroxide and α-cumyl hydroperoxide in different solvents, and at various temperatures (Table I), completely rules out reaction (*d*) as the source of the $(RO—)_2$ compounds. It is also doubtful to what extent reaction (*c*) contributes to the formation of the α,α-dimethylbenzyl carbinol. Actually, reactions (*c*) and (*d*) cannot be reconciled with the following phenomena recorded in Table I: (a) the variation in yield of α,α-dimethylbenzyl alcohol with temperature when cumene is the solvent, (b) the formation of a mixed peroxide (α-phenethyl α-cumyl peroxide) when ethylbenzene is the solvent and the reaction is conducted at 75°, and (c) the preferential attack upon the 1-phenylethanol when the latter material and α-cumyl hydroperoxide are heated with acetyl peroxide.

Whereas all the evidence thus far available indicates that free RO· radicals do not dimerize (and this point is of importance in kinetic studies, for no such reaction should be assumed as a chain-terminating step), another explanation of the results cited must be sought. Provisionally, reactions (*e*) to (*j*) are suggested.

(*e*)[2] $C_6H_5(CH_3)_2CH + CH_3\cdot \rightarrow C_6H_5(CH_3)_2C\cdot + CH_4$

(*f*) $C_6H_5(CH_3)_2C\cdot + C_6H_5(CH_3)_2C—OOH \rightarrow [C_6H_5(CH_3)_2C—OOH\cdot C(CH_3)_2C_6H_5]$ complex $\{A\}$

(*g*)[3] $\{A\} + C_6H_5(CH_3)_2C—OOH \rightarrow [C_6H_5(CH_3)_2CO—]_2 + C_6H_5(CH_3)_2CO\cdot + H_2O$

(*h*) $\{A\} + (CH_3COO—)_2 \rightarrow [C_6H_5(CH_3)_2CO—]_2 + CH_4 + CO_2 + CH_3COO\cdot$

(*i*) $\{A\} + C_6H_5(CH_3)_2CH \rightarrow 2\ C_6H_5(CH_3)_2COH + C_6H_5(CH_3)_2C\cdot$

(*j*) $C_6H_5(CH_3)_2CO\cdot + C_6H_5(CH_3)_2CH \rightarrow C_6H_5(CH_3)_2COH + C_6H_5(CH_3)_2C\cdot$

The formation (when cumene is the solvent) of larger amounts of α,α-dimethylbenzyl alcohol at 100° than at 75°, may be explained in either or both of the following ways. At the lower temperature (75°), the decomposition of acetyl peroxide is slow; and therefore the concentration of acetyl peroxide in the solution is high, and reaction (*h*), which is wasteful of the initiating material, is favored. At the higher temperature (100°), the concentration of the acetyl peroxide in solution is low (for it is introduced very slowly and is rapidly decomposed); therefore reaction (*g*) predominates. Since reaction (*i*) takes place readily at 100°, but less readily at 75°, somewhat longer reaction chains are possible under the latter conditions; hence more α-cumyl hydroperoxide is consumed (Table I), and the yield of α,α-dimethylbenzyl alcohol is larger. These con-

[2] The gas formed in these reactions is pure methane.

[3] Reaction (*g*) could also be written so as to make it yield the peroxide, α,α-dimethylbenzyl alcohol, and a free hydroxyl radical. The data now at hand do not justify an unequivocal choice.

clusions are strikingly supported by consideration of the reaction products at 75° and 100° with ethylbenzene as a solvent.[4]

Additional evidence for the formation of the peroxide by reactions (*e*), (*f*), (*g*), and (*h*) is the formation of *tert*-butyl α-cumyl peroxide when acetyl peroxide is decomposed in a mixture of cumene and *tert*-butyl hydroperoxide.

$$(CH_3)_3C{-}OOH + C_6H_5(CH_3)_2CH + (CH_3COO{-})_2 \xrightarrow{85\text{–}100^\circ} C_6H_5(CH_3)_2C{-}OO{-}C(CH_3)_3 + CH_4 + CO_2$$

It is of interest that no *tert*-butyl peroxide nor α-cumyl peroxide is formed under these conditions.

Two other points invite comment. First, the oxygen-to-oxygen bond in α-cumyl peroxide is remarkably stable in the presence of free radicals, as evidenced by the fact that when the peroxide, dissolved in ethylbenzene, is treated with acetyl peroxide at 85–100°, practically all of it is recovered unchanged, and the reaction

TABLE II

DECOMPOSITION OF ACETYL PEROXIDE (1 MOLE) IN α,α-DIMETHYLBENZYL ALCOHOL (5 MOLES)

	MOLES
α,α-Dimethylbenzyl alcohol (consumed)	0.23
CO_2	1.0
CH_4	0.27
C_2H_6	.27
Acetic acid	.65
Methyl acetate	.10
Polymer (average mol. wt., 617)	.04

product is a mixture of the *meso* and racemic forms of 2,3-diphenylbutane (2). Second, the hydrogen atoms of tertiary alcohols are highly resistant to an attack by alkyl free radicals as evidenced by the data of Table II, which show that the products of decomposition of acetyl peroxide in α,α-dimethylbenzyl alcohol are approximately those of a simple thermal decomposition.

PROPERTIES OF α-CUMYL PEROXIDE

α-Cumyl peroxide melts at 39°, and can be sublimed, without decomposition, at 100°/0.2 mm. Thermally it is less stable than α-cumyl hydroperoxide. It does not oxidize hydrogen iodide under the conditions ordinarily used for the deter-

[4] The somewhat shorter chain where ethylbenzene, instead of cumene, is the solvent (Table I) may be explained as follows: the free radical complex {**A**} first formed, namely $\{C_6H_5(CH_3)_2C{-}OOH\cdot C_6H_5(CH_3)(H)C\cdot\}$ disproportionates preferentially at the higher temperatures $2\,\mathbf{A}' \rightarrow 2\,C_6H_5(CH_3)_2OH + C_6H_5COCH_3 + C_6H_5CHOHCH_3$, and therefore reactions (*g*), (*h*), and (*i*) are suppressed. The fact that no 1-phenylethanol can be isolated is readily understood, since it reacts faster with acetyl peroxide than any of the other substances present in solution.

mination of peroxides (3). Sodium powder, in ether, reduces the peroxide quantitatively to α,α-dimethylbenzyl alcohol. A solution of the peroxide in glacial acetic acid is transformed by small amounts of perchloric acid, into acetone, phenol, and the dimer of α-methylstyrene.

EXPERIMENTAL PART

Preparation of α-cumyl peroxide in the presence of charcoal. To 10 g. of α-cumyl hydroperoxide (purified as specified in the preceding paper) was added 0.6 g. of Norit A, (Pfanstiehl Chemical Company). The reaction mixture was kept at 95° for 36 hours. Gas (15 mole-%) was evolved at the beginning of the reaction. The reaction mixture was separated from the Norit by filtration, and the residual liquid was removed from the Norit by washing with ether. The Norit recovered corresponded in weight to the amount used originally. Only a small amount (0.1 g.) of the reaction product was soluble in alkali. The low-boiling fractions (acetophenone and α,α-dimethylbenzyl alcohol) were removed from the filtrate by distillation at 1 mm. The products obtained were: α-cumyl peroxide, 24%; high-boiling residue, 16%; acetophenone, 12%; α,α-dimethylbenzyl alcohol, 48%. Use of another sample of Norit (of unknown origin) resulted in the formation of α-cumyl peroxide, 43%; high-boiling oil, 31%; acetophenone, 10%; α,α-dimethylbenzyl alcohol, 16%. Decolorizing charcoal (of unknown origin) led to a reaction product (73%) containing high-boiling oils from which no α-cumyl peroxide could be recovered.

Acetophenone was estimated as the dinitrophenylhydrazone. The carbinol was estimated by a quantitative adaptation of Holmberg's (4) method of converting α,α-dimethylbenzyl alcohol into its thioglycolic acid derivative. To the mixture suspected to contain 0.5–1.0 g. of carbinol, 1.0 g. of thioglycolic acid and 10 cc. of 2 *N* hydrochloric acid was added. The resulting mixture was agitated at reflux temperature for 2.5 hours, cooled, washed with water, and then extracted with alkali. The alkaline extract was acidified, and the resulting thioglycolic acid derivative was allowed to crystallize. The α,α-dimethylbenzyl alcohol derivative may be separated from the corresponding 1-phenylethanol derivative by making use of the greater solubility of the latter in petroleum ether. Thus, by merely shaking an aqueous suspension of a mixture of the two derivatives with petroleum ether the α,α-dimethylbenzyl alcohol-thioglycolic acid compound may be made to crystallize. It should be mentioned that in this determination no distinction is made between α-methylstyrene and α,α-dimethylbenzyl alcohol.

To the higher-boiling residue remaining after removal of the acetophenone and carbinol was added 95% ethanol. When the ethanol solution was cooled to −70°, α-cumyl peroxide crystallized. The crystals were collected from the cold solution.

Preparation of α-cumyl peroxide in acetic acid. α-Cumyl hydroperoxide (15.2 g. of 99% titre) dissolved in 18 g. of glacial acetic acid (Niacet) was held at 94° for 2 hours. By this time the peroxide titre had fallen to zero. Practically all the acetic acid was removed by distillation at reduced pressure (15 mm.). From the residue phenol was extracted with alkali, and isolated as crystalline phenol (27%). Acetone was estimated in the acetic acid distillate; it corresponded in amount to the amount of phenol. From the residue remaining after alkaline extraction, acetophenone was distilled; traces of α,α-dimethylbenzyl alcohol were found. The oil remaining after removal of the acetophenone, was heated to 70°/0.01 mm., and the α-cumyl peroxide which sublimed was collected (35%). A small amount (0.2 g.) of oily residue remained. Samples of glacial acetic purified by crystallization gave decreased amounts (15–20%) of α-cumyl peroxide, along with a correspondingly increased amount of phenol.

Lowering the reaction temperature, addition of small amounts of water to the acetic acid, or higher dilution of the α-cumyl hydroperoxide decreased the yield of the peroxide. Increased amounts (52%) of peroxide were formed when α,α-dimethylbenzyl alcohol was added (in amount equivalent to the hydroperoxide present) to the acetic acid solution.

α-Cumyl peroxide formation in benzoic acid.—α-Cumyl hydroperoxide (15.2 g.) and ben-

zoic acid (15 g.) were heated at 105° for 20 hours. From the reaction mixture were obtained: phenol, 30%; acetophenone, 6%; α,α-dimethylbenzyl alcohol, 12%; α-cumyl peroxide, 40%; high-boiling residue, 0.3 g.

When 1-phenylethanol (0.15 mole) and α-cumyl hydroperoxide (0.1 mole) in benzoic acid (0.5 mole) were heated at 105° for 48 hours a gas was evolved. This gas (12 mole-%) contained 5–10 mole-% of methane. From the reaction product the following substances were isolated: phenol 20%; high-boiling residue, 30%. From this residue only small amounts of α-cumyl peroxide could be separated. The small yield of α-cumyl peroxide is not surprising in view of the extended duration of the heating.

Preparation of α-cumyl peroxide in α,α-dimethylbenzyl alcohol.[5] A mixture of α-cumyl hydroperoxide (15.2 g.) and dimethylbenzyl alcohol (22 g.) was heated at 95° for 48 hours. During this time 6.7 mole-% of gas was evolved. The unchanged carbinol, the α-methylstyrene, and the acetophenone were removed at reduced pressure. The amount of acetophenone formed in this reaction (estimated from the weight of the 2,4-dinitrophenylhydrazone derivative) was 25 mole-%. From the oily residue 50 mole-% of α-cumyl peroxide was obtained by crystallization from ethanol. The oil remaining after the crystallization was heated to 70°/0.01 mm., and the material that sublimed was collected. The additional amount of α-cumyl peroxide thus obtained was 50 mole-% on the basis of the hydroperoxide used (total yield, 13.5 g., *ca* 100 mole %). A very small amount of oily residue still remained.

Decomposition of α-cumyl hydroperoxide in tert-amyl alcohol. α-Cumyl hydroperoxide (10 g.) in *tert*-amyl alcohol (14 g.) was refluxed for 3 days. During this time 430 cc. of gas was evolved. Analysis showed that 50% of this gas was not condensible in liquid nitrogen; it was therefore assumed to be oxygen. The remainder of the gas was fractionated on a vacuum line. It consisted of 5–10% of methane (identified by its vapor pressure at liquid nitrogen temperature, 11 mm.), and a mixture of 2-methyl-1-butene and 2-methyl-2-butene (mol. wt., 63; calc'd mol. wt., 70; vapor pressure at −10°, 122 mm.).

The liquid reaction product was distilled at reduced pressure to remove the more volatile fractions. The distillate was analyzed for acetophenone (26%) and α,α-dimethylbenzyl alcohol (39%) in the manner previously described. A high-boiling oil remained; from this only traces (1%) of α-cumyl peroxide could be isolated. The remainder of the oil (mol. wt., 297 in benzene) was not further investigated.

Decomposition of α-cumyl hydroperoxide in 1-phenylethanol. 1-Phenylethanol (free of acetophenone) was prepared as follows. To a stirred solution of lithium aluminum hydride (12 g.) in 250 cc. of ether, 120 g. of acetophenone was added dropwise. After the reaction was completed, water was added slowly; the ether layer was separated and dried, and the ether was distilled. 1-Phenylethanol was distilled at reduced pressure (yield 95%). It gave a negative test for acetophenone.

α-Cumyl hydroperoxide (15.2 g.) in 1-phenylethanol (24 g.) was heated at 90° for 96 hours. During this time 340 cc. of gas was evolved, and all the α-cumyl hydroperoxide was consumed. The gas consisted of a mixture of methane and oxygen. Calculated on the basis of α-cumyl hydroperoxide used, there was 2% methane and 15% oxygen. The reaction mixture was analyzed for acetophenone (75%) and α,α-dimethylbenzyl alcohol (55%) as previously described.

The acetyl peroxide-induced decomposition of α-cumyl hydroperoxide in the presence of cumene. To a mixture of 0.188 mole of α-cumyl hydroperoxide and 0.45 mole of cumene at 100° a solution of 0.10 mole of acetyl peroxide in 0.50 mole of cumene was added dropwise over a period of two hours. Provision was made for absorbing carbon dioxide and collecting the methane evolved in the decomposition. The products formed are recorded in Table I. The reaction was considered complete when there was no further evolution of gas. Titration of the reaction mixture indicated the presence of 0.056 mole of unchanged α-cumyl hydroperoxide. There was no significant change in titre after two-hours additional heating at

[5] It is noteworthy that the presence of some impurities, particularly traces of alkali, prevents the formation of α-cumyl peroxide by the method here described.

100°. The reaction mixture was distilled at reduced pressure. α,α-Dimethylbenzyl alcohol and cumene were collected between 60–80° at 12 mm. The carbinol was determined as the thioglycolic acid derivative as previously described. The amount of acetophenone found was less than 3%. Unused α-cumyl hydroperoxide was removed by distillation at 0.1 mm.; an oily residue remained. Under conditions suitable for crystallizing bi-α-cumyl in the presence of α-cumyl peroxide, namely in methanol solution cooled to 0°, no bi-α-cumyl was found. Crystalline α-cumyl peroxide, however, was isolated when an ethanolic solution of the oil was cooled to −80°. The product thus obtained melted sharply at 39°; recrystallizations indicated that no bi-α-cumyl was present. The oil remaining from the first crystallization of the α-cumyl peroxide could not be crystallized. This oil in benzene had a molecular weight of 300.

When the decomposition was carried out at 75°, the rate of gas evolution was slow, and consequently the acetyl peroxide was added at a slower rate to prevent, insofar as possible, an accumulation of the peroxide. Thus 30 hours elapsed before addition of all the acetyl peroxide solution. The reaction products, which were isolated as usual, are recorded in Table I.

Properties of α-cumyl peroxide. α-Cumyl peroxide is a white crystalline compound, m.p. 39°.

Anal. Calc'd for $C_{18}H_{22}O_2$: C, 80.00; H, 8.13; Mol. wt., 270.
Found: C, 79.64; H, 8.10; Mol. wt., 274.

A supercooled solution had n_D^{21} 1.5360. It may be purified by crystallization from ethanol or by sublimation at reduced pressure. The material is stable at room temperature, but on prolonged standing in the light it gradually turns slightly yellow. The peroxide does not oxidize hydriodic acid under the usual conditions. It reduces neutral permanganate in acetone, and reacts violently with concentrated sulfuric acid; the product thus formed gives a qualitative test for tertiary alcohols (probably α,α-dimethylbenzyl alcohol). The peroxide does not react with concentrated nitric acid or hydrochloric acid. In contrast to α-cumyl hydroperoxide, which is stable up to 140°, α-cumyl peroxide decomposes rapidly at 120°, and slowly, but appreciably, above 100° to form compounds of higher molecular weight.

Proof of structure of α-cumyl peroxide. α-Cumyl peroxide (3.0 g.) and 1.2 g. of sodium powder (prepared under ligroin in absence of air) were added to absolute ether. The mixture was allowed to stand at room temperature for five hours. The excess sodium was decomposed with ethanol, the reaction mixture was poured on ice, and the ether layer was separated and dried over sodium sulfate. After removal of the ether, the residue was distilled, and the fraction boiling at 48–50°/0.5 mm. was collected (2.9 g.). This substance melted at 36°, and when supercooled had n_D^{21} 1.5223. The thioglycolic acid derivative had m.p. 67°. There was no depression of the melting point upon admixture with the authentic thioglycolic acid derivative of α,α-dimethylbenzyl alcohol. It is noteworthy that the values in the literature for the refractive index of the alcohol are usually higher than that here reported. This difference is undoubtedly due to the presence of α-methylstyrene or acetophenone in the materials reported as pure α,α-dimethylbenzyl alcohol. After several crystallizations, α,α-dimethylbenzyl alcohol of a constant refractive index (n_D^{21} 1.5221) was obtained.

Acidic decomposition of α-cumyl peroxide. α-Cumyl peroxide (7.2 g.) in 50 cc. of glacial acetic acid was treated with 0.2 cc. of 5% perchloric acid solution in acetic acid. The temperature of the reaction mixture was maintained below 30°. After 24 hours it was poured into water, and the mixture was extracted with ether. The ether solution was extracted, first with sodium bicarbonate solution to remove acetic acid, and then with 5% sodium hydroxide to remove phenolic materials. From the alkaline extract, phenol (40%) was obtained by acidification and subsequent extraction with ether. The neutral residue was distilled at 62°/0.001 mm. The distillate was identified by refractive index, molecular weight, and elementary analysis as the dimer of α-methylstyrene.

When the decomposition was carried out in acetic acid (50 cc.) containing 10 g. of α,α-

dimethylbenzyl alcohol less than 2% of phenol was obtained. The major part of the peroxide was converted to the dimer of α-methylstyrene.

The acetyl peroxide-induced decomposition of α-cumyl hydroperoxide in the presence of ethylbenzene. The reactions were carried out in a fashion similar to that when cumene was used as the solvent. The products found are shown in Table I.

1-Phenylethanol was estimated by oxidation of the reaction mixture with chromic oxide in acetic acid; the oxidation mixture was extracted with petroleum ether, and the extract was examined for the presence of acetophenone.

α-Phenethyl α-cumyl peroxide. This mixed peroxide has the following properties: b.p. 110-116°/0.3-0.5 mm.; n_D^{20} 1.5397.

Anal. Calc'd for $C_{17}H_{20}O_2$: Mol. wt., 256; C, 79.7; H, 7.8.

Found: Mol. wt., 250; C, 79.6; H, 7.7.

The peroxide was reduced with sodium powder in ether in the same manner as α-cumyl peroxide. The α,α-dimethylbenzyl alcohol formed was determined by conversion to the thioglycolic acid derivative. It amounted to 50 mole-%. The 1-phenylethanol formed was

TABLE III

REACTION OF *tert*-BUTYL HYDROPEROXIDE (1.6 MOLE) WITH ACETYL PEROXIDE (1 mole) IN THE PRESENCE OF CUMENE (4.8 moles)

	MOLES
tert-Butyl hydroperoxide (consumed)	0.85
Methane	*ca* 1.1
Carbon dioxide	*ca* 1.7
tert-Butyl α-cumyl peroxide	0.62
α,α-Dimethylbenzyl alcohol	*ca* .1
tert-Butyl alcohol	.22[a]

[a] Calculated from the difference of the *tert*-butyl hydroperoxide consumed and the peroxide formed.

determined by oxidation with chromic acid to acetophenone, and by comparing the conversion thus obtained with that obtained from known mixtures of the two carbinols. Thus 30 mole-% of 1-phenylethanol was found in the reduction products.

The acetyl peroxide-induced decomposition of tert-butyl hydroperoxide in cumene. The reaction was carried out as with the induced decomposition of α-cumyl hydroperoxide. The products isolated are shown in Table III.

The *tert*-butyl α-cumyl peroxide (n_D^{20} 1.4831) thus formed was identical with the compound formed by the acid-catalyzed reaction of *tert*-butyl hydroperoxide with α,α-dimethylbenzyl alcohol (see paper IV in this series).

Anal. Calc'd for $C_{13}H_{20}O_2$: C, 75.0; H, 9.68; Mol. wt., 208.

Found: C, 75.9; H, 9.2; Mol. wt., 195.

The refractive index of this material indicates that it contains a small amount of an impurity with a higher refractive index. In harmony with this we find that, when the peroxide (2.5 g.) is dissolved in acetic acid and perchloric acid is added to it, the yield of phenol (0.5 g.) is somewhat less than the amount obtained when the pure peroxide is used (paper IV in this series).

Decomposition of acetyl peroxide in the presence of α-cumyl peroxide in ethylbenzene. This decomposition was carried out in the usual fashion at 85°. After gas evolution ceased the reaction products were isolated. There was thus obtained by fractional crystallization from ethanol: *meso*-2,3-diphenylbutane (0.132 mole per mole of acetyl peroxide); α-cumyl peroxide (80% of the starting material).

Decomposition of acetyl peroxide in the presence of α-cumyl hydroperoxide in 1-phenyl-

ethanol. This decomposition was carried out at 85° in the manner described previously. The results obtained are tabulated below.

REAGENTS	MOLES	PRODUCTS	MOLES
Acetyl peroxide	1.0	α-Cumyl hydroperoxide (consumed)	none
α-Cumyl hydroperoxide	2.5	Carbon dioxide	1.0
1-Phenylethanol	9.5	Methane	1.0
		Acetophenone	1.0
		Acetic acid	0.7

Decomposition of acetyl peroxide in α,α-dimethylbenzyl alcohol. Acetyl peroxide (1.0 mole) in α,α-dimethylbenzyl alcohol was added dropwise to α,α-dimethylbenzyl alcohol at 95–100°. After cessation of gas evolution, the carbinol was removed by distillation; a glassy resin remained. This residue had a molecular weight (cryoscopic in benzene) of 617, or (Rast method in camphor) of 580. The other products obtained are shown in Table II.

SUMMARY

1. α-Cumyl peroxide is formed from α-cumyl hydroperoxide under the following conditions: (a) heating the hydroperoxide in the presence of Norit at 100°; (b) heating the hydroperoxide in acetic acid at 100°; (c) heating the hydroperoxide in the presence of dimethylbenzyl alcohol at 100° (in the presence of *tert*-amyl alcohol and 1-phenylethanol at 100° no α-cumyl peroxide was formed); (d) decomposition of acetyl peroxide in a solution of α-cumyl hydroperoxide and cumene.

2. α-Phenethyl α-cumyl peroxide was prepared by decomposing acetyl peroxide in a solution of α-cumyl hydroperoxide and ethylbenzene at 75°.

(3) *tert*-Butyl α-cumyl peroxide was formed by the decomposition of acetyl peroxide in a solution of *tert*-butyl hydroperoxide and cumene.

4. The formation of the various reaction products, the relative amounts of these formed, and the short chain-reaction encountered, are best explained by assuming the formation of an intermediate complex. This complex is formed by the addition of the solvent free radical to the hydroperoxide. The experiments with acetyl peroxide indicate that peroxide formation in free-radical reactions is not necessarily a chain-terminating event.

CHICAGO 37, ILLINOIS

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE CHEMISTRY OF HYDROPEROXIDES. III. THE FREE-RADICAL DECOMPOSITION OF HYDROPEROXIDES

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In the first paper of this series (1), it was indicated that α-cumyl hydroperoxide, when decomposed under various conditions, gives many different reaction products. It was, however, established that this compound when dissolved in glacial acetic acid and treated with very small amounts of perchloric acid decomposes to give phenol and acetone exclusively.

$$C_6H_5(CH_3)_2C{-}OOH \xrightarrow[H^+]{HOAc} C_6H_5OH + CH_3COCH_3$$

However, when a water solution of ferrous ammonium sulfate is slowly added to a water suspension of α-cumyl hydroperoxide, and the reaction mixture is stirred, the products formed are indicated by the following equation.

$$1.\ C_6H_5(CH_3)_2C{-}OOH\ (1\ \text{mole}) \xrightarrow[(0.47\ \text{mole})]{Fe^{++}} CH_3COC_6H_5\ (71\%) + CH_3OH\ (44\%) + C_6H_5(CH_3)_2COH\ (12\%) + \text{gas}^1\ (15\%) + \text{high-boiling oil}\ (10\%)$$

The present paper deals with the latter type of decomposition.

DISCUSSION

The hydroperoxides decomposed by ferrous salts in the present study were of the following types: (a) α-cumyl, (b) *tertiary*-alkyl, and (c) triphenylmethyl.

(a) *Decomposition of α-cumyl hydroperoxide by ferrous salts.* The data recorded in Table I are best accounted for by assuming one or more of the reactions indicated in Chart I. It is assumed that the first step in the reaction is the one-electron reduction of the hydroperoxide[2]:

$$(A)\ C_6H_5(CH_3)_2C{-}OOH + Fe^{++} \rightarrow C_6H_5(CH_3)_2CO\cdot + FeOH^{++}$$

The formation of free RO· radicals in the decomposition of hydroperoxides by ferrous salts, or by heat, has been assumed without actual proof by many investigators (2). Excellent evidence of the initial formation (in the water phase) of such free radicals has been obtained by decomposing α-cumyl and other hydroperoxides with ferrous salts in the presence of olefins. Under the specified condi-

[1] The 15% of gas obtained in the reaction accounts for 26% of the α-cumyl hydroperoxide; it consists of ethane (73%) and methane (27%). The amount of oxygen (if any) formed is small (maximum 0.2–0.4%).

[2] In the present discussion the exact mechanism of the oxidation of ferrous ion is irrelevant; however, the authors prefer the representation $FeOH^{++}$ to $Fe^{+++} + OH^-$. In this connection see: Rabinowitch, *Rev. Modern Physics*, **14**, 112 (1942); Farkas and Farkas, *Trans. Faraday Soc.*, **34**, 1113 (1938).

tions these radicals add to olefins to give identifiable adducts.[3] In the absence of reactive olefins, the free RO· radical may undergo a variety of reactions. Those possible for the RO· radical derived from α-cumyl hydroperoxide are indicated in the accompanying reaction scheme (Chart I).

Obviously, such a complication of potential reactions may be profoundly influenced not only by the materials added to the reaction mixture, but by the

TABLE I

EFFECTS OF VARIOUS ADDITIVES ON THE REACTION OF α-CUMYL HYDROPEROXIDE[a] WITH FERROUS SALTS

ADDITIVE (equiv.)[b]	Fe^{++} CONSUMED (equiv.)[b]	PRODUCTS[c] (equiv.)[b]				
		GAS	$CH_3COC_6H_5$	$C_6H_5(CH_3)_2COH$	$(CH_3)_2CO$	OIL
None	0.47	0.15[d]	0.71	0.12	—	10% (wt.)
None[e]	?[e]	.12	.37	.63	—	—
Octane (5.0)	.58	.12	.65	.20	—	—
Octane (5.0) + Dextrose (0.27)	.08	.38[g]	.50	.30	—	14% (wt.)
$C_6H_5CHOHCH_3$ (2.0)	.43	.42[g]	1.20[h]	.61	—	—
2-Propanol (2.0)	.29	.38	0.42	+[f]	+	—
2-Propanol (6.0) + H_2SO_4 (0.22)	.29	.24	.21	.77	0.70	—
$C_6H_5(CH_3)_2COH$ (5.0)	.60	.20	.85	+	—	—
Cumene (5.0)	.62	.18[i]	.68	.30	—	—
HCO_2H (5.0)	.35	.60[j]	+	+	—	—

[a] One mole of α-cumyl hydroperoxide, suspended in 300 cc. of water, was gently agitated during gradual addition of the iron solution. [b] Moles per mole of hydroperoxide. [c] Methanol is always present among the reaction products, but its quantitative isolation from the reaction mixtures is troublesome. In no experiment here reported was α-cumyl peroxide detected. [d] The gas consists of approximately 73% ethane and 27% methane, with possibly 1% oxygen. [e] To 6 moles of a stirred 0.5-molar solution of ferrous ammonium sulfate was added dropwise one mole of α-cumyl hydroperoxide in water suspension. [f] The sign (+) indicates that the material was present in the reaction mixture, but that the amount was not determined. [g] The gas was chiefly methane (<7% ethane). [h] About 0.4 mole of acetophenone is formed from the hydroperoxide; the remainder is formed by oxidation of 1-phenylethanol. [i] The gas was nearly pure ethane (apparent mol. wt., 29.2). [j] The gas was a mixture of carbon dioxide (50%) and methane (50%).

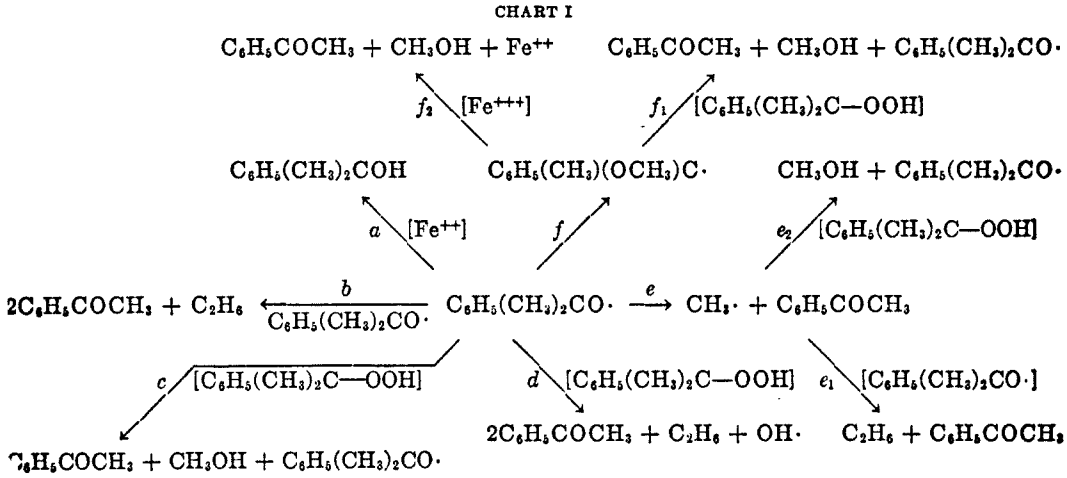
amount of α-cumyl hydroperoxide in the water phase. This latter factor is of course influenced by the amount of the inert hydrocarbon diluent added to the reaction mixture. The substances recorded in Table I were selected as additives in the hope that their properties (especially their respective solubilities in the water and oil phases) would throw some light on the behavior of the free $C_6H_5(CH_3)_2CO$· radical.

[3] These results will be presented in another article of this series.

The extensive experience with free RO· radicals accumulated in this laboratory, (only part of which is reported here) can best be interpreted by assuming that, when α-cumyl hydroperoxide (suspended in water) reacts with a water solution of a ferrous salt, the free RO· radicals are formed in the water phase. The major reaction products are then readily accounted for by the reactions *a* and *b*, which are chain-terminating events, and *c*, f_1, and f_2, which are chain-sustaining steps leading to the formation of methanol and acetophenone (Chart I).

The total amount of gas formed when ferrous ammonium sulfate is slowly added to a slightly agitated water suspension of α-cumyl hydroperoxide is small (about 15 mole-per cent on the basis of the hydroperoxide used). The consump-

CHART I



tion of ferrous ion is high (indicating short chains). The gas is a mixture of ethane (73%) and methane (23%). Here the decomposition of the free-radical plays but

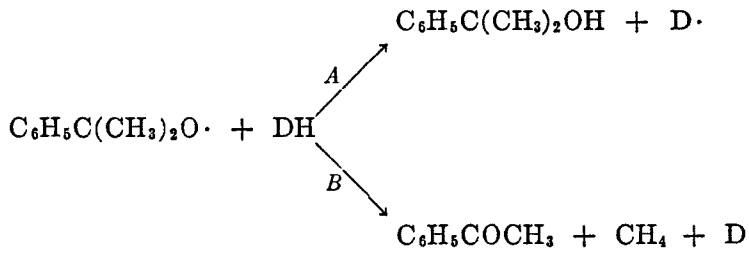
$$(e)\ C_6H_5C(CH_3)_2CO\cdot \rightarrow C_6H_5COCH_3 + CH_3\cdot$$

a minor part.[4] The methane formed in the reaction must arise from the interaction, in a manner indicated later, of the free $C_6H_5(CH_3)_2CO\cdot$ radical with some hydrogen "donor" which, in this instance, may be a reaction product. The carbinol is undoubtedly formed by the interaction of the free radical with a ferrous ion. This reaction leads to termination of the chain.

These views are substantiated by a study of the gaseous and other reaction products formed when α-cumyl hydroperoxide is decomposed in water solution

[4] The following are some of the reasons why the decomposition reaction is considered to be relatively unimportant. (a) The data in Table I indicate that the formation of ethane is a chain-terminating event. (b) It is known from previous experience that the formation of ethane by the dimerization of two methyl radicals in solution is highly improbable. (c) In the case of *tert*-amyl hydroperoxide decomposition analogous to (*e*) (Figure 1) should lead to both ethylene and butane; only butane was found.

fbyerrous salts in the presence of a hydrogen donor (DH). Under these conditions the reactions are *A* and *B* rather than *b*, *c*, *d*, *e*, and *f* (Chart I).



When poor hydrogen donors (*e.g.*, dextrose) are used, the part played by reaction *B* becomes more prominent.

Moreover, as indicated in Table II, the ratio of methane to ethane may be widely varied (in the presence of dextrose) by changes in the concentration of α-cumyl hydroperoxide in the water phase.

TABLE II

DECOMPOSITION OF α-CUMYL HYDROPEROXIDE (1 mole) BY FERROUS SALTS (0.08 mole) IN WATER[a]

ADDITIVES	MOLE-% OF GAS[b]	COMPOSITION OF GAS, (%)	
		CH_4	C_2H_6
1. Dextrose[a] (0.3 mole)	35	55	38
2. Dextrose (0.3 mole) + heptane (18 moles)[b]	45	81	15
3. Dextrose (0.3 mole) + heptane (72 moles)[b]	50	95	5

[a] The mixture was gently agitated. Here, presumably, the rate of diffusion would be the rate-determining step. [b] Calculated on the basis of the amount of α-cumyl hydroperoxide used.

These results are readily explicable by consideration of the relative concentrations of the free RO· radical in the respective water phases. In the presence of a large excess of heptane, the concentration of the hydroperoxide in the water phase is very low and consequently the concentration of free radicals is also low; these radicals, therefore, react preferentially with the "donor" molecule (as in *B*); reactions *b*, *d*, *e*, and f_1 are excluded, and the gas is almost pure methane. With less solvent, the concentration of the hydroperoxide and thus concentration of the RO· radicals in the water is increased; the free RO· radical, therefore, reacts not only as in *B* but also with another RO· radical (*b*, Chart I) giving rise to ethane.

The extremely long chain noted for the decomposition of α-cumyl hydroperoxide by ferrous salt in the presence of dextrose (0.08 mole per mole of hydroperoxide), is probably not due to the regeneration of ferrous ions from ferric

by the dextrose, but to the rapid interaction of the ferric ion with the free donor radical formed in *B*.[5,6]

$$D\cdot + Fe^{+++} \rightarrow D^+ + Fe^{++}$$

The strongly reducing sugars formed by the oxidation of the dextrose may also play an important role in sustaining the chain.

The views here developed suggest that, in the presence of excellent hydrogen donors, the free $C_6H_5(CH_3)_2CO\cdot$ radical may give α,α-dimethylbenzyl alcohol exclusively. This reaction does occur when an aqueous ethanolic solution of α-cumyl hydroperoxide and hydroquinone is treated with a trace of ferrous salt. In the absence of ferrous salts, the mixture is stable for many hours; but as little as 0.002 mole of ferrous ion causes an immediate exothermic reaction, and (when a large excess of hydroquinone is used) the separation of quinhydrone. Furthermore, no gas is formed under these conditions. Probably the reaction here proceeds according to the following scheme:

$$(C)\ C_6H_5(CH_3)_2C{-}OOH \xrightarrow{Fe^{++}} C_6H_5(CH_3)_2CO\cdot + FeOH^{++}$$

$$(D)\ C_6H_5(CH_3)_2CO\cdot + HOC_6H_4OH \rightarrow C_6H_5(CH_3)_2COH + \cdot OC_6H_4OH$$

$$(E)\ C_6H_5(CH_3)_2CO\cdot + Fe^{++} \xrightarrow{H_2O} C_6H_5(CH_3)_2COH + Fe^{+++}$$

From this point on, the reaction may be represented schematically by a chain reaction involving either step *F* or *H*, or both.

$$(F)\ [\cdot OC_6H_4OH] + C_6H_5(CH_3)_2C{-}OOH \rightarrow \text{Quinone} + C_6H_5(CH_3)_2CO\cdot + H_2O$$

$$(G)\ 2[\cdot OC_6H_4OH] \rightarrow \text{Quinhydrone}$$

$$(H)\ HOC_6H_4OH + Fe^{+++} \rightarrow Fe^{++} + \cdot OC_6H_4OH$$

[5] Another way of sustaining the chain reaction is:

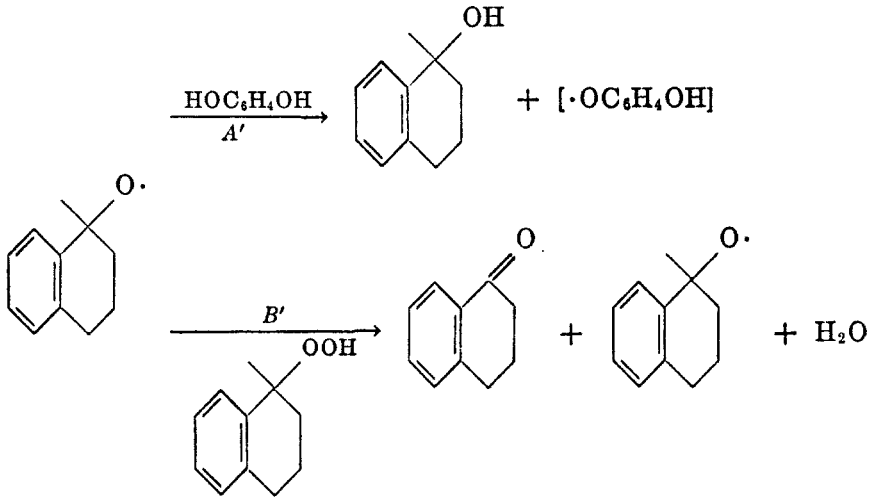
$$D\cdot + C_6H_5(CH_3)_2C{-}OOH \xrightarrow{(a)} D^+ + C_6H_5(CH_3)_2CO\cdot + HO^- \text{ (or DOH)}$$

$$D\cdot + C_6H_5(CH_3)_2C{-}OOH \xrightarrow{(b)} D^+ + [C_6H_5(CH_3)_2CO]^- + HO\cdot$$

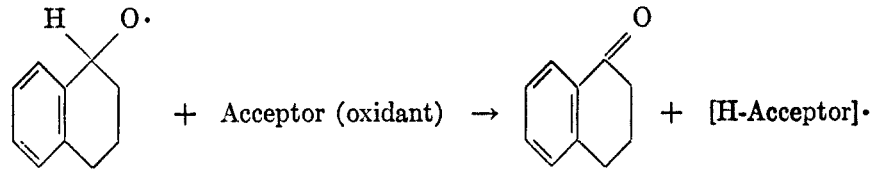
The above reaction plays an important part when α-cumyl hydroperoxide is decomposed by ferrous salts in the presence of 2-propanol. Here the chain length is about six, and the formation of methanol (c, e_2, f_1, f_2, Chart I) is suppressed even more than it is by dextrose, although this latter compound decreases methanol formation to the extent of 70% as compared with a reaction in which ferrous ion alone is the reductant.

[6] In these reactions, the presence of ferrous ion in the solution was demonstrated by the immediate production of a blue color when $K_3Fe(CN)_6$ was added to an acidified sample of the reaction mixture. On the other hand, no ferrous ion could be demonstrated, even after many hours, when a solution of a ferric salt was treated with dextrose. These facts are additional corroborative evidence that the regeneration of the ferrous ions proceeds by a mechanism different from the one usually postulated, *i.e.*, the reduction of the ferric ion by dextrose.

The above statements do not imply that all free RO· radicals react with hydroquinone or pyrogallol to give exclusively ROH compounds. Probably most of the free radicals derived from *tertiary*-alkyl hydroperoxides do react in this way; but some of those derived from secondary hydroperoxides behave differently. In fact, α-tetralyl hydroperoxide is decomposed by ferrous salts, even in the presence of a large excess of hydroquinone, to give appreciable amounts of α-tetralone. This fact may well mean that, of the two possible reactions *A'* and *B'*, *A'* is the slower.



Here the difference between the free secondary and free tertiary radicals may be due to a rapid decomposition of the secondary radical into tetralone and a hydrogen atom:



This reaction would endow the radical with reducing properties, and would therefore favor the reaction with the oxidant (α-tetralyl hydroperoxide).

(b) *Decomposition of tertiary-alkyl hydroperoxides by ferrous salts.* It is of considerable interest that the ferrous ion-induced decompositions of the two *tertiary*-alkyl hydroperoxides (Table III) are not chain decompositions. The reactions of types *c*, e_2, and *f* (Chart I), where the O—O bond is broken by the RO· radical do not occur. Thus, when a dilute solution of ferrous salt is added to a water solution or suspension of either *tert*-butyl or *tert*-amyl hydroperoxide, at least one mole of ferrous ion is required for complete decomposition.

The course of the decomposition of *tert*-butyl hydroperoxide (Table IV) is influenced by additives in a fashion similar to that observed in the decomposition of α-cumyl hydroperoxide. But, in interpreting some of the results, the greater

water-solubility (12%) of the *tert*-butyl hydroperoxide should be considered. Thus, when the decomposition was carried out in the presence of dextrose as the only additive, no chain decomposition was observed until the concentration

TABLE III

DECOMPOSITION OF *tertiary*-ALKYL HYDROPEROXIDES WITH FERROUS SALTS

HYDROPEROXIDE	Fe^{++} CONSUMED[a]	GAS[b]			ACETONE
		CH_4	C_2H_6	C_4H_{10}	
tert-Butyl[c]	1.25	0.16	0.16	None	0.5[d]
tert-Amyl[c]	1.00	None	.37	.16	.7[d]

[a] All products are calculated in moles per mole of the hydroperoxide. [b] The behavior of organic hydroperoxides toward ferrous salts and potassium iodide is in striking contrast to the behavior of hydrogen peroxide toward these reagents. The latter substance in the presence of traces of potassium iodide or somewhat larger amounts of ferrous salts is decomposed quantitatively into oxygen and water; whereas the *tertiary*-alkyl hydroperoxides under these conditions give practically no oxygen. [c] The amount (if any) of methyl ethyl ketone formed in this reaction is very small. [d] Besides the product here mentioned, the corresponding alcohols and small quantities of the corresponding peroxides are also formed. The quantitative isolation of these products was not attempted.

TABLE IV

EFFECT OF ADDITIVES ON THE REACTION OF *tert*-BUTYL HYDROPEROXIDE WITH FERROUS SALTS

ADDITIVE	MOLES Fe^{++}/MOLE HYDROPEROXIDE	MOLES OF GAS
None	1.25	0.32
Heptane (10 moles)	1.25	.12[a]
Dextrose (1 mole)	0.88[b]	.40
Dextrose (0.33 mole)	.88[b]	.40
Dextrose (0.33 mole) + Heptane (10 moles)	.10	.47
2-Propanol (3 moles) + Heptane (10 moles)	.20	.035[c]
2-Propanol (3 moles) + Dextrose (0.5 mole) + Heptane (10 moles)	.15	.12
Hydroquinone (3 moles)	.001	none

[a] The gas is pure methane. [b] When the ferrous salt solution was slowly added to the reaction mixture the amount of gas evolved was proportional to the amount of iron solution added until 0.84 mole of ferrous ion had been added and 0.28 mole of gas evolved. From this point on only 0.04 mole of iron salt was required to evolve the remaining 0.12 mole of gas. [c] The amount of gas evolved depends upon the rate of addition of the ferrous solution, *i.e.*, faster addition increases, slower addition decreases, the total amount of gas formed.

of the *tert*-butyl hydroperoxide (and consequently of the RO· radicals) in the water phase had diminished appreciably. The presence of inert organic solvent diminishes the concentration of the RO· radicals in the water phase, and thus the probability of ending the chain by disproportionation (scheme *b*, Chart I) is decreased.

The results obtained in the decomposition of *tert*-butyl hydroperoxide differ from those with α-cumyl hydroperoxide in the following respects:

(a) In the absence of potential hydrogen donors, no chain decomposition can be observed [the $(CH_3)_3CO\cdot$ radical does not break the O—O bond].

(b) In the reaction with 2-propanol, the amount of gas formed is negligible. This result indicates that in the presence of donor reagents reaction *A* rather than reaction *B* tends to occur.

(c) When heptane is the sole additive only small amounts of gas are formed (as in the similar decomposition of α-cumyl hydroperoxide with ferrous salts); here, however, the gas formed is pure methane. The absence of ethane indicates that with the $(CH_3)_3CO\cdot$ radical the reaction is *a* rather than *b* (Figure 1).

The decomposition of *tert*-butyl hydroperoxide in the presence of a mixture of dextrose and 2-propanol indicates that 2-propanol is a better hydrogen donor than dextrose. This observation substantiates the claim that reaction *A* is favored with good hydrogen donors.

One may also conclude that in *tert*-butyl hydroperoxide the O—O bond is stronger than the corresponding bond in α-cumyl hydroperoxide, and that the $(CH_3)_3CO\cdot$ radical is more reactive than the $C_6H_5(CH_3)_2CO\cdot$ radical.

(c) *Decomposition of triphenylmethyl hydroperoxide with ferrous salts.* In none of the examples cited is there any clue which justifies a single choice among the many elimination mechanisms indicated in Chart I. On the other hand, a careful study of the reaction of triphenylmethyl hydroperoxide with ferrous salts shows unequivocally that the compound reacts as follows:

$$(C_6H_5)_3C{-}OOH \xrightarrow{Fe^{++}} (C_6H_5)_3CO\cdot \xrightarrow{Fe^{++}} (C_6H_5)_3COH\ (60\%)^{7}$$

$$\downarrow$$

$$C_6H_5O(C_6H_5)_2C\cdot \longrightarrow [C_6H_5O(C_6H_5)_2C{-}]_2\ (30\%)^{8}$$

The formation of benzopinacol diphenyl ether has previously been observed in the decomposition of triphenylmethyl peroxide (3) and of triphenylmethyl hyponitrite (4).

On the basis of the evidence now at hand, it appears unlikely that free radicals in which at least two of the groups are aliphatic and one is aromatic rearrange as follows:

$$Ar(Alk)_2CO\cdot \rightarrow ArO(Alk)_2C\cdot$$

Further study of this problem is under way. The relative tendencies of radicals R, R′, and R″ to migrate from carbon to oxygen in the free radical RR′R″CO· is also under investigation.

[7] Losses in recrystallization are probably responsible for the 10% deficit of organic matter.

[8] The experimental part of this paper should be consulted for details of the proof of structure for this compound. Note also that one of the compounds which Wieland obtained by treating this substance with zinc dust and glacial acetic acid, and which he claimed to be "a third isomer of triphenylmethyl peroxide" (m.p. 198°) should be stricken from the literature; the compound is actually benzopinacolone.

EXPERIMENTAL

Reagents. Commercial α-cumyl hydroperoxide (Hercules Powder Company[9]) was purified by the method of Hock and Lang (5). In most experiments the peroxide regenerated from the sodium salt was distilled at reduced pressure (0.1 mm.); in others, the peroxide, generated from the sodium salt, was used as such. The α-cumyl hydroperoxide used was 98–100% pure.

Ferrous ion was added in the form of a 0.5 *N* solution of ferrous ammonium sulfate, $[Fe(NH_4)_2(SO_4)_2 \cdot 6\ H_2O$, Mallinckrodt].

The carbinols (free of acetophenone) used as additives were prepared as described in the preceding paper of this series.

Gaseous reaction products were collected, fractionated from materials which remain condensed below 0°, and determined by the method described by Kharasch, Lewis, and Reynolds (6). The relative amounts of methane and ethane were estimated by molecular-weight determination of the hydrocarbon mixture, as well as by gas analysis with the Burrell modification of the Orsat apparatus.

Acetophenone was determined by the method described by Kharasch and Cooper (7).

α,α-Dimethylbenzyl alcohol was estimated by weighing its product with thioglycolic acid (8).

Decomposition of α-cumyl hydroperoxide by ferrous salts. The decomposition of α-cumyl hydroperoxide by ferrous salts was carried out as follows. Ferrous ammonium sulfate solution was introduced dropwise into a reaction vessel containing an aqueous suspension of α-cumyl hydroperoxide (0.1 mole of hydroperoxide and 30 cc. of distilled water) and, whenever so indicated, of the additive agent. The reaction mixture was stirred with the aid of a magnetic stirrer. The evolved gas was collected over water. The rate of addition of the iron salt was slow enough so that there was no appreciable temperature rise in the reaction vessel; when gas evolution had ceased the reaction was considered complete; a test for peroxides was negative. The results obtained in the presence of various agents are shown in Table I. The effect of an inert organic solvent on the decomposition of α-cumyl hydroperoxide in the presence of dextrose is shown in Table II. In these experiments, the total amounts of ferrous salt solution and dextrose indicated in the table were added at once to the hydroperoxide solution.

Ferrous ion-induced decomposition of hydroperoxides in the presence of hydroquinone. Hydroquinone fails to react at an appreciable rate with hydroperoxides in the absence of catalysts. To a mixture of α-cumyl hydroperoxide (0.1 mole) and hydroquinone (0.18 mole) in aqueous methanol (100 cc. of water, sufficient methanol to produce a homogeneous solution) was added 0.5 cc. of 0.5 *N* ferrous ammonium sulfate solution (0.25 mole-%). A vigorous reaction ensued, with complete depletion of the peroxide within two minutes. The quinhydrone formed separated as crystals which were collected, washed carefully with aqueous methanol, and dried on a clay plate; m.p. 168°. The amount of quinhydrone thus isolated was 0.088 mole. The filtrate was shaken vigorously with sodium hydrosulfite solution, made alkaline, and then extracted with ether. The ether was removed, and the residue was distilled at 105°/25 mm. The distillate solidified (m.p. 36°), and when this was mixed with authentic α,α-dimethylbenzyl alcohol there was no melting-point depression. The alcohol thus obtained amounted to 98% of the calculated amount based on the hydroperoxide used. No acetophenone was found. When less than equivalent amounts of hydroquinone were used only quinone was formed.

Similar results were obtained with *tert*-butyl hydroperoxide and hydroquinone in the presence of ferrous salts.

The description of the decomposition of α-tetralyl hydroperoxide by ferrous salts under various conditions is summarized in Table V.

Decomposition of tert-butyl hydroperoxide by ferrous salts. To 0.083 mole of *tert*-butyl

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[9] We are grateful to the Hercules Powder Company for a generous supply of the hydroperoxide.

hydroperoxide (93% titre), suspended in 30 cc. of water, was added dropwise a solution of ferrous ammonium sulfate (0.5 *N*). Gas was evolved as soon as the first drop was added. After the addition of 0.1 mole of ferrous ammonium sulfate the evolution of gas ceased. At this point the peroxide was completely consumed. The volume of gas evolved was 590 cc. The results are recorded in Table III. The amount of gas produced (0.032 mole) accounted for 0.48 mole of the *tert*-butyl hydroperoxide consumed. The acetone formed (0.051 mole) was estimated by reaction of an aliquot portion of the solution with 2,4-dinitrophenylhydrazone, and determination of the weight of product formed. The large amount of iron required for complete utilization of the hydroperoxide indicates that 31% of the peroxide was converted by two-electron reduction to *tert*-butyl alcohol. No attempt was made to isolate the alcohol nor the small amounts of *tert*-butyl peroxide which may have been formed.

The results obtained with *tert*-butyl hydroperoxide in the presence of additives are shown in Table IV.

Decomposition of hydrogen peroxide with (a) ferrous salts and (b) potassium iodide. When 50 equivalent-percent of ferrous ammonium sulfate solution (18 cc., 0.5 *N*) was added

TABLE V

EFFECT OF ADDITIVES ON THE DECOMPOSITION OF α-TETRALYL HYDROPEROXIDE BY FERROUS IONS

ADDITIVE	EQUIV. Fe^{++}[a]	GAS	PRODUCTS (MOLES)	
			α-Tetralone	Quinhydrone
None	0.2–0.4	None	0.88	—
None	5.0[b]	None	.79	—
Hydroquinone	0.002	None	.51[c]	0.22
Pyrogallol	.002	None	.54[c]	—

[a] To a stirred solution of crystalline tetralin hydroperoxide (0.05 mole) in 50 cc. of ethanol was added dropwise an aqueous solution (0.5 *N*) of ferrous ammonium sulfate. The tetralone formed was estimated as the 2,4-dinitrophenylhydrazone. [b] To 5 moles of a stirred solution of 0.5 *N* ferrous ammonium sulfate was added dropwise an alcoholic solution of 1 mole of α-tetralyl hydroperoxide. [c] The other reaction product is probably α-tetralol.

dropwise to an ether solution of hydrogen peroxide (20 ml. of 3% H_2O_2 in ether) 180 cc. of oxygen was evolved. When neutral potassium iodide was used in place of the ferrous salt in a similar experiment with hydrogen peroxide only catalytic amounts of the iodide were required to decompose the peroxide quantitatively into oxygen and water. It is noteworthy that no oxygen evolution occurs with the organic hydroperoxides here studied.

Decomposition of tert-amyl hydroperoxide by ferrous salts. To *tert*-amyl hydroperoxide 0.075 mole (98% titre), suspended in 50 cc. of water, sufficient aqueous 0.5 *N* ferrous ammonium sulfate (0.075 mole) was added dropwise to cause complete decomposition of the hydroperoxide. The gas evolved, (900 cc.), contained no oxygen. It was scrubbed with silver sulfate-nickel sulfate-sulfuric acid solution (9) for removal of olefins; however, none were detected. Vapor pressure measurements, after removal of the ethane, indicated butane to be the only other constituent. An aliquot portion of the reaction mixture was treated with 2,4-dinitrophenylhydrazine, and the resulting hydrazone was fractionally crystallized. All crude fractions melted above 120°; (ethyl methyl ketone dinitrophenylhydrazone melts at 115°). On recrystallization the melting points were raised to 128–130°, and the material proved to be identical with an authentic sample of the 2,4-dinitrophenylhydrazone of acetone. The total amount of acetone formed in the reaction was 0.07 mole. The organic layer was washed well with water, and dried. It weighed 1 g., and boiled with decomposition at 150°; the material reduced permanganate; the molecular weight of this fraction

in benzene (cryscopic) was 165. These properties correspond closely with those of *tert*-amyl peroxide (mol. wt., 174).

Decomposition of triphenylmethyl hydroperoxide in the presence of ferrous salts. Triphenylmethyl hydroperoxide was prepared according to method of Wieland and Maier (10), with the slight modification that the calculated amount of 50% potassium hydroxide was added to the acetone solution of hydrogen peroxide and trityl chloride. The hydroperoxide used for this experiment melted at 78–80°. Triphenylmethyl hydroperoxide (1 g.) was dissolved in ethanol (10 cc.). To the well-stirred solution a solution of ferrous ammonium sulfate (3 g. in 10 cc. of water) was added. The reaction mixture was stirred for one hour after addition of the iron salt, and was then acidified to Congo Red with 2 *N* hydrochloric acid. The insoluble organic material was collected and washed with absolute ethanol. In this fashion the triphenylcarbinol was separated from the insoluble benzopinacol diphenyl ether. The triphenylcarbinol was crystallized from aqueous ethanol to give 0.6 g. of material which melted at 160° and did not depress the melting point of an authentic sample of triphenylcarbinol. The insoluble diphenyl ether of benzopinacol, after washing with hot ethanol and small amounts of ether, weighed 0.3 g. The crude product was crystallized from a chloroform-ethanol mixture. In an evacuated tube the crystals turned yellow at 180° and melted at 218°, to give a melt of deep red color. The product gave no melting-point depression with an authentic sample of the material prepared according to Wieland.

Anal. Calc'd for $C_{38}H_{30}O_2$: C, 88.03; H, 5.77; Mol. wt., 518.

Found: C, 87.91; H, 5.99; Mol. wt., 498.

Hydrolysis of benzopinacol diphenyl ether. To benzopinacol diphenyl ether (0.15 g.), suspended in glacial acetic acid, powdered zinc (0.15 g.) was added, and the mixture was refluxed (see Wieland, *loc. cit.*) until solution took place. Upon addition of water, benzopinacolone (0.1 g., 99% yield) separated. When crystallized from ethanol, the substance melted at 195–200° in an evacuated tube, and at 175–178° in an open tube. The melting point of this substance was not depressed upon mixture with an authentic sample of benzopinacolone.

Anal. Calc'd for $C_{26}H_{30}O$: C, 89.9; H, 5.79; Mol. wt., 348.

Found: C, 89.8; H, 6.0; Mol. wt., 343.

In the reaction with zinc and acetic acid the yields of benzopinacolone varied between 60 and 99%. The cause of these variations was not investigated. Where the yield was lower, the other product was benzohydrol, as reported by Wieland.

SUMMARY

1. In the presence of aqueous ferrous salt solutions α-cumyl hydroperoxide decomposes into acetophenone, methanol, ethane, and α,α-dimethylbenzyl alcohol. Methane can also be formed.

2. The results obtained suggest the following scheme.

(*a*) The first step is a one-electron reduction resulting in the formation of the $C_6H_5(CH_3)_2CO\cdot$ radical.

(*b*) The radical thus formed may be reduced by another ferrous ion; it may disproportionate into acetophenone and ethane; or, by attack on an α-cumyl hydroperoxide molecule, may form methanol, acetophenone, and a new $C_6H_5(CH_3)_2CO\cdot$ radical, thus sustaining a chain reaction.

(*c*) In the presence of a potential hydrogen donor (dextrose, 2-propanol, 1-phenylethanol, formic acid, hydroquinone) the $C_6H_5(CH_3)_2CO\cdot$ radical may abstract a hydrogen atom, thereby forming (a) α,α-dimethylbenzyl alcohol, or (b) methane and acetophenone. With loosely held hydrogen atoms (hydroquinone) reaction (a) is favored. The donor radical formed may contribute to sustaining a chain reaction.

3. The RO· radical formed from α-tetralyl hydroperoxide is less reactive towards hydrogen donors than that from α-cumyl hydroperoxide.

4. The reaction of *tert*-butyl, and *tert*-amyl hydroperoxides with ferrous salts follows a course similar to that of α-cumyl hydroperoxide. These hydroperoxides, however, differ in having a stronger O—O bond; thus the chain reaction to yield methanol and acetone, or ethanol and acetone is suppressed. Furthermore, the $(CH_3)_3CO\cdot$ radical is more reactive toward hydrogen donors than the $C_6H_5(CH_3)_2CO\cdot$ radical.

5. The relative tendency of groups R, R′, or R″ in the radical RR′R″CO· to participate in cleavage of the R—C bond increases in the order: phenyl, methyl, ethyl, hydrogen.

6. The $(C_6H_5)_3CO\cdot$ radical formed from triphenylmethyl hydroperoxide rearranges without elimination, and dimerizes to benzopincol diphenyl ether.

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY OF THE UNIVERSITY OF CHICAGO]

THE CHEMISTRY OF HYDROPEROXIDES. IV. OXIDATION OF TERTIARY AROMATIC ALCOHOLS WITH HYDROGEN PEROXIDE OR HYDROPEROXIDES

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In a previous paper it was shown that α-cumyl hydroperoxide, when treated in glacial acetic acid with a small amount of perchloric acid, gives phenol and acetone (1).

$$C_6H_5(CH_3)_2C{-}OOH \xrightarrow[HClO_4]{HOAc} C_6H_5OH + CH_3COCH_3$$

It is of interest to determine the migration (or elimination) tendencies of various groups in molecules of the type RR′R″C—OOH, where at least two of the groups, R, R′, and R″ are aromatic groups.[1] Because the preparation of such hydroperoxides is rather troublesome, a new approach to the problem was sought.

It was found that when α,α-dimethylbenzyl alcohol, in glacial acetic acid, was treated with *tert*-butyl hydroperoxide or hydrogen peroxide in the presence of a small amount of perchloric acid, considerable heat was evolved, and the alcohol was converted to phenol and acetone. The reaction time was about ten minutes.

$$C_6H_5(CH_3)_2COH + H_2O_2 \xrightarrow{HOAc + HClO_4} C_6H_5OH + (CH_3)_2CO + HOH$$

$$(CH_3)_3C{-}OOH + C_6H_5(CH_3)_2COH \xrightarrow{HOAc + HClO_4} C_6H_5OH + (CH_3)_2CO + (CH_3)_3COH$$

Similar results were obtained (in the absence of perchloric acid) when α-cumyl chloride, the triarylmethyl chlorides, and other substances of the type RR′R″CCl or olefins (RR′C=CH$_2$) and concentrated hydrochloric acid, were treated with hydrogen peroxide in acetic acid (at least one of the radicals R, R′, or R″ must be an aromatic radical).

DISCUSSION

The results summarized in Table I can best be interpreted by assuming that, in the presence of strong acids, tertiary alcohols containing at least one aryl group react with hydrogen peroxide[2,3] or tertiary alkyl hydroperoxides to give

[1] The strictly aliphatic hydroperoxides, when treated with perchloric acid, give mainly the corresponding peroxides. The work leading to this conclusion will be reported in another article of this series.

[2] It has been established that hydrogen peroxide and glacial acetic acid react to give an equilibrium mixture in the presence of a strong acid:

$$CH_3CO_2H + H_2O_2 \rightleftharpoons CH_3CO{-}OOH + HOH$$

However, the equilibrium in the absence of a carbinol is attained slowly as compared with the rate of the reactions here studied [D'Ans and Frey, *Ber.*, **45**, 1845 (1912)]; the question therefore arises whether the reactions described are caused by hydrogen peroxide or the

the following intermediate products:[4]

1. $RR'R''COH + H_2O_2 \overset{H^+}{\rightleftharpoons} RR'R''C\text{-}OOH + H_2O$
2. $RR'R''COH + (CH_3)_3C\text{-}OOH \rightarrow RR'R''COOC(CH_3)_3 + H_2O$

In reaction 2, if little of the strong acid is used, the peroxide can be isolated. However, with somewhat larger amounts of the strong acid (perchloric) the products undergo decomposition.

To account for the fact that only small traces of perchloric acid are necessary to produce the rearrangements indicated, the following chain reaction was suggested:

1. $C_6H_5(CH_3)_2C\text{—}OOH \xrightarrow[H^+]{HOAc} H_2O + \underset{(B)}{[C_6H_5(CH_3)_2CO]^+}$
2. $(B) \rightarrow \underset{(C)}{[C_6H_5O(CH_3)_2C]^+}$
3. $(C) + C_6H_5(CH_3)_2C\text{-}OOH \rightarrow C_6H_5OH + CH_3COCH_3 + (B)$

Table I discloses that the groups which, according to the latter mechanism, migrate and which, in any case, are eliminated, may be arranged in the same ordered series obtained by the cleavage of unsymmetrical mercurials with hydrochloric acid (2). This series was called "the electronegativity series" of organic radicals.[5]

With two exceptions, this same series of radicals corresponds well with the "migration aptitudes" of radicals in the rearrangements of symmetrical pinacols (3). The discrepancies observed are that, in the rearrangement of symmetrical

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peracetic acid. It has been established that when α,α'-dimethylbenzyl alcohol, dissolved in acetic acid, is treated with peracetic acid in the presence of a small amount of perchloric acid, only about 50% of phenol was formed; the other oxidation product was probably α-phenyl-α-methylethylene glycol. The addition of small amounts of water to the acetic acid solution caused an increase in reaction time and an increase in the yield of phenol. These results indicate that hydrogen peroxide and not peracetic acid is the active reagent in the oxidation of α,α-dimethylbenzyl alcohol (and other tertiary alcohols) to yield phenol.

[3] Of tremendous importance in all such reactions is the concentration and strength of the acid used, particularly in the case of olefins.

[4] Both the formation of these peroxides (from the hydroperoxides and a tertiary alcohol) and their decomposition in the presence of an acid are readily formulated as follows:

(a) $RR'R''COH + H^+ \rightarrow RR'R''C^+ + H_2O$

(b) $(CH_3)_3C\text{—}OOH + RR'R''C^+ \rightarrow \{[(CH_3)_3C\text{—}OOH]\,[RR'R''C^+]\}$ (A)

(c_1) $A \rightleftharpoons (CH_3)_3COOCRR'R'' + H^+$

(c_2) $A \xleftarrow{RR'R''COH} (CH_3)_3COOCRR'R'' + RR'R''C^+ + H_2O$

(c_3) $A \rightarrow (CH_3)_3COH + [RR'R''CO]^+$

Reactions c_1 and c_2 are reversible; the reverse reaction is favored by increasing the amount of strong acid. The extent to which each one of the reactions occur (c_1, c_2, and c_3) depends further on the strength of the carbon-to-oxygen bond in the peroxide. (The factors governing the decomposition of unsymmetrical peroxides will be discussed in one of the succeeding articles.)

[5] The word "electronegativity" has now many connotations. As originally applied, it indicates the tendency of the organic radical to exist as a negative ion.

pinacols, *o*-tolyl and *o*-anisyl groups migrate less readily than phenyl groups, the reverse of the results obtained by the cleavage of unsymmetrical organomercu-

TABLE I

REACTIONS OF TERTIARY ALCOHOLS OR OLEFINS WITH HYDROGEN PEROXIDE AND A STRONG ACID[a]

ALCOHOL OR OLEFIN	PRODUCTS[b]		
	PHENOLIC	KETONIC	NON-PHENOLIC, NON-KETONIC
1. α,α-Dimethylbenzyl alcohol	Phenol (95%)	Acetone	None
2. α,α-Diphenylethylene	Phenol (70%)	Acetophenone (68%)	Original olefin (30%)
3. Triphenylcarbinol[c, d]	Phenol	Benzophenone (93%)	Original carbinol (5%)
4. 1-Phenyl-1-*p*-tolylethanol[e]	*p*-Cresol (70%)[e]	Acetophenone	Phenyl-*p*-tolylethylene (20%)
5. α-Phenyl-α-*p*-anisylethylene[c]	*p*-Hydroxyanisole (55%)[e]	Acetophenone	α-Phenyl-α-*p*-anisylethylene (20%)
6. *o*-Anisyldiphenylcarbinol[c]	Guaiacol (60%)	Benzophenone (75%) *o*-Methoxybenzophenone (10%)	Original carbinol (12%)
7. Diphenyl-*o*-tolylcarbinol	*o*-Cresol (80%)[e]	Benzophenone (56%)	Unidentified (30%)
8. Diphenyl-α-naphthylcarbinol[f]	α-Naphthol (70%)[e]	Benzophenone (70%)	Unidentified (30%)
9. 1-Phenyl-1-*o*-tolylethanol	*o*-Cresol (12%)	Acetophenone	α-Phenyl-α-*o*-tolylethylene (80%)
10. 4,4′-Diphenoxytriphenyl[g] carbonium perchlorate		Phenoxybenzophenone	
11. 4-Nitrotriphenyl[g] carbonium perchlorate	Phenol	*p*-Nitrobenzophenone	

[a] The reactions were carried out in glacial acetic acid solution. [b] The quantitative separation of all the reaction products was not always considered essential. In all cases however the presence of each compound listed among the reaction products was demonstrated. [c] *tert*-Butyl hydroperoxide was used in place of hydrogen peroxide (see experimental part). [d] With triphenylcarbinol and hydrogen peroxide some 5–10% of triphenylmethyl peroxide is formed, in addition to the phenol and acetophenone. [e] No phenol could be isolated (see experimental part). [f] Because the phenolic material is easily oxidized, the use of excess hydrogen peroxide is undesirable. [g] These data are taken from the paper by Dilthey, Quint, and Dierichs, *J. prakt. Chem.*, [2], **151**, 25 (1938). No yields are recorded. However, the authors do not mention the formation of products other than those recorded.

rials. It is of considerable interest, therefore, that the *o*-tolyl and the *o*-anisyl groups are eliminated preferentially when *o*-tolyldiphenylcarbinol and *o*-anisyl-

diphenylcarbinol are treated with hydrogen peroxide in acetic acid in the presence of small amounts of perchloric acid. Perhaps the discrepancies noted in connection with the *ortho*-substituted pinacols may be due to a steric factor,[6] and not to the weaker "electronegativity" of these radicals.

EXPERIMENTAL

Oxidation of α,α-dimethylbenzyl alcohol. tert-Butyl hydroperoxide (0.05 mole), α,α-dimethylbenzyl alcohol (0.05 mole), and acetic acid (14 cc.) were treated with 0.001 mole of perchloric acid in acetic acid. The temperature of the reaction mixture was maintained below 30°. The peroxide titre reached zero in 10 minutes. The reaction mixture was poured into water, and the resultant mixture was extracted with ether. The ether extract was washed with sodium bicarbonate solution to remove acetic acid, and was then treated with 5% sodium hydroxide solution. No phenol was found. The ether solution was dried, and ether was removed under reduced pressure. The residue was distilled at reduced pressure, and the fraction distilling at 40°/0.2 mm., was collected. This fraction constituted a 95% yield (based on the amount of *tert*-butyl hydroperoxide used) of *tert*-butyl α-cumyl peroxide, n_D^{20} 1.4792.

Anal. Calc'd for $C_{13}H_{20}O_2$: C, 75.10; H, 9.61; mol. wt., 208.

Found: C, 75.10; H, 9.75; mol. wt., 200.

One gram of the unsymmetrical peroxide was reduced by treatment with 0.4 g. of powdered sodium in ether. From the reaction mixture was obtained, after washing with water, 0.6 g. of α,α-dimethylbenzyl alcohol; m.p. 36°, n_D^{20} (supercooled) 1.5219.

When perchloric acid (10 mole-%) is added to the acetic acid solution of the peroxide, the latter is converted to a mixture of phenol, acetone, and α-methylstyrene dimer. Furthermore, when increased amounts of perchloric acid (10 mole-%) are used in the original reaction mixture the same products are formed immediately. Thus *tert*-butyl hydroperoxide (0.05 mole) and α,α-dimethylbenzyl alcohol (0.07 mole) dissolved in 12 cc. of glacial acetic acid, when treated with 0.01 mole of perchloric acid formed phenol (0.025 mole), α-methylstyrene dimer (0.015 mole), and acetone (not isolated).

Oxidation of α,α-diphenylethylene. as-Diphenylethylene (b.p. 162°/16 mm., n_D^{15} 1.6080), 0.016 mole, in 20 cc. of glacial acetic acid was treated with 30% hydrogen peroxide (0.028 mole), and a 70% aqueous solution of perchloric acid (0.01 mole) was added. The reaction mixture was maintained at a temperature below 30°. After 12 hours, the reaction mixture was worked up as usual. There were obtained: phenol (0.011 mole) and acetophenone, identified as the dinitrophenylhydrazone, m.p. 228°.

Oxidation of triphenylcarbinol. Triphenylcarbinol (0.05 mole) suspended in a solution of *tert*-butyl hydroperoxide (0.05 mole) in acetic acid (45 cc.) was treated with 0.0025 mole of perchloric acid. The carbinol dissolved rapidly. After four hours water was added to the reaction mixture. The aqueous suspension was stored at 0° for 12 hours. The solid which separated was collected and dried. It was taken up in boiling 60°-ligroin. Unchanged triphenylcarbinol separated when the ligroin solution was cooled to 4°. The carbinol was collected and the mother liquor was cooled to −80°, whereupon the solid *tert*-butyl triphenylmethyl peroxide separated. Additional amounts of solid were obtained by concentrating the filtrate from the first crop of crystals. The crude peroxide melted at 66°, and was formed to the amount of 85–90%. The recrystallized (ligroin) material melted at 70°.

Anal. Calc'd for $C_{23}H_{24}O_2$: C, 83.1, H, 7.22; mol. wt., 332.

Found: C, 83.23; H, 7.24; mol. wt., 320.

tert-Butyl triphenylmethyl peroxide (5.3 g.) suspended in 24 cc. of glacial acetic acid was treated with 1 cc. of 70% perchloric acid; the temperature was maintained below 30°.

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[6] Molecular models (Fisher-Hershfelder-Taylor) show that the migration of the phenyl group, in α,β-diphenyl-α,β-di-*o*-tolylethylene glycol, may occur readily, whereas that of an *o*-tolyl group is greatly hindered.

After 45 minutes the reaction mixture was extracted with ether; the ether solution was washed with bicarbonate solution to remove acetic acid. Phenol was extracted from the ether with 5% sodium hydroxide, and, after acidification of the alkaline extract, was identified as its tribromo derivative. The neutral residue from the ether extract was taken up in absolute alcohol. A few drops of water was added to the boiling-alcoholic solution. When the solution cooled, triphenylcarbinol (0.3 g.) crystallized; m.p. 158°; no depression of melting point upon mixture with an authentic sample. Addition of water to the filtrate from the carbinol precipitated 2.7 g. (93%) of crystalline benzophenone; m.p. 46°; no depression upon mixture with authentic sample.

Oxidation of triphenylcarbinol. Triphenylcarbinol (0.01 mole), suspended in a solution of 30% hydrogen peroxide (0.03 mole) and 20 cc. of glacial acetic acid, was treated with perchloric acid (0.01 mole, 30% solution in acetic acid). The triphenylcarbinol dissolved completely in 2–4 hours and then a small amount of solid (5–10%) separated from the solution. This solid, which was insoluble in ether, was recrystallized from benzene; it proved to be triphenylmethyl peroxide, m.p. 175°; the melt is orange-colored. The acetic acid solution of the reaction mixture was worked up in the usual fashion. The oily neutral fraction solidified completely when seeded with a crystal of benzophenone; the crystals melted at 46–47°; yield, 93%. The phenol formed was identified as its tribromo derivative (m.p. 93°).

Oxidation of 1-phenyl-1-p-tolylethanol. 1-Phenyl-1-*p*-tolylethanol (b.p. 120–125°/0.3 mm., n_D^{20} 1.5828) (0.05 mole) and *tert*-butyl hydroperoxide (0.06 mole) were added to 16 cc. of glacial acetic acid. To the resulting solution was added 0.01 mole of perchloric acid in acetic acid (50% solution). Two liquid layers formed when the perchloric acid solution was added. The reaction mixture was maintained at a temperature below 30°, and, after 20 hours, water was added. The resulting mixture was extracted with ether; the ether extract was washed with sodium bicarbonate solution, and then extracted with 5% sodium hydroxide. From the alkaline extract, by acidification, 0.035 mole *p*-cresol was obtained. That phenol was not present, was shown by the following observations: (a) the phenolic fraction gave a negative Liebermann nitroso test; (b) only traces of the fraction were soluble in sodium benzenesulfonate solution (5), and even this material failed to give a Liebermann test; (c) the tribromo derivative melted at 108°.

The neutral ether-soluble fraction was distilled at 0.3 mm. Acetophenone was collected at 42°; n_D^{20} 1.5338 (lit. n_D^{9} 1.5342), dinitrophenylhydrazone, crude, m.p. 228–230° uncorr., agreeing with that of an authentic sample. At 90° and 0.3 mm. α-phenyl-α-*p*-tolylethylene distilled (15–20%, based on the carbinol used); n_D^{20} 1.5862.

Oxidation of α-phenyl-α-anisylethylene. This olefin (6) was prepared by the addition of anisylmagnesium bromide to acetophenone. The Grignard reaction product was decomposed with dilute acetic acid, and was worked up in the usual fashion. The olefin was distilled; b.p. 144–147° at 0.3 mm. The distillate crystallized on cooling; recrystallization from ethanol gave a product melting at 74°. The purified olefin (0.045 mole) and 0.050 mole of *tert*-butyl hydroperoxide in 20 cc. of glacial acetic acid were treated with 0.004 mole of perchloric acid in acetic acid. The temperature was maintained below 30°; after 20 hours, the reaction mixture was worked up as described for the preceding carbinol. The crude phenolic material thus obtained melted at 47–52°; the same materials, after crystallization from 1:1 ligroin-benzene melted at 53°, and did not depress the melting point of hydroquinone monomethyl ether. The *p*-methoxyphenol formed amounted to 0.025 mole. The neutral fraction was treated with ethanol, and from this solution, by cooling to −80°, there was obtained 0.009 mole of unchanged ethylene, m.p. 74°; this material did not depress the melting point of the original ethylene derivative. After distillation of acetophenone from the neutral fraction, there remained some high-boiling tar.

Oxidation of o-anisyldiphenylcarbinol. This carbinol (0.04 mole) and *tert*-butyl hydroperoxide (0.05 mole in 25 cc. of acetic acid) were treated with 0.02 mole of perchloric acid; the temperature was maintained below 30°. After 20 hours, water was added, and the reaction mixture was worked up in the usual way. The alkaline-soluble material (3 g.) was crude

guaiacol; the tribromo derivative melted at 117° (recorded, m.p. 116°). The neutral fraction (8.0 g.) was taken up in ethanol, a few drops of water were added, and the unchanged carbinol (0.006 mole) which separated was collected. This recovered carbinol melted at 127°, and did not depress the melting point of an authentic sample. The mixture of ketones which remained in ethanol solution was recovered from the ethanol by addition of water and extraction with ether. After removal of the ether this fraction weighed 6.5 g. The ketone mixture was refluxed with 48% hydrogen bromide in acetic acid (7) in order to hydrolyze any methoxy compound present. The hydrolyzed reaction product was treated with water, extracted with ether, and washed with bicarbonate; then the phenolic ketone was extracted with alkali. By acidification of the alkaline extract, there was obtained 0.004 mole of *o*-hydroxybenzophenone; this material, when recrystallized, melted at 37°. The neutral ketonic material was recrystallized from dilute alcohol; there was thus obtained 0.03 mole of benzophenone, m.p. 47°.

Oxidation of diphenyl-o-tolylcarbinol. The carbinol (4), m.p. 94°, (10.9 g., 0.04 mole) was treated with 30% hydrogen peroxide (5 cc., 0.045 mole) and glacial acetic acid (50 cc.). To the resulting mixture was added 70% perchloric acid (0.01 mole), and the solution was allowed to stand at room temperature for three hours. The reaction mixture was worked up in the usual fashion.

For identification and estimation of the amount of the phenolic materials formed in the reaction the following procedure was used. The phenolic fraction (3.5 g.) was dissolved in 12% sodium hydroxide solution and the resulting solution was treated with 5 g. of chloroacetic acid. This mixture was heated on the steam-bath for 5 hours; during this time an additional 5 g. of chloroacetic acid and sufficient alkali to maintain alkalinity were added. The reaction mixture was cooled, acidified with dilute sulfuric acid, and extracted with ether. The ether solution was extracted with sodium bicarbonate solution; and by acidification of the bicarbonate extract there was obtained 3.6 g. of the *o*-cresoxyacetic acid, m.p. 148–152° (without crystallization). The amount of aryloxyacetic acid formed accounts for 67% of the phenolic fraction. When a model experiment was carried out with pure *o*-cresol the recovery of the aryloxy derivative was 75%. The filtrate from the *o*-cresoxyacetic acid gave less than 0.2 g. of precipitate when treated with bromine water. This result indicates the presence of only insignificant amounts of the more water-soluble phenoxyacetic acid, which readily forms a tribromo derivative insoluble in water. From the neutral fraction (7.0 g.) of the reaction mixture was obtained 4.0 g. of benzophenone, m.p. 47–48°. The residual oil remaining after crystallization of the benzophenone was not further investigated.

Oxidation of α-naphthyldiphenylcarbinol. The carbinol, m.p. 135–136°, (0.04 mole) was treated with 30% hydrogen peroxide (0.045 mole) in glacial acetic acid (75 cc.). To the resulting mixture was added 70% perchloric acid (0.01 mole). The temperature was maintained below 25°. After one hour, the reaction mixture was separated from the small amount of amorphous solid (1.2 g.) which had precipitated. The mixture was then worked up in the usual fashion. The phenolic fraction isolated amounted to 4.0 g. It was identified by conversion to its aryloxyacetic acid derivative as previously described. The naphthoxyacetic acid thus formed melted at 180–184° (crude). No phenol could be detected. From the neutral fraction was obtained, by distillation, 5.0 g. of crystalline benzophenone, m.p. 47–48°, and 3.0 g. of higher-boiling nonketonic oil (b.p. 160–190°/2 mm.). The amorphous solid and the high-boiling oil which amounted to 30% of the starting materials, were not further investigated.

Oxidation of 1-phenyl-1-o-tolylethanol. This carbinol was prepared by addition of *o*-tolylmagnesium bromide to acetophenone; b.p. 137–140° at 0.4 mm., n_D^{20} 1.5862.

Anal. Calc'd for $C_{15}H_{16}O$: C, 84.94; H, 7.55; Mol. wt., 212.

Found: C, 84.77; H, 7.56; Mol. wt., 215.

1-Phenyl-1-*o*-tolylethanol (0.05 mole) and *tert*-butyl hydroperoxide (0.05 mole) were dissolved in 20 cc. of glacial acetic acid. To the solution was added 0.02 mole of perchloric acid. After 2 hours, the reaction mixture was worked up in the usual fashion. The phenolic

fraction amounted to 0.006 mole; the properties (color reactions, water-solubility, etc.) of the phenolic fraction were consistent with those of *o*-cresol: The neutral fraction was distilled under reduced pressure. The fraction collected at 40°/0.3 mm. contained the ketones. This fraction was treated with dinitrophenylhydrazine, and the hydrazone was fractionally crystallized. Two fractions were obtained [(a) m.p. 230°; (b) m.p. 233°; (uncorr.)]. These were identical with the derivative obtained from authentic acetophenone. The major portion of the neutral fraction distilled at 108–110° at 0.3 mm., and proved to be α-phenyl-α-*o*-tolylethylene (80 mole-%); n_D^{20} 1.5929; molecular weight (cryoscopic, benzene), 198; calc'd for $C_{15}H_{14}$, 194. Elementary analysis showed the absence of oxygen, and catalytic hydrogenation in ethanol in the presence of Adams' catalyst resulted in the absorbtion of 1 mole of hydrogen; thus, 0.65 g. of material absorbed 77 cc. (corrected) of hydrogen (calc'd for one double bond, 76 cc.).

SUMMARY

1. Tertiary alcohols, containing at least one aromatic group, or the olefins derived therefrom are converted in the presence of non-corresponding hydroperoxides under mildly acidic conditions to unsymmetrical peroxides.

2. Tertiary alcohols, containing at least one aromatic group, or the corresponding olefins can be oxidized under acidic conditions with *tert*-butyl hydroperoxide or hydrogen peroxide to phenolic and ketonic materials. The corresponding hydroperoxides and unsymmetrical peroxides yield the same products and are assumed to be intermediates.

3. With compounds of the type RR′R″COH comparison of the elimination aptitudes of the various groups is possible. The elimination aptitude of groups follows the electronegativity series. The relative aptitudes differ from those derived from the pinacol rearrangement in the case of *ortho*-substituted groups. It is suggested that in the case of the pinacols steric factors also play an important part.

CHICAGO 37, ILLINOIS

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF THE UNIVERSITY OF MISSOURI]

THE REACTION OF NITROPARAFFINS AND ALICYCLIC KETONES. I. THE PREPARATION OF NITROALKYLCYCLOHEXANOLS

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The purpose of the investigation was to prepare a series of α-nitroalkylcyclohexanols by the reaction of alicyclic ketones with nitroparaffins in the presence of sodium ethoxide or piperidine, and to reduce the nitro compounds to the corresponding amines with hydrogen and Raney nickel.

All efforts to prepare 1-nitromethyl-1-cyclohexanol from cyclohexanone and nitromethane by the procedure of Fraser and Kon (1), using their directions for the preparation of the sodium ethoxide catalyst, were fruitless. Hass and Riley (2) quoting Bourland reported similar negative results.

When the sodium ethoxide was prepared with a ratio of 1 g. of sodium to 11 cc. of absolute alcohol and used at once, it was possible to obtain 1-nitromethyl-1-cyclohexanol in 33% yield, if the reaction mixture was heated to 50° for an hour and a half.

The 3- and 4-methyl-1-cyclohexanone would not react with nitroethane or nitropropane when sodium ethoxide was used, but with piperidine as the catalyst, the corresponding α-nitroalkylcyclohexanols were obtained in yields of 5–13%. 2-Methyl-1-cyclohexanone did not react with nitroethane or nitropropane.

The reduction of 1-nitromethyl-1-cyclohexanol with hydrogen and Raney nickel at pressures ranging from 44 to 3000 p.s.i. was unsatisfactory; the product in each case was a mixture from which no pure 1-(aminomethyl)cyclohexanol or cyclohexanemethylamine could be isolated. The presence of methylamine, ammonia, and cyclohexanol among the reduction products indicated some hydrogenolysis.

Bis-(cyclohexanemethyl)amine, methylamine, and ammonia were isolated from the reduction of 1-nitromethyl-1-cyclohexene, and 4-methylcyclohexanemethylamine was obtained from 1-nitromethyl-4-methyl-1-cyclohexanol. Yields were poor.

These results were rather surprising, in view of the fact that several nitrocyclohexanes and nitrocyclohexenes were reduced with hydrogen and Raney nickel to the corresponding amines in good yield (3), and Lambert and Lowe (4) reported the reduction of 1,1-*bis*-(nitromethyl)cyclohexene to 1,1-*bis*-(aminomethyl)cyclohexane by this means.

[1] Abstract of a portion of the Ph.D. dissertation of Floyd B. Erickson, August, 1949, and the Master's dissertation of Nina C. Knight, June, 1944.

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[4] The carbon-hydrogen analyses were done by D. R. Smith and J. R. Janes

EXPERIMENTAL

Preparation of the sodium ethoxide catalyst. Clean, freshly cut sodium was added in small pieces to absolute alcohol in the ratio of 1 g. of sodium to 11 cc. of alcohol. This solution of sodium ethoxide was added at once to the nitro paraffin-cyclohexanone mixture.

1-(Nitromethyl)-1-cyclohexanol. A mixture of 30 cc. (0.29 mole) of cyclohexanone, 17 cc. (0.32 mole) of nitromethane, and 6 ml. of freshly prepared sodium ethoxide solution was heated at 50° for 1½ hours, and allowed to stand at room temperature for 36 hours. The solution was then acidified with dilute acetic acid and extracted with ether. The ether extract was washed with sodium bicarbonate solution, dried over Drierite, and fractionated; yield 14.5 g. (33.7%), b.p. 128–129° (17 mm.). If the mixture was not heated, the yield was 26%.

Anal. Calc'd for $C_7H_{13}NO_3$: C, 52.83; H, 8.17.
Found: C, 53.18; H, 8.22.

1-(Nitromethyl)-3-methyl-1-cyclohexanol was obtained similarly from 3-methylcyclohexanone. The mixture stood for 79 hours; yield, 29%, b.p. 98–102° (2 mm.).

Anal. Calc'd for $C_8H_{15}NO_3$: C, 55.45; H, 8.72.
Found: C, 55.72; H, 8.77.

1-(Nitromethyl)-4-methyl-1-cyclohexanol was obtained from 4-methylcyclohexanone. The mixture stood for one week; yield, 42%, b.p. 105–107° (4 mm.); m.p. 52–53°.

Anal. Calc'd for $C_8H_{15}NO_3$: C, 55.45; H, 8.72.
Found: C, 55.70; H, 9.00.

2-Methylcyclohexanone, cyclohexene-2-one-1, and 3-methylcyclohexene-2-one-1 did not react with nitromethane, nitroethane or 1-nitropropane with sodium ethoxide as the catalyst.

1-(α-Nitroethyl)-4-methyl-1-cyclohexanol. The procedure is essentially that of Fraser and Kon (1). 4-Methylcyclohexanone (67 cc., 0.45 mole), 45 cc. of nitroethane, and 4 cc. of piperidine were allowed to stand two weeks at room temperature. The nitroalkylcyclohexanol was isolated as already described; yield, 11.5 g. (13.7%), b.p. 125–128° (20 mm.), n_D^{20} 1.4565.

Anal. Calc'd for $C_9H_{17}NO_3$: C, 57.71; H, 9.09.
Found: C, 57.54; H, 9.13.

1-(α-Nitroethyl)-3-methyl-1-cyclohexanol was obtained from 3-methylcyclohexanone in 9.4% yield, b.p. 131–136° (20 mm.), n_D^{20} 1.4727.

Anal. Calc'd for $C_9H_{17}NO_3$: C, 57.71; H, 9.09.
Found: C, 57.41; H, 9.08.

1-(α-Nitropropyl)-4-methyl-1-cyclohexanol was obtained from 1-nitropropane and 4-methylcyclohexanone in 10.6% yield, b.p. 135–140° (21 mm.); n_D^{20} 1.4488.

Anal. Calc'd for $C_{10}H_{19}NO_3$: C, 59.70; H, 9.51.
Found: C, 59.74; H, 9.34.

1-(α-Nitropropyl)-3-methyl-1-cyclohexanol was obtained from 1-nitropropane and 3-methylcyclohexanone in 5% yield, b.p. 130–135° (20 mm.); n_D^{20} 1.4550.

Anal. Calc'd for $C_{10}H_{19}NO_3$: C, 59.70; H, 9.51.
Found: C, 59.75; H, 9.64.

With piperidine as the catalyst, 2-methylcyclohexanone reacted with neither nitroethane nor 1-nitropropane.

Reduction of 1-(nitromethyl)-1-cyclohexanol with hydrogen and Raney nickel catalyst. The nitro compound (38 g.) was dissolved in 100 cc. of anhydrous methanol and placed in the copper liner of a rocking steel autoclave with 3 g. of Raney nickel, at an initial hydrogen pressure of 3000 lbs. Absorption of hydrogen began at 80° and this temperature was maintained until the pressure was constant; the reduction was complete in five hours.

The catalyst was separated and the methyl alcohol was distilled. The residue was dissolved in ether and extracted with dilute hydrochloric acid. The aqueous acid layer and the ether layer were separated and processed by the usual procedures to yield, respectively, a mixture of high-boiling amines and cyclohexanol. The amine fraction was con-

verted to the hydrochloride, but no one pure amine could be separated from the mixture. The amine hydrochlorides melted over a wide range and analyses indicated that the principal product was probably *bis*-(cyclohexanemethyl)amine. The methyl alcohol distillate was neutralized with conc'd hydrochloric acid and evaporated to dryness to yield ammonium chloride and methylamine hydrochloride. The latter melted at 125–126° and did not depress the melting point of an authentic sample. The cyclohexanol was identified by its *phenylurethan*, m.p. 82–83°.

The reduction was repeated with an initial hydrogen pressure of 44 lbs., but the product was an intractable mixture.

Reduction of 1-(nitromethyl)-1-cyclohexene. The nitro olefin (21.7 g.) dissolved in 100 cc. of methanol was reduced as described above. Only small amounts of pure compounds could be separated from the mixture of amines.

The amine fraction yielded *bis*-(cyclohexanemethyl)amine; methylamine and ammonia were isolated from the methanol distillate. The yield of crude *bis*-(cyclohexanemethyl)-amine hydrochloride was 45%.

The *bis*-(cyclohexanemethyl)amine distilled at 120–121° (2 mm.).

Anal. Calc'd for $C_{14}H_{27}N$: C, 80.38; H, 12.92.
Found: C, 80.23; H, 13.13.

Bis-(cyclohexanemethyl)amine hydrochloride crystallized from alcohol as plates, m.p. 264–265°.

Anal. Calc'd for $C_{14}H_{27}N \cdot HCl$: C, 68.4; H, 11.4.
Found: C, 68.32; H, 11.54.

The reduction was repeated in an ethanol-glacial acetic acid solution at an initial hydrogen pressure of 1490 p.s.i., but no pure compound could be isolated from the amine fraction.

Reduction of 1-(nitromethyl)-4-methyl-1-cyclohexanol. 4-Methylcyclohexanemethylamine hydrochloride, m.p. 266–267° d., was isolated from the amine fraction.

Anal. Calc'd for $C_8H_{17}N \cdot HCl$: C, 58.71; H, 11.01.
Found: C, 58.57; H, 11.08.

SUMMARY

Nitromethane will react with cyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone with sodium ethoxide as the catalyst to form the corresponding 1-nitromethyl-1-cyclohexanol.

Nitroethane and 1-nitropropane will react at room temperature with cyclohexanone, 3-methylcyclohexanone, and 4-methylcyclohexanone to form the corresponding 1-(α-nitroalkyl)-1-cyclohexanol in low yield.

A mixture of amines was obtained from the reduction of 1-nitromethyl-1-cyclohexanol with hydrogen and Raney nickel catalyst.

4-Methylcyclohexanemethylamine was obtained from the reduction of 1-nitromethyl-4-methyl-1-cyclohexanol.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE USE OF ORGANOCADMIUM REAGENTS FOR THE PREPARATION OF SUBSTITUTED β-AROYLPROPIONIC ACIDS

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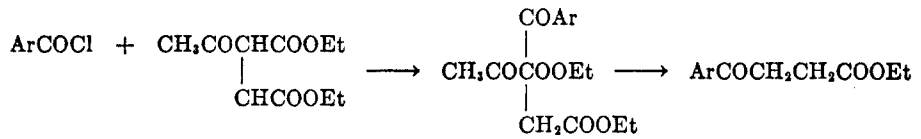
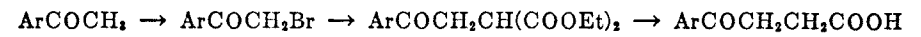
The preparation of *para*-substituted β-aroylaliphatic acids in which the *para*-substituent is an *ortho-para*-directing substituent is easily accomplished by means of the Friedel and Crafts reaction involving an anhydride or an ω-carbalkoxylacid chloride (1). Such a method is not generally applicable for the preparation of *ortho*- and *meta*-substituted acids of this series.

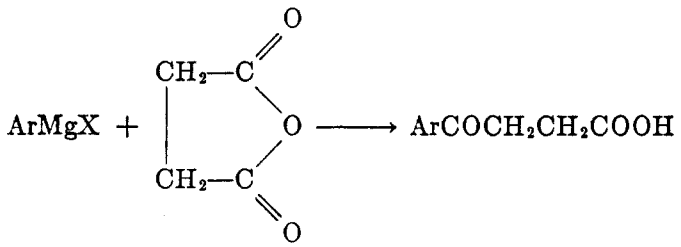
These latter types of acids usually have been prepared in one of three general ways. One method has been the acylation of diethyl acetosuccinate and subse-



quent hydrolysis but this method has not found wide application and the yields have generally been low (2, 3). A second method has been the stepwise lengthen-

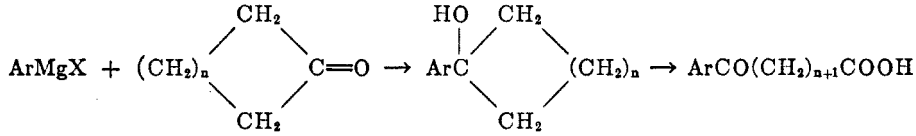


ing of the side-chain of a methyl aryl ketone by a laborious procedure involving bromination of the ketone, alkylation of malonic ester, and hydrolysis of the substituted malonic ester. This scheme usually has been used only in those cases where acetylation and succinoylation in the Friedel and Crafts reaction do not occur at the same position (1). A third method has made use of the reaction of a Grignard reagent with succinic anhydride.



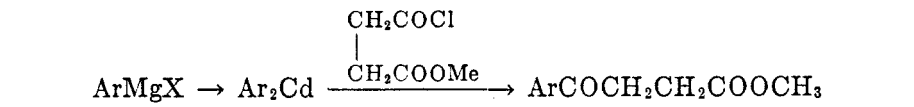
The yields generally have been poor (4, 5, 6, 7, 8) except in cases of hindered anhydrides such as dimethylsuccinic anhydride (9) or bulky bromides such as 1-bromonaphthalene (10). Newman has recently reported that better yields of keto acids can be obtained from the unhindered reagents when the reaction is conducted at −70° (11, 12). For example, phenylmagnesium bromide and succinic anhydride give a 50–70% of β-benzoylpropionic acid. The only other aromatic halide studied by these workers was *o*-bromotoluene which gave only 35% yield. Although this modification has greatly increased the utility of such a reaction, the new manipulations involved make it somewhat troublesome to execute.

An extremely novel approach has been developed by Fieser and Szmuszkovicz (13), who have found that good yields of keto acids may be obtained by the oxidation of the tertiary alcohol, resulting from the reaction of a Grignard reaction and a cyclic ketone.



This method suffers from the limitation in that to introduce four carbon atoms, cyclobutanone would be required.

In view of the limitations of the above-mentioned schemes for the preparation of aroylpropionic acids by methods other than the Friedel and Crafts reaction, an easily executed process which will proceed in good yield is still desired. The development by Cason (14) of the cadmium reaction for the synthesis of aliphatic keto acids has prompted us to investigate the use of the diaryl cadmium reagent for the preparation of aromatic keto acids of the above type.



Riegel and his associates (15) have previously reported the preparation of β-(α-naphthoyl)propionic acid in a yield of 45% from the reaction of di-α-naphthyl cadmium and β-carbomethoxypropionyl chloride. The preparation of methyl β-(*o*-methoxybenzoyl)propionate in a 45% yield by the same general procedure has also been reported by Dauben and Tanabe (16). Soffer and co-workers (17) have prepared methyl 10-keto-10-phenyldecanoate in a yield of 40% from diphenyl cadmium and 9-carbomethoxynonanoyl chloride. The present study has extended the application of the cadmium reaction and the results are summarized in Table I.

It was found that with most of the compounds studied the yield of aroylpropionic ester was relatively good (40–60%) and that those aryl bromides which were substituted so that they possessed a +I inductive effect appeared to proceed in the highest yield. It is interesting to note that in the bromotoluene series the yields obtained from all three isomers were about the same (56–62%). In the bromoanisole group, however, the *o*- and *p*-isomers gave good results (50–54%) whereas the *m*-isomer yielded only 27% of the desired keto ester. This latter low yield may be due to the extreme insolubility of the reaction complex; a factor which has been shown to be definitive in the success of the cadmium reaction with ester acid chlorides (14). From these reactions, it would appear that there is no "*ortho* effect" (18) in the reaction of a diaryl cadmium reagent with an acid chloride. This result is consistent with evidence (19, 20) that such a reaction may possibly proceed by direct displacement, either intra- or inter-molecularly, rather than by primary addition to the carbonyl linkage.

α-Naphthyl bromide was reinvestigated and was found to yield the desired

ester in 64% yield as compared to the previously reported 45%. The much lower yield (34%) obtained with β-bromonaphthalene is consistent with other work reported on the relative usefulness of these two isomers in the Grignard reaction (21).

Various workers (14, 22, 23) have reported that the preparation of a cadmium derivative from an alkylmagnesium iodide proceeds in poor yield. It has been found in the present work that this generality is apparently also true in the aromatic series. When phenylmagnesium iodide was employed as the source of diphenyl cadmium, the yield of methyl β-benzoylpropionate was only 17% as compared to 51% from the corresponding bromide.

TABLE I

YIELDS AND PROPERTIES OF METHYL β-AROYLPROPIONATES

AROYL GROUP	YIELD, %	B.P. °C.	MM.	n_D°C	ANALYSES			
					Calc'd		Found	
					C	H	C	H
Benzoyl	51	119–120[a]	0.4	1.5260^{19}				
o-Toluyl	58	110–111	.3	1.5203^{25}	69.88	6.84	70.06	7.04
m-Toluyl	62	118–119	.5	1.5258^{27}	69.88	6.84	69.95	6.68
p-Toluyl	56	119–120[b]	.5					
o-Methoxybenzoyl	50	135–136[c]	.6	1.5296^{25}				
m-Methoxybenzoyl	27	150–151	.5	1.5432^{29}	64.85	6.35	65.08	6.31
p-Methoxybenzoyl	54	149–150[d]	.5					
o-Chlorobenzoyl	32	149–150[e]	1.0	1.5274^{28}	58.29	4.89	58.43	4.88
p-Chlorobenzoyl	40	134–135[f]	0.8					
α-Naphthoyl	64	173–174[g]	.8	1.5921^{25}				
β-Naphthoyl	34	178–179[h]	.7					

[a] Kugel (28) reports b.p. 187–187.5° (30 mm.). [b] The solid ester was recrystallized from ether, m.p. 49–51°; Limpricht (29) reports 43°. [c] Dauben and Tanabe (16) report b.p. 161–162° (1.5 mm.), n_D^{27} 1.5311. [d] The solid ester was recrystallized from ether, m.p. 48–49°; Soffer and Hunt (30) report 47.5–49.5°. [e] *Anal.* Calc'd for $C_{11}H_{11}ClO_3$: Cl, 15.64. Found: Cl, 15.65. [f] The solid ester was recrystallized three times from ether, m.p. 51.6–52.8°. The reported melting point is 63° (31). [g] Riegel and co-workers (15) report 184–185° (1 mm.). [h] The solid ester was recrystallized from ether, m.p. 74–75°; Giua (32) reports 74°.

EXPERIMENTAL

Microanalyses are by the Microanalytical Division of the Department of Chemistry of the University of California. All melting points are corrected; all boiling points are uncorrected. The halides used as starting materials were purified commercial products except *m*-bromoanisole and *o*-chlorobromobenzene. These latter two compounds were prepared in the usual manner (24, 25). The cadmium reactions were conducted in an atmosphere of nitrogen and with 0.3 mole of halide, 0.3 mole of magnesium, 0.18 mole of anhydrous cadmium chloride, and 0.3 mole of β-carbomethoxypropionyl chloride (26). All reactions were carried out in a manner similar to that described for methyl β-benzoylpropionate. The yields and properties of the keto esters are reported in Table I. The esters were saponified and the acids purified by recrystallization from aqueous methanol. The properties of the acids are reported in Table II.

Methyl β-benzoylpropionate. A solution consisting of 47.1 g. (0.3 mole) of bromobenzene

dissolved in 150 cc. of dry ether and 50 cc. of anhydrous benzene was added dropwise over the course of one hour to 7.25 g. (0.3 mole) of magnesium turnings. The Grignard solution was cooled in an ice-bath and 33 g. (0.18 mole) of anhydrous cadmium chloride was added in one portion. The resulting mixture was heated under reflux with stirring until a negative Gilman test (27) was obtained. This required about 30 minutes. The ether was distilled until the mixture in the flask became a thin slurry and the distillation became slow. Anhydrous benzene (200 cc.) was then added and 25 cc. of benzene was distilled.

A solution containing 45.2 g. (0.3 mole) of β-carbomethoxypropionyl chloride dissolved in 50 cc. of dry benzene was added with vigorous stirring to the hot mixture as rapidly as possible. A very exothermic reaction ensued and during the addition the cadmium complex precipitated as small grey granules. The mixture was then heated under reflux with stirring for one hour and processed in the usual manner. There was obtained 29.5 g. (51%) of *methyl β-benzoylpropionate*, b.p. 119–120° (0.4 mm.), $n_D^{18.5}$ 1.5260.

TABLE II

PROPERTIES OF β-AROYLPROPIONIC ACIDS

AROYL GROUP	M.P., °C.		REF.
	Found	Reported	
Benzoyl	115–117	116	2
o-Toluyl	104.3–104.7	98–102	12
m-Toluyl	114–115	115–117	3
p-Toluyl	127–128	129	29, 33, 34, 35
o-Methoxybenzoyl	93.5–95	94–95	16
m-Methoxybenzoyl	146–148[a]	107–108, 111	36, 37
o-Chlorobenzoyl	71.5–73.5[b]		
p-Chlorobenzoyl	130–131.5	131	31
α-Naphthoyl	130–131	132–133	38, 39

[a] *Anal.* Calc'd for $C_{11}H_{12}O_4$: C, 63.45; H, 5.81; Neut. Equiv., 208.2.
Found: C, 63.75; H, 5.69; Neut. equiv., 209.7.

The acid was converted into a *semicarbazone* which was recrystallized twice from ethanol, m.p. 177.5–178°; reported (36, 37) 177–178°.

Anal. Calc'd for $C_{12}H_{15}N_3O_4$: C, 54.33; H, 5.70; N, 15.84.
Found: C, 54.65; H, 5.74; N, 15.16.

[b] *Anal.* Calc'd for $C_{10}H_9ClO_3$: C, 56.48; H, 4.27; Cl, 16.68.
Found: C, 56.34; H, 4.40; Cl, 16.54.

The ester was saponified and the *β-benzoylpropionic acid* recrystallized from aqueous methanol, m.p. 115–117°. DeBenneville (23) reports a 30% yield of this acid directly by the reaction of diphenylcadmium and succinic anhydride.

SUMMARY

The preparation of substituted β-aroylpropionic acids by means of the reaction of a diaryl cadmium reagent with β-carbomethoxypropionyl chloride has been studied. In most cases, the reaction proceeds in relatively good yield. Such a method is quite useful for the preparation of *ortho*- and *meta*-substituted acids of this series. It appears that there is no steric effect in this reaction.

BERKELEY 4, CALIFORNIA

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REACTIONS OF 2-THENYL CHLORIDE AND 5-CHLORO-2-THENYL CHLORIDE

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In the course of a general investigation of thiophene chemistry, the reactions of 2-thenyl chloride (1) and 5-chloro-2-thenyl chloride (2, 3) were studied. The chlorine of 2-thenyl chloride is readily replaced by nucleophilic reagents, and in this way tri-2-thenylamine and 2-thenyl propionate, benzoate, ethylxanthate, and amyl ether were prepared. Similarly, 5-chloro-2-thenyl chloride was converted to the corresponding acetate, ethylxanthate, thiocyanate, ethyl ether, N-substituted-ϵ-caprolactam, and cyanide. The cyanide[1] was subsequently hydrolyzed to 5-chloro-2-thiopheneacetic acid *via* an imido ester hydrochloride.

2-Thenyl chloride is similar in properties to its analog, benzyl chloride, but it shows important differences. It is more prone to solvolysis in the presence of bases so that substances such as alcohols are often undesirable reaction media for 2-thenyl chloride. Thus, 2-thenyl chloride reacted with sodium cyanide in aqueous ethanol to give a mixture of ethyl 2-thenyl ether (25% yield) and 2-thenyl cyanide (32% yield); under the same conditions, benzyl chloride is known to give a high yield of benzyl cyanide uncontaminated by ethyl benzyl ether (9). It seems to be more readily attacked by nucleophilic reagents than is benzyl chloride. For example, when one mole of sodium amoxide in amyl alcohol was added to a mixture of one mole each of benzyl chloride and 2-thenyl chloride, the product, a mixture of amyl benzyl ether and amyl 2-thenyl ether, contained 78 mole-per cent of the latter.

The preparation and properties of 2-thenyl alcohol were studied briefly. Although it can be prepared from 2-thiophenecarboxaldehyde by reduction with lithium aluminum hydride, this method is inferior to that of Emerson and Patrick (13). The reduction procedure is of more value when applied to 2-acetylthiophene; it gives a good yield of α-(2-thienyl)ethanol and is probably the best laboratory synthesis of this alcohol, which is of interest because it is easily dehydrated to the polymerizable ethene, 2-vinylthiophene (7, 11, 12, 14). An attempt to prepare α-(2-thienyl)ethanol by hydrogenation of 2-acetylthiophene led instead to α-(2-tetrahydrothienyl)ethanol in low yield.

EXPERIMENTAL

Physical constants and analytical data of many of the new compounds are listed in Table I.

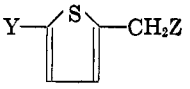
Thenyl chlorides. A slight modification of the chloromethylation procedures given in the literature (1, 16) was used. The best yield (50%) of 2-thenyl chloride (1), n_D^{25} 1.5630, was

[1] Note added in proof: Ford, Prescott, and Colingsworth, *J. Am. Chem. Sos.*, **72**, 2109 (1950), described this cyanide and the acid, amide, and methyl ester derived from it in a paper which appeared after this paper had been accepted for publication.

obtained at −5° to −10°. The optimum temperature for preparing 5-chloro-2-thenyl chloride (2, 3) was 45°; yield 85%; b.p. 95–96° (15 mm.); n_D^{25} 1.5722; d_4^{25} 1.385.

Thenyl esters. 5-Chloro-2-thenyl acetate was prepared by adding 134 g. of 5-chloro-2-thenyl chloride dropwise to a stirred solution of 118 g. of potassium acetate in 240 ml. of acetic acid at 100°. After an hour at 100°, the mixture was cooled to 25°, diluted with 500 ml. of water, and extracted with ether. The extract was washed with water and 10% sodium carbonate solution before being dried over magnesium sulfate and distilled. 2-Thenyl

TABLE I

THENYL COMPOUNDS 

Y	Z	BOILING POINT[a] °C.	BOILING POINT[a] MM.	M.P. OR n_D^{25}	d_4^{25}	YIELD %	FORMULA	ANALYSIS, % Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found
H	$OCOC_2H_5$	108–110	18	1.5112	1.135	65	$C_8H_{10}O_2S$	56.4	56.3	5.9	6.2
H	$OCOC_6H_5$	134–135	0.9	58–59°[a]		60	$C_{12}H_{10}O_2S$	66.0	65.8	4.6	4.6
H	OC_5H_{11}-*n*	104–105	13	1.4922	0.9844	69	$C_{10}H_{16}SO$	65.2	64.8	8.8	9.0
H	$SCSOC_2H_5$	120–127	0.4	1.6157	1.239	84	$C_8H_{10}OS_3$	38.0	38.6	3.6	3.6
Cl	$OCOCH_3$	130–132	24	1.5249	1.285	86	$C_7H_7ClO_2S$	44.1	44.2[b]	3.7	3.9
Cl	OC_2H_5	81–82	6	1.5183	1.1757	47	C_7H_9ClOS	47.6	48.2	5.1	5.3
Cl	$SCSOC_2H_5$	145–147	1.4	1.6188	1.328	77	$C_8H_9ClOS_3$	38.0	38.6[c]	3.6	3.6
Cl	SCN	121–123	1.4	1.6242	1.379	75	$C_6H_4ClNS_2$	38.0	38.2	2.1	2.2
Cl	CN	117–119	7	1.5551	1.3144	39	C_6H_4ClNS	45.7	45.8	2.6	2.7
Cl	$CONH_2$			121–122°[d]		6	C_6H_6ClNOS	41.0	41.4	3.4	3.7
Cl	CO_2CH_3	67–72	0.5	1.5301		29	$C_7H_7ClO_2S$	44.1	44.9	3.7	4.3
Cl	CO_2H	115–112	0.5	65.5–66°[e]		64	$C_6H_5ClO_2S$	40.8	40.9	2.9	3.1
Cl	$N(CH_2)_5C{=}O$			71–73.5°[a]		40	$C_{11}H_{14}ClNOS$	54.2	54.4[f]	5.8	5.9

[a] Recrystallized from hexane.
[b] Sap. equiv.: Calc'd, 191; Found, 191.
[c] Chlorine: Calc'd, 14.0; Found, 14.65.
[d] Recrystallized from benzene.
[e] Recrystallized from cyclohexane.
[f] Chlorine, nitrogen, sulfur: Calc'd, 14.6, 5.8, 13.1; Found, 14.6, 5.5, 12.7.
[g] Distillations were through a six-inch, indented, Claisen-type head.

propionate was prepared similarly. 2-Thenyl benzoate was obtained by stirring and refluxing a solution of 144 g. of sodium benzoate in 220 ml. of water with 49 g. of 2-thenyl chloride for one hour; 2-thenyl alcohol (6.0 g.) was a by-product.

Alkaline hydrolysis of 5-chloro-2-thenyl acetate gave 5-chloro-2-thenyl alcohol. Aqueous permanganate at 10° oxidized the alcohol to 5-chloro-2-thiophenecarboxylic acid, m.p. and mixture m.p. 150–151° (8). 5-Chloro-2-thenyl alcohol soon splits out water with formation of *bis*-(5-chloro-2-thenyl) ether (13) unless stored over solid potassium carbonate. The alcohol has been prepared before (13) but not analyzed.

Anal. Calc'd for C_5H_5ClOS: Cl, 23.9. Found: Cl, 24.2.

Ethylxanthates. Carbon disulfide (107 g.) was added with cooling to a solution of 50 g. of sodium hydroxide in 50 ml. of water and 500 ml. of 95% ethanol. The solution was stirred

and gently refluxed as 150 g. of 2-thenyl chloride was added over a period of 15 minutes. The mixture was refluxed 45 minutes, cooled, and poured into water. The xanthate was extracted with ether. Distillation gave 206 g. of yellow 2-thenyl ethylxanthate. 5-Chloro-2-thenyl ethylxanthate was prepared similarly.

5-Chloro-2-thenyl thiocyanate. A solution of 87.5 g. of potassium thiocyanate in 50 ml. of water and 220 ml. of acetone was stirred and refluxed while 100 g. of 5-chloro-2-thenyl chloride was added over a period of 30 minutes. Heating was continued for three hours, the mixture was poured into 750 ml. of water, and the product was taken up in ether and distilled. The thiocyanate is a skin irritant.

Thenyl ethers. To prepare amyl 2-thenyl ether, 20 g. of 2-thenyl chloride was added to a solution of 3.8 g. of sodium in 75 ml. of *n*-amyl alcohol and the mixture was heated at 100° for an hour. Water and ether were added and the organic layer was separated and distilled. 5-Chloro-2-thenyl ethyl ether was prepared similarly.

The competitive reaction of benzyl chloride and 2-thenyl chloride with sodium amoxide. A solution of 23.0 g. (1.00 g.-atom) of sodium in 490 ml. of amyl alcohol was added to a well-stirred solution of 132.6 g. (1.00 mole) of 2-thenyl chloride and 126.6 g. (1.00 mole) of benzyl chloride in 250 ml. of amyl alcohol at 65–70°. The mixture was stirred at 95–100° for 45 minutes, cooled to room temperature, and stirred with 400 ml. of water to dissolve sodium chloride. The organic layer was distilled. The main fraction, b.p. 127–129° (26 mm.), n_D^{25} 1.4906, weighed 181 g. From its sulfur content (13.7%) it was, on a mole basis, 78% amyl 2-thenyl ether and only 22% amyl benzyl ether (4).

Tri-2-thenylamine. 2-Thenyl chloride (182 g.) was added to 600 ml. of well-stirred liquid ammonia over a period of 20 minutes. The mixture stood at room temperature for 16 hours to allow the ammonia to evaporate. Then 700 ml. of 10% sodium hydroxide and 400 ml. of ether were added to the residue. The ether layer was separated and heated on a steam-bath to remove the ether. A solid mass remained; it weighed 117 g. and was no longer completely soluble in ether. Ether extraction effected the separation of 85 g. of pasty solid from insoluble matter. The pasty solid was pressed on a clay plate to remove 2-thenylamine, di-2-thenylamine, and other oils. Subsequent crystallization from hexane gave 45 g. (32% yield) of tri-2-thenylamine, m.p. 67–69°. After several recrystallizations it melted at 70.5–71°.

Anal. Calc'd for $C_{15}H_{15}NS_3$: C, 59.0; H, 4.95; N, 4.6.
Found: C, 58.7; H, 5.2; N, 4.6.

N-(5-Chloro-2-thenyl)-ε-caprolactam.[2] The N-sodio derivative of ε-caprolactam was prepared by adding 9.6 g. of sodium hydride in small portions with stirring to 45.2 g. of ε-caprolactam in 300 ml. of dry xylene. A solution of 66.8 g. of 5-chloro-2-thenyl chloride in 50 ml. of xylene was added dropwise and the mixture was refluxed five hours. Sodium chloride and xylene were removed by filtration and distillation *in vacuo*, respectively, and the crystalline residue was extracted with 650 ml. of boiling hexane. Cooling the hexane solution caused 46 g. of crude N-(5-chloro-2-thenyl)-ε-caprolactam to separate. This after recrystallization from hexane weighed 38.5 g.

5-Chloro-2-thiopheneacetonitrile. Fifty grams of 5-chloro-2-thenyl chloride was added in a period of 15 minutes to a stirred solution of 29 g. of potassium cyanide in 30 ml. of water at 105°. After 45 minutes of heating and stirring, the mixture was cooled, ether, water, and diatomaceous earth were added, the mixture was filtered to remove resin, and the ether layer was distilled; yield 39%.

Under six other sets of conditions, including the use of xylene or aqueous acetone as the reaction medium, even lower yields of nitrile were obtained. In some cases considerable *bis*-(5-chloro-2-thenyl) ether (13) was formed.

5-Chloro-2-thiopheneacetamide and methyl 5-chloro-2-thiopheneacetate. Hydrogen chloride was passed into a mixture of 6.7 g. of methanol and 31.5 g. of 5-chloro-2-thiopheneacetonitrile at 0–5° until 8.0 g. (10% excess) had been absorbed. Dry ether (55 ml.) was added. The mixture was held at 0° for six hours and then filtered to remove 15.0 g. of crude imido ester hydrochloride. The hydrochloride was heated at 100° with 50 ml. of water. This caused

[2] Prepared by Dr. R. E. Benson.

oil mixed with 2.0 g. (6% yield) of a solid, 5-chloro-2-thiopheneacetamide, to separate. Distillation of the oil gave 4.4 g. of methyl 5-chloro-2-thiopheneacetate. An additional 6.7 g. (total yield, 29%) was obtained from the ether solution from which the imido ester hydrochloride had been filtered by saturating it with hydrogen chloride and then pouring it into ice-water. Analysis indicated that the ester was slightly impure.

5-Chloro-2-thiopheneacetic acid. 5-Chloro-2-thiopheneacetonitrile was not easily hydrolyzed by acid, and alkaline hydrolysis converted it to tar. However, 5-chloro-2-thiopheneacetic acid was readily obtained by refluxing 5-chloro-2-thiopheneacetamide or, better, methyl 5-chloro-2-thiopheneacetate with 10% aqueous sodium hydroxide for 15 minutes.

2-Thenyl alcohol (13, 15, 17, 18, 19). 2-Thiophenecarboxaldehyde was prepared as described by Dunn, Waugh, and Dittmer (5). The intermediate salt of 2-thenyl chloride with hexamethylenetetramine, not previously analyzed, melted at 189–190°.

Anal. Calc'd for $C_{11}H_{17}ClN_4S$: C, 48.4; H, 6.3.
Found: C, 48.2; H, 6.3.

The Nystrom-Brown method of reduction (6) was used. Twenty grams of 90% lithium aluminum hydride was stirred in 600 ml. of boiling ether for three hours. The reaction flask was immersed in cold water and 170 g. of 2-thiophenecarboxaldehyde was added over a period of three hours at such a rate that gentle refluxing occurred. Then 150 ml. of 12 *N* hydrochloric acid in 500 ml. of water was added to the mixture at 10–20° with stirring. The ether layer was separated, washed with water and aqueous sodium carbonate, dried over magnesium sulfate, and distilled over 0.5 g. of potassium carbonate. The yield of 2-thenyl alcohol, b.p. 101–102° (16 mm.), n_D^{25} 1.5593, was 129 g. (75%). It gave a negative test with 2,4-dinitrophenylhydrazine. Oxidation with aqueous permanganate at 10° gave 2-thiophenecarboxylic acid, m.p. and mixture m.p. 125–126° (8), in 20% yield.

Except for slight discoloration, 2-thenyl alcohol was unaffected by being held under nitrogen in a 225°-bath for 15 hours. At 200° a small amount of oxalic acid converted it to an orange resin; some formaldehyde, detected by odor, was formed in the process. Orange resins were also obtained at 25° under the influence of sulfuric acid, phosphoric acid or stannic chloride. 2-Thenyl alcohol gradually dehydrates to 2-thenyl ether (13) unless stored over potassium carbonate; one such unstabilized sample contained 15% 2-thenyl ether and 18% higher-boiling material after two years at 25°. Similar dehydration occurs when 2% by weight of 12 *N* hydrochloric acid is dissolved in 2-thenyl alcohol and the solution allowed to stand 24 hours at 25°.

Reduction of 2-acetylthiophene. A. By lithium aluminum hydride. Under the conditions used above for the reduction of 2-thiophenecarboxaldehyde, α-(2-thienyl)ethanol (7, 10, 11, 14) was obtained in 75% yield; b.p. 83° (8 mm.); m.p. 20–21°; n_D^{25} 1.5429. Its phenylurethan (14) melted at 84.5–85.5°.

B. By hydrogen. A solution of 126 g. (1.00 mole) of 2-acetylthiophene (Socony-Vacuum Oil Co.; n_D^{25} 1.5629) and 50 ml. of absolute ethanol was hydrogenated for six hours at 150° and a pressure of 2000–2800 lbs./sq. in. in the presence of 3.0 g. of ruthenium dioxide. An uptake corresponding to 0.7 mole of hydrogen was observed. Distillation gave 100 g. of material of b.p. 68–69° (4 mm.); n_D^{25} 1.5552. Eight grams of the distillate was mixed with 4.0 g. of phenyl isocyanate and 3 drops of pyridine and the mixture was allowed to stand for two days at 25°. Removal of material volatile at 100° (0.5 mm.) left 2.0 g. of oil from which, by treatment with hexane, 0.44 g. of the *phenylurethan of α-(2-tetrahydrothienyl)-ethanol* was isolated. It melted at 80.5–81° after several crystallizations from chloroform-hexane mixtures. A mixture with the phenylurethan of α-(2-thienyl)ethanol melted at 60–74°.

Anal. Calc'd for $C_{13}H_{17}NO_2S$: C, 62.1; H, 6.8; N, 5.6.
Found: C, 62.2; H, 6.75; N, 5.7.

Evidently a low yield of α-(2-tetrahydrothienyl)ethanol, and little or no α-(2-thienyl)-ethanol, was formed by this method.

Acknowledgments. We wish to express our appreciation to Dr. P. R. Austin and Dr. D. D. Coffman for valuable suggestions.

SUMMARY

2-Thenyl chloride and 5-chloro-2-thenyl chloride have been converted to corresponding esters, ethers, ethylxanthates, cyanides, and other similar compounds.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF MAINE]

SULFENYL CHLORIDE STUDIES. I. THE ANHYDROUS CHLORINATION OF CERTAIN *s*-TRITHIANES[1]

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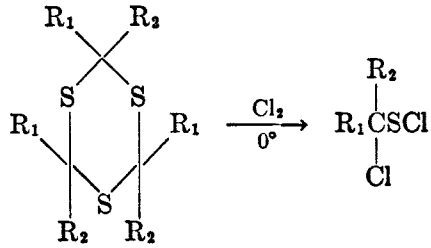
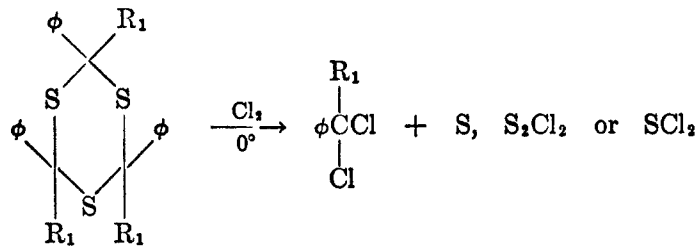
Earlier work in this laboratory (1) has shown that anhydrous chlorine reacts with *s*-trithiane to form chloromethanesulfenyl chloride, $ClCH_2SCl$. The present paper is concerned with a further study of this reaction and its extension to other trimeric thioaldehydes and thioketones.

It has been found that the 2,4,6-trialkyl-*s*-trithianes and 2,2,4,4,6,6-hexamethyl-*s*-trithiane react smoothly with chlorine at low temperatures to form 1-chloroalkanesulfenyl chlorides. It appears, however, that when the substituted *s*-trithiane has phenyl groups in the 2,4,6-positions the action of chlorine is to eliminate sulfur completely and form 1,1-dichloro compounds.



(a) R_1 = H, R_2 = H, CH_3, C_2H_5 or $n-C_3H_7$
(b) R_1 = R_2 = CH_3



R_1 = H, CH_3

The 1-chloroalkanesulfenyl chlorides are yellow, highly refractive and unstable liquids with unpleasant odors. Their instability appears to be associated with the presence of hydrogen atoms on the *alpha*-carbon atoms. Great difficulty was encountered, for example, in avoiding the over-chlorination of chloromethanesulfenyl chloride, $ClCH_2SCl$, but dimethylchloromethanesulfenyl chloride, $(CH_3)_2CClSCl$, was prepared and distilled with comparative ease. Wood, in a recent patent (2), has described the preparation of dichloromethanesulfenyl

[1] This paper reports a portion of the work done on project NR 055 165 under contract N8onr 77000 with the Office of Naval Research, United States Navy.

chloride, Cl_2CHSCl, by the reaction of chlorine with *s*-trithiane at higher temperatures than those employed in this study and has provided an explanation for some of the difficulties encountered in the preparation of chloromethanesulfenyl chloride. The instability of the compounds is reflected in the number of significant figures used in reporting their densities and refractive indices. We have found that the density in particular varies markedly with small changes in chlorine content.

The reactions of the 1-chloroalkanesulfenyl chlorides have not been thoroughly investigated but preliminary tests indicate that they are similar to those of other sulfenyl chlorides (10, 11). Chloromethanesulfenyl chloride reacts readily with acetone, olefins, mercaptans, phenols, secondary amines, potassium iodide and alcohol. The products formed, however, are themselves highly reactive in some cases and tend to decompose during the process of purification. It is planned to report later on further studies of the derivatives of the 1-chloroalkanesulfenyl chlorides.

EXPERIMENTAL PART

Chlorination procedure. A one-liter, three-necked flask fitted with stirrer, chlorine inlet tube, outlet tube, and thermometer was surrounded by ice and salt. In the more successful experiments the temperature of the reaction mixture was maintained constantly below 0°.

Method A. In some trials the solid *s*-trithiane was introduced in successive 2–5 g.-portions to the dry flask. The solid rapidly became liquefied and the accumulating liquid acted as a suspending medium for later portions of the solid. This method had the disadvantage that until a quantity of liquid had accumulated, the exothermic nature of the reaction and the low thermal conductivity of the dry solid made it difficult to control the temperature of the reaction at the solid-gas interface.

Method B. Another procedure which made more efficient cooling possible was to introduce 25–50 cc. of inert solvent, such as carbon tetrachloride or methylene chloride, along with 20–25 g. of the substance being chlorinated.

In all cases the flask with its contents was weighed before chlorinating and at intervals during the reaction. Chlorination was terminated when three moles of chlorine per mole of trithiane had been taken up.

Other experimental procedures. It was originally intended to carry out the purification of the new sulfenyl chlorides in a Todd Fractionation Assembly (3) in order to make possible the determination of precise physical constants. It was found, however, that the compounds were too unstable to withstand the prolonged refluxing of such close fractionation. A ten-inch wrapped Vigreux column was finally adopted as a compromise which would give reasonably good fractionation and still permit distillation in a minimum of time.

After distillation, the determination of refractive index, density, molecular weight, and chlorine content of the sulfenyl chlorides had to be made immediately, for standing overnight, even in the ice-chest, allowed decomposition to begin. Density determinations were carried out with the pycnometer described by Lipkin, Davison, Harvey, and Kurtz (4). All molecular weights were determined cryoscopically in benzene.

s-Trithiane. *s*-Trithiane was prepared by a more rapid method than that generally employed (5). The mixture of formalin and concentrated hydrochloric acid was placed in a flask fitted with a stirring device and hydrogen sulfide was passed in from a Kipp generator as rapidly as it could be generated. Heat was liberated but no attempt was made to cool the reaction mixture. When solid *s*-trithiane had formed to such an extent as to interfere with the stirring, the mixture was filtered, the filtrate returned to the flask and the passage of hydrogen sulfide continued. The solid was washed repeatedly with water and after drying was used for chlorination without further purification.

Chloromethanesulfenyl chloride, $ClCH_2SCl$. The chlorination of *s*-trithiane was repeated many times by both methods A and B with yields of 10–20%. The following properties of chloromethanesulfenyl chloride are probably more accurate than those previously reported (1) although it is doubtful if the compound has yet been prepared in a chemically pure condition: b.p. 33°/18 mm., n_D^{20} 1.542, d_4^{20} 1.52, d_4^0 1.55.

Anal. Calc'd for CH_2Cl_2S: Cl, 60.61; Mol. wt., 117.0.

Found: Cl, 60.5, 61.2; Mol. wt., 121, 122.

1-Chloroethanesulfenyl chloride, $CH_3CHClSCl$. When 20 g. of trithioacetaldehyde prepared by the method of Baumann and Fromm (6) was chlorinated by method A, 7 g. (16% yield) of a golden yellow liquid was obtained having the following properties: b.p. 47–50°/40 mm., n_D^{20} 1.5102, d_4^{20} 1.347, d_4^0 1.363.

Anal. Calc'd for $C_2H_4Cl_2S$: Cl, 54.12; Mol. wt., 131.

Found: Cl, 54.0, 54.3; Mol. wt., 136.

Trithiopropionaldehyde, 2,4,6-Triethyl-s-trithiane. Freshly distilled propionaldehyde (174 g.) was added to 500 cc. of cold ethanol into which previously 95 g. of hydrogen chloride had been absorbed. The mixture was then held at 5° or lower while hydrogen sulfide was passed in for three hours and there had been an increase in weight of 75 g. After standing overnight in the ice-chest the mixture separated into two layers. The lower layer was washed well with water and then with sodium bicarbonate solution, dried over calcium chloride, and subjected to vacuum-distillation. There was no sharp separation into fractions but a steady rise in temperature from 25°/23 mm. to 185°/13 mm. The principal fractions (53.4 g.) were collected between 135–160°/13 mm. After stopping the distillation at 185°/13 mm. there was 47 g. of residue undistilled.

Several of the fractions yielded white crystals on standing at room temperature or in the ice-chest. One fraction had b.p. 143°/10 mm., n_D^{25} 1.5472.

Anal. Calc'd for $C_9H_{18}S_3$: Mol. wt., 222. Found: Mol. wt., 228.

It solidified almost completely to a white solid which melted over a range of several degrees near 54°. This solid was resolved into two components by recrystallization from alcohol, one melting at 36° and the other at 76°.

The component melting at 36° was also obtained in pure condition by the partial crystallization of a liquid fraction, b.p. 135–143°/10 mm., n_D^{25} 1.5461. The solid was analyzed.

Anal. Calc'd for $C_9H_{18}S_3$: S, 43.24. Found: S, 42.6, 42.2.

The component melting at 76° was also obtained by the partial crystallization of a fraction b.p. 150-155°/10 mm., n_D^{25} 1.5478.

Anal. Calc'd for $C_9H_{18}S_3$: S, 43.24. Found: S, 44.0, 43.5.

Less than 15 g. of solid was obtained from all fractions.

It seems probable that the solids melting at 36° and 76° respectively are the *alpha* and *beta* isomers of 2,4,6-triethyl-*s*-trithiane which structural theory leads one to expect. The failure of the entire preparation to boil over a narrow temperature range may be due to the presence of a relatively large proportion of the dehydration and condensation products of propionaldehyde or thiopropionaldehyde in addition to linear polymers of the latter.

A dramatic description of the malodorous volatile by-products accompanying the preparation of trithioacetone has been recorded (7). The odors of certain compounds formed in the reaction of propionaldehyde with hydrogen sulfide and hydrogen chloride are fully as bad. Both the crude reaction mixture and the more volatile products of distillation have an exceedingly offensive smell somewhat resembling onions, hence the preparation of trithiopropionaldehyde should not be attempted without taking due precautions for the complete disposal of the waste liquids and the efficient trapping of all uncondensed vapors during distillation.

1-Choropropane-1-sulfenyl chloride, $C_2H_5CHClSCl$. A 28.2 g.-portion of liquid trithiopropionaldehyde, b.p. 143–160°/8 mm., was chlorinated until 26.8 g. of chlorine had been absorbed. Upon distillation 19.6 g. of yellow liquid boiling over the range 58°/29 mm. to 80°/39 mm. was collected. Upon redistillation there was obtained as the principal fraction 8.1 g. (14% yield) of a yellow liquid, b. p. 62–64°/27 mm.; n_D^{20} 1.501, d_4^{20} 1.276, d_4^0 1.301.

Anal. Calc'd for $C_3H_6Cl_2S$: Cl, 48.89; Mol. wt., 145.

Found: Cl, 48.2, 48.8; Mol. wt., 145.

Trithiobutyraldehyde. The preparation of trithiobutyraldehyde was attempted by essentially the same method as that used in the preparation of trithiopropionaldehyde but no pure compound was isolated. Four fractions collected within the range 120-200°/8 mm. had molecular weights of 234, 252, 261, and 320 respectively. Calc'd for $(C_3H_7CHS)_3$, 264. The fraction with molecular weight 261 and b.p. 155–180°/8 mm. was analyzed for sulfur.

Anal. Calc'd for $C_{12}H_{24}S_3$, S, 36.36. Found: S, 29.0, 28.7.

The fractions with molecular weights of 252, 261, and 320 were assumed to contain some trithiobutyraldehyde or closely related compounds, and were combined for chlorination without further attempts at fractionation.

1-Chlorobutane-1-sulfenyl chloride, $C_3H_7CHClSCl$. The combined liquid fractions of trithiobutyraldehyde referred to above (20 g.) were chlorinated in the absence of inert solvent. After 16 g. of chlorine had been absorbed the mixture was distilled. Three small fractions boiling in the range 67–73°/20 mm. were collected and immediately recombined. Redistillation yielded 4.9 g. of a yellow, sour-smelling, lacrymatory liquid with the following properties: b.p. 62–65°/15 mm., n_D^{20} 1.490, d_4^{20} 1.202.

Anal. Calc'd for $C_4H_8Cl_2S$: Cl, 44.58; Mol. wt., 159.

Found: Cl, 43.5, 43.8, 43.9; Mol. wt., 155.

Trithioacetone, 2,2,4,4,6,6-Hexamethyl-s-trithiane. By employing the method of Baumann and Fromm (7), except that steam-distillation was omitted, 81 g. (36% yield) of trithioacetone was obtained from 174 g. of acetone. The product had the properties: b.p. 105-107°/10 mm., n_D^{24} 1.5400.

Anal. Calc'd for $C_9H_{18}S_3$: Mol. wt., 222. Found: Mol.. wt., 218.

2-Chloropropane-2-sulfenyl chloride, $(CH_3)_2CClSCl$. Purified trithioacetone (18.5 g.) was chlorinated in the usual manner and distilled when the theoretical amount of chlorine had been absorbed. A total of 23.8 g. (67% yield) of yellow liquid was collected at 37–43°/27 mm. A principal fraction of 13.9 g. (38% yield) had b.p. 40°/26 mm.; n_D^{20} 1.493, d_4^{20} 1.249, d_4^0 1.273.

Anal. Calc'd for $C_3H_6Cl_2S$: Cl, 48.89; Mol. wt., 145.

Found: Cl, 48.9, 49.3; Mol. wt., 150.

Chlorination of trithiobenzaldehyde, 2,4,6-triphenyltrithiane. Twenty grams of trithiobenzaldehyde, in the presence of 25 cc. of methylene chloride, was chlorinated until 12.6 g. of chlorine (3.6 moles/mole trithiane) had been absorbed. Distillation of the product gave 24 g. (90%) of crude benzal chloride boiling at 77–82°/10 mm. Redistillation gave a purified product, b.p. 82°/10 mm.; n_D^{20} 1.5507, d_4^{20} 1.2485, d_4^0 1.2691.

Anal. Calc'd for $C_7H_6Cl_2$: Cl, 43.74; Mol. wt., 161; MR_D, 41.01 (8).

Found: Cl, 44.3, 44.1, 44.3; Mol. wt., 161; MR_D, 41.12.

Chlorination of trithioacetophenone, 2,4,6-trimethyl-2,4,6-triphenyl-s-trithiane. Twenty grams of trithioacetophenone, prepared by the method of Reid (9), was mixed with 25 cc. of methylene chloride and chlorinated as described. The prinicpal product was 1,1-dichloroethylbenzene, $C_6H_5CCl_2CH_3$, which was obtained in 57% yield. Although 1,1-dichloroethylbenzene has been prepared by several previous workers no physical properties have been reported because the compound could not be prepared in a pure condition. The reaction given here, however, takes place readily and no special difficulty was encountered in obtaining a purified product; b.p. 87–88°/11 mm., n_D^{20} 1.5432, d_4^{20} 1.2173, d_4^0 1.2339.

Anal. Calc'd for $C_8H_8Cl_2$; Cl, 40.51; Mol. wt., 175; MR_D, 45.66 (8).

Found: Cl, 40.54, 40.28, 40.68; Mol. wt., 175; MR_D, 45.33.

On standing several weeks this purified sample of 1,1-dichloroethylbenzene changed from colorless to dark green and fumed when the moist breath was blown across the opened container.

SUMMARY

1. The trimers of thioformaldehyde, thioacetaldehyde, thiopropionaldehyde, thiobutyraldehyde, and thioacetone yield upon chlorination under anhydrous conditions 1-chloroalkanesulfenyl chlorides.

2. The action of chlorine upon trithiobenzaldehyde and trithiobenzophenone is to eliminate sulfur and replace it with two chlorine atoms on the same carbon.

3. The *alpha* and *beta* forms of 2,4,6-triethyl-*s*-trithiane have been isolated.

ORONO, MAINE

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[CONTRIBUTION FROM THE VENABLE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

PARTIAL HYDROLYSIS OF ADIPONITRILE AND SEBACONITRILE BY HYDROGEN PEROXIDE

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Of the ω-cyanocarboxamides having six or more carbon atoms, only ω-cyanovaleramide, a derivative of adipic acid, has been prepared and it has not been fully characterized (1, 2). It was prepared from adipic acid in 67% yield (2). In the present study ω-cyanovaleramide and ω-cyanopelargonamide have been prepared by partial hydrolysis of adiponitrile and sebaconitrile with alkaline 3% hydrogen peroxide (3) in 31% and 6% yields respectively. Other methods including alkaline and acid hydrolysis gave lower yields or no cyanoamide at all.

RESULTS AND DISCUSSION

The preferred procedures given in the experimental section for the preparation of ω-cyanovaleramide and ω-cyanopelargonamide were selected after a study of time, temperature, and ratio of reactants as process variables. They are procedures which give the best yields obtained and are at reasonable conversions.[2] As usual in such partial reactions, it is necessary to balance conversion against yield. Higher conversions than those associated with the maximum yields gave lower yields of cyanoamide. Thus, in a run at 52% conversion, 25% yield of ω-cyanovaleramide was obtained and at 89% conversion, 9% yield. Experiments with adiponitrile showed that of the factors examined, the temperature at which the peroxide is added to the dinitrile and the ratio of hydrogen peroxide to dinitrile were the most important factors controlling yields. Increase in temperature during addition increased both yield of amide and conversion over the range −10° to 70° with optimum yields of 24.6% and 89% conversion at 70°. An increase in the ratio of hydrogen peroxide to dinitrile is associated with a two-fold increase in the yield of amide at 5° but at 35–40° a similar change in ratio of reactants results in a decreased yield of amide. The result is that the maximum yield of amide was obtained at 5°. Conditions which gave a 31% yield of cyanovaleramide from adiponitrile gave only 1.8% yield of cyanopelargonamide from sebaconitrile. An increase in the temperature to 40° gave the best yields observed under any conditions, 6%. Further increase in temperature gave no increase in yield. It is possible that an extended study of these variables may disclose more favorable conditions for preparative procedures for these cyanoamides.

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[2] Conversions are determined on the basis of recovered dinitrile. Thus, if one mole of dinitrile were reacted and 0.5 mole of unchanged dinitrile recovered, conversion is calculated on the basis of the 0.5 mole of dinitrile that has reacted. If 0.25 mole of cyanoamide were formed, the yield for this hypothetical case would be 25%; the conversion 50%.

EXPERIMENTAL PART

ω-Cyanovaleramide. A solution prepared by adding 2 g. of potassium hydroxide dissolved in 2 ml. of water to 130 ml. of fresh 3% hydrogen peroxide is placed in a 500-ml. three-necked round-bottom flask fitted with an efficient stirrer, a dropping-funnel, and a thermometer. Acetone (20 ml.) is then added to the flask which is immersed in an ice-bath and the contents cooled to 3–5°. A solution of 27 g. (0.25 mole) of adiponitrile[3] dissolved in 20 ml. of acetone is added dropwise over a one-hour period to the reaction mixture with stirring and at 3°. The mixture is then refluxed one-half hour on the steam-bath.

The acetone is removed on a steam-bath under a slight vacuum. The residue, if acid, is made alkaline with potassium hydroxide and saturated with sodium chloride, and continuously extracted with ethyl acetate for 24 hours. The extracts are filtered to remove any precipitated diamide. The ethyl acetate is removed under reduced pressure, and the residue, which consists of unreacted adiponitrile and the cyanoamide, is distilled rapidly from a Claisen flask, using a metal bath which has been pre-heated to 250°. As soon as all of the adiponitrile, b.p. 169–171° at 25–26 mm., has been removed the temperature rises rapidly and the distillation is stopped when a solid appears in the condenser. The residue is impure ω-cyanovaleramide, m.p. 62–64°. Recrystallization from a mixture of acetone and ethyl ether gives 9.8 g. of a white solid, m.p. 66–67°, conversion 43%, yield 31%.

Anal. Calc'd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99; N, 22.21.
Found: C, 57.07; H, 8.14; N, 22.00.

ω-Cyanopelargonamide. A solution of 63.8 g. (0.39 mole) of sebaconitrile (4), b.p. 151–155° at 4–5 mm., in 50 ml. of acetone, is placed in the reaction vessel equipped as above. A solution prepared from 200 ml. of 3% hydrogen peroxide to which has been added 4 g. of potassium hydroxide dissolved in 4 ml. of water and 50 ml. of acetone is added dropwise through the separatory-funnel over a one-hour period while the temperature of the reaction mixture is 40–45°. The ω-cyanopelargonamide is then isolated following the procedure used above. The crude material is recrystallized from a mixture of ethyl ether and petroleum ether to give 4.2 g. of a white solid, m.p. 74–75°, conversion 12%, yield 6%. A mixture melting point using a sample prepared by treating ω-cyanopelargonic acid with thionyl chloride and ammonium hydroxide gave no depression.

Anal. Calc'd for $C_{10}H_{18}N_2O$: C, 65.89; H, 9.95; N, 15.37; M.W., 182.
Found: C, 66.21; H, 10.60; N, 15.19; M.W., 189 (Method of Rast).

SUMMARY

ω-Cyanovaleramide has been characterized and the previously unknown ω-cyanopelargonamide has been prepared, isolated, and characterized. A study of the variables in the partial hydrolysis of adiponitrile and sebaconitrile to the corresponding cyanocarboxamides has been made and preferred conditions for isolation of the cyanoamides have been described.

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[3] The authors are indebted to the DuPont Company for graciously supplying the adiponitrile used in this study.

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OXAZOLINE RING-OPENING

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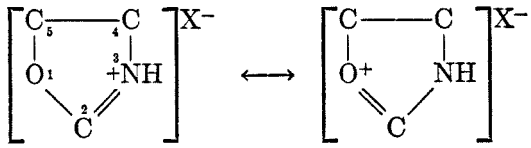
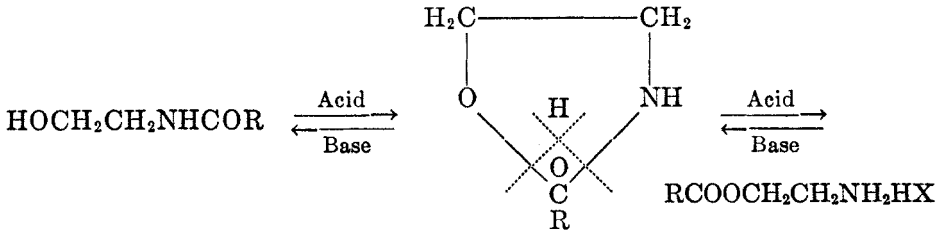
The alkyl- or aryl-substituted oxazoline ring is normally opened between positions 2 and 3 by acid hydrolysis as well as by the action of acid anhydrides followed by water (1). Hydrogen sulfide opens the ring between positions 1 and 2 (2) and between positions 1 and 5 (3), and alkaline hydrolysis also involves either or both of these positions (4, 2). The rearrangement of hydrohalide salts causes rupture between positions 1 and 5 (2, 5). The present report deals with the reactions of organic acids and acid chlorides and attempts to correlate these findings with the foregoing observations.

Goldberg and Kelly have recently suggested that the place of opening may be influenced by the predominant form of an oxonium-ammonium ion equilibrium as well as by external factors (2). This resonance concept provides a reasonable explanation for the vulnerability of the ionic form to nucleophilic attack at positions 2 and 5 which are analogous to the positions adjacent to electropositive oxygen and nitrogen centers in the benzopyrrylium (6) and dihydroisoquinoline systems (7) which also behave as carbonium ions.

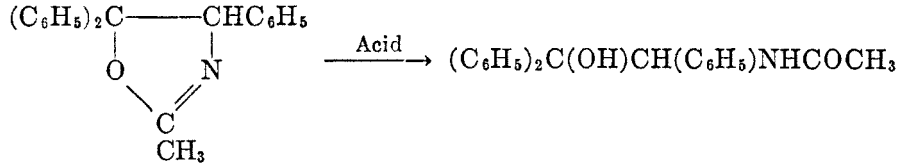


This formulation easily leads to a rational mechanism for the reactions mentioned above. The salts are stable as long as the anion is below the energy state necessary to add to position 5. Unlike the reversible addition to position 2, addition at 5 breaks the ring to give the stable chloroethylamide. However, a hydroxyl or sulfhydryl group at 2 can lose a proton to either the oxygen or nitrogen with ring opening between 1 and 2 or between 2 and 3. This hypothetical hydroxyoxazolidine was first proposed to explain the O → N transfer of an acyl group in a β-aminoethyl ester (8). The subsequent rearrangement to the

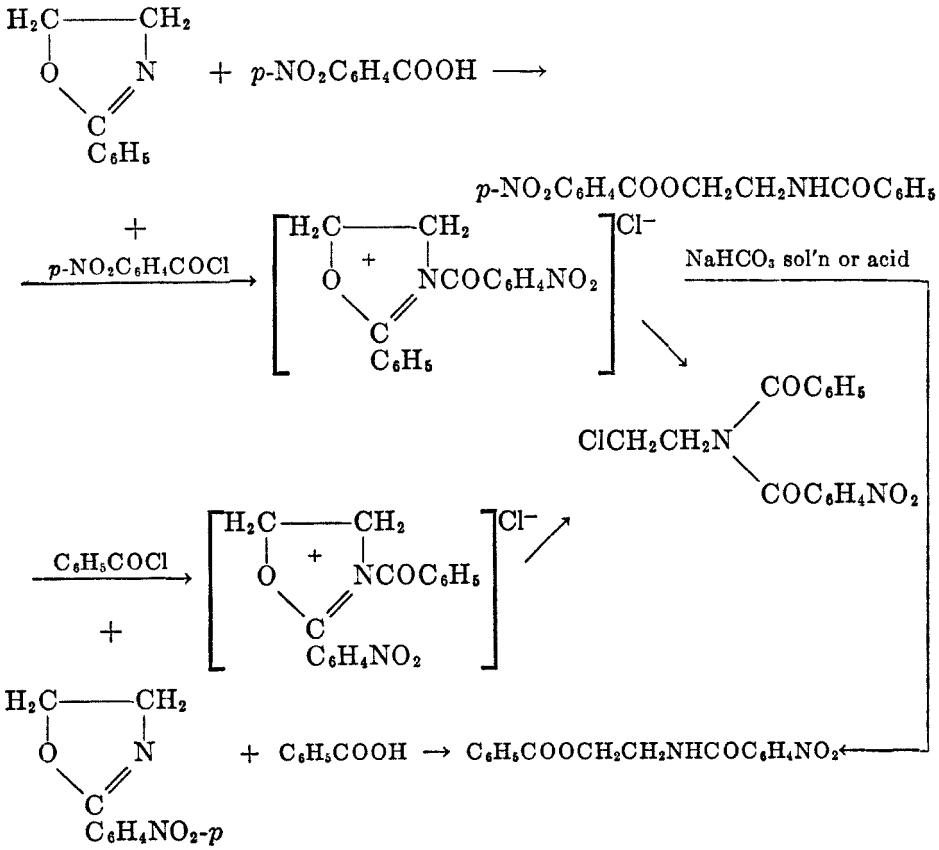


amide involves transfer of a proton to oxygen and this might take place with or without intercession of solvent, but that such is not necessary was demonstrated by conducting one such isomerization in anhydrous triethylamine.

Since the solvent need not participate in this proton transfer it is inferred that the electronic state of the unstable hydroxyoxazolidine ring induced by substituents and solvent is the primary determinant of direction of ring opening. Acid hydrolysis of the oxazoline ring may involve this same rearrangement but in the reverse direction. However, at least one example of anomalous behavior on acid hydrolysis appears in the literature (9). 2-Methyl-4,5,5-triphenyloxazoline yielded 2-acetamido-1,1,2-triphenylethanol.



In this case the phenyl groups at position 5 could have stabilized the charge on the carbonium ion at this point (10) so that hydroxylation occurred here rather than at position 2. That there may be competition between these centers is indicated by the results of two experiments in which the sulfhydryl ion in alkaline medium was the hydrolytic agent. In the first case 2-phenyloxazoline



yielded the thioamide (2-mercaptoöxazolidine intermediate) (2), and in the other 2-phenyl-4-carboxymethyloxazoline gave the cysteine derivative in very small yield (3). Probably the thioamide was here also the main product. Hydrolysis of the oxazoline ring in alkaline medium could similarly take place by two mechanisms.

Results of the action of acid chlorides are shown in the chart and involve the same type rearrangement as the hydrohalide salts with the exception that whereas the acid is removed in alkaline solution, the N-acyloxazoline salt undergoes hydroxylic ring-opening between positions 2 and 3 as was reported for acid anhydrides and water (1). The salts probably have only a transient existence and were not isolated. Again assuming the primary formation of a 2-hydroxyoxazolidine, it would appear that ring opening in this manner in alkaline solution is at variance with the other evidence cited above, but it may be significant that both the acetylated nitrogen and the free nitrogen in acid solution have lost basicity and this factor rather than the *p*H of the solvent may determine direction of ring opening.

Thioacids react in an unexceptional manner to give thiol esters and a synthesis of cystine using this method has been described (3). Other examples are given in the experimental section as are structure proofs based on alkaline hydrolysis of the esters.

EXPERIMENTAL

2-(p-Nitrophenyl)oxazoline. Ethanolamine reacted with *p*-nitrobenzoylchloride in sodium bicarbonate solution to give N-(β-hydroxyethyl)-*p*-nitrobenzamide, m.p. 130–132°. The previously reported value is 132–133° (11). By the action of thionyl chloride this was converted to a crystalline compound, probably the sulfinyl chloride, which rearranged in dioxane to give the oxazoline salt. This salt was decomposed with sodium carbonate solution to give the oxazoline. Purified from alchol it melted at 178–179°. The literature gives the melting point 178–178.5° (12).

N-(β-Chloroethyl)-N-benzoyl-p-nitrobenzamide. A mixture of 0.83 g. of benzoyl chloride and 0.113 g. of 2-(*p*-nitrophenyl)oxazoline was heated on the steam-bath for 3 min. The product was recrystallized from alcohol; wt. 0.152 g. (77%), m.p. 129–130.5°.

Anal. Calc'd for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3,93; Cl, 10.66.
Found: C, 57.87; H, 3.92; Cl, 10.62.

This compound was also obtained by the addition of *p*-nitrobenzoyl chloride to 2-phenyloxazoline. The identities were checked by a mixture melting point.

β-Benzamidoethyl p-nitrobenzoate. A mixture of 0.55 g. of *p*-nitrobenzoic acid and 0.45 g. of 2-phenyloxazoline was heated on the steam-bath for 50 min. The crystalline product was triturated with sodium bicarbonate solution to remove excess acid, then recrystallized from alcohol, wt. 0.55 g., m.p. 143–148°. After purification it melted at 148.5–150°.

Anal. Calc'd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49.
Found: C, 61.04; H, 4.58.

This compound readily dissolved in 2 *N* NaOH. Acidification and separation of the hydrolysis products gave an 86% recovery of *p*-nitrobenzoic acid and a 93% recovery of β-hydroxyethylbenzamide.

β-(p-Nitrobenzamido)ethyl benzoate. A mixture of 0.10 g. of 2-(*p*-nitrophenyl)oxazoline and 0.12 g. of benzoic acid was heated for 15 min. at 130°. The melt crystallized on cooling.

It was triturated with acid and sodium bicarbonate solutions and then purified from alcohol. Weight, 0.09 g.; m.p. 145–146° which was lowered on admixture with the above isomer.

Anal. Calc'd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49.
Found: C, 61.27; H, 4.60.

To a chilled suspension of 0.197 g. of 2-phenyloxazoline, 0.4 g. of sodium bicarbonate, 1 ml. of water, and 0.3 ml. of dioxane was added 0.5 g. of *p*-nitrobenzoyl chloride. After stirring for 20 min. in the ice-bath, during which time carbon dioxide was evolved, the suspension was diluted with water and the solid product recovered, extracted with sodium bicarbonate solution, and purified from alcohol; weight 0.42 g. (58%), m.p. 144–146°. A mixture melting point showed it to be identical with the above described compound.

The same compound was recovered when sodium bicarbonate was omitted, but the yield was lower probably due to removal of oxazoline as the hydrochloride. In the presence of sodium hydroxide hydrolysis of the acid chloride took precedence over the condensation.

β-Benzamidoethyl thiolbenzoate. Thiobenzoic acid was made by the method of Kym (13). A mixture of 0.181 g. of 2-phenyloxazoline and 0.17 g. of thiobenzoic acid reacted exothermally and the product crystallized on cooling, wt. 0.3 g. (86%). It was purified by adding petroleum ether to an alcohol solution, m.p. 92–93°.

Anal. Calc'd for $C_{16}H_{15}NO_2S$: C, 67.34; H, 5.30.
Found: C, 67.31; H, 5.33.

This compound was hydrolyzed by heating a few minutes in alcoholic sodium hydroxide. After acidification and oxidation with potassium iodide solution the product crystallized. It was washed with sodium carbonate solution and recrystallized from alcohol; m.p. 131–133°. It was identified as *bis*-(β-benzamidoethyl)disulfide by comparison with an authentic sample prepared as follows: ethylenimine prepared according to Wenker (14) was converted to mercaptoethylamine by the method of Mills and Bogert (15). After oxidation to the disulfide by means of iodine, benzoylation yielded the above compound, m.p. 131.5–132.5°. The value 132° has been reported (16).

β-Benzamidoethyl p-chlorothiolbenzoate was similarly made. It was purified from alcohol and melted at 140–141°.

Anal. Calc'd for $C_{16}H_{14}ClNO_2S$: C, 60.09; H, 4.41.
Found: C, 59.99; H, 4.55.

β-(p-Nitrobenzamido)ethyl thiolbenzoate. A mixture of 2-*p*-nitrophenyloxazoline and thiobenzoic acid in equivalent amounts was heated briefly on the steam-bath. The product was obtained in 78% yield after purification from alcohol; m.p. 156–157° with a slight sinter at 152°.

Anal. Calc'd for $C_{16}H_{14}N_2O_4$: C, 58.17; H, 4.27.
Found: C, 57.96; H, 4.50.

2-(3-Chloro-1-amino-n-propyl) p-nitrobenzoate hydrochloride (5), 0.10 g., was suspended in dry (over KOH) triethylamine. On manipulation the solid became oily and in about 5 minutes recrystallized. Excess amine was removed under reduced pressure and excess 3 *N* HCl was added to the solid. The solid was washed with water; weight 0.070 g., m.p. 95–96°. After recrystallization from ethyl acetate-benzene it melted at 102–104° and the melting point was not depressed on mixing it with another sample of *N-(3-chloro-2-hydroxy-n-propyl)-p-nitrobenzamide.*

Acknowledgement. The analyses are by courtesy of Mr. W. C. Alford, Mrs. M. O. Ledyard, and Mrs. E. G. Peake of this Institute.

SUMMARY

Rather meager observations of oxazoline ring-openings have been rationalized with a carbonium ion structure having a charge distribution between positions 2 and 5. Reactions with organic acids, thioacids, and acid chlorides are reported.

BETHESDA 14, MD.

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[CONTRIBUTION NO. 193 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. IX. REDUCTION OF THIENYL NITROÖLEFINS WITH LITHIUM ALUMINUM HYDRIDE[1]

R. T. GILSDORF AND F. F. NORD

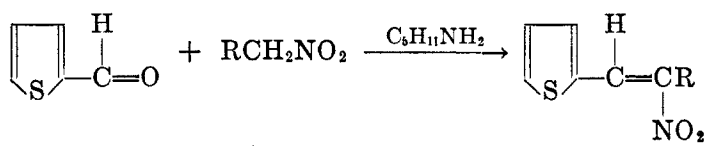
Received January 16, 1950

A new and *direct* synthesis of the pharmacologically active β-(2-thienyl)ethylamine (1, 2) and β-(2-thienyl)isopropylamine (2, 3), the thiophene analogue of Benzedrine, has been developed. The successful condensation of the readily available 2-thenaldehyde and various substituted 2-thenaldehydes (4) with nitromethane and 2-thenaldehyde with nitroethane to form the corresponding nitroölefins, was recently reported (5). These latter compounds have now been satisfactorily reduced to the desired saturated amines.

This was accomplished by the use of lithium aluminum hydride, shown to be an effective agent for reducing a nitroölefin to a saturated amine (6). This reagent is particularly suitable in view of the mild conditions which it affords for the reduction of the relatively unstable thienyl nitroölefins and the inherent capacity of thiophene and its derivatives to complicate catalytic hydrogenations.

It was found that the yield of 1-(2-thienyl)-2-nitropropene-1 was substantially increased by employing a Knoevenagel-Walter type catalyst (7) rather than alkali which was used as the condensing agent in the previous preparation (4), for the condensation of 2-thenaldehyde with nitroethane. Utilizing tenth-molar quantities of *n*-amylamine as the catalyst (8) it was found that the above unsaturated nitro compound was formed in 73% yields. Although the time of reaction in such a condensation is lengthy the actual operations are simple; the aldehyde, nitroparaffin, and catalyst are mixed together and allowed to stand for two weeks at the end of which time the mixture is taken up in hot alcohol and allowed to cool whereupon the solution deposits the crystalline product.

This method of condensation also made available the hitherto unknown 1-(2-thienyl)-2-nitrobutene-1. This product, obtained in 53% yields (conversion of 88%), was separated by distillation rather than by crystallization due to its low melting point. The above reactions may be indicated as follows:



(A)

R = CH_3 or C_2H_5

Not only has the method for preparing β-(2-thienyl)ethylamine and β-(2-thienyl)isopropylamine *via* the nitroölefins proven to be more direct than the procedures recorded in the literature, but the over-all yields show significant

[1] This investigation was aided, in part, by a grant from the Office of Naval Research. The analyses were conducted by Dr. F. Bühler and A. A. Sirotenko of this department.

improvement. Table I contains a comparison of previous methods with the one presented in this paper.

Other new substituted thienylethylamines were also prepared according to this procedure. The transformations may be indicated as follows:

When R″ = H, R′ = H, CH_3, C_2H_5, C_3H_7, or Cl
When R′ = H, R″ = H, CH_3 or C_2H_5.

TABLE I

COMPARISON OF METHODS OF PREPARATION OF β-(2-THIENYL)ETHYLAMINE AND β-(2-THIENYL)ISOPROPYLAMINE

PRODUCT	REF.	METHOD	NO. OF STEPS[a]	YIELD[a], %
β-(2-Thienyl)ethylamine	(1)	Hofmann degradation of β-(2-thienyl) propionamide	6	15
	(2)	Amination of β-(2-thienyl)ethyl bromide with ammonia	4	6
	(11)	Reduction of 2-thienylacetonitrile with lithium aluminum hydride	6	17
		Reduction of ω-nitro-2-vinylthiophene with lithium aluminum hydride	3	33
β-(2-Thienyl)isopropylamine	(2)	Amination of β-(2-thienyl)isopropyl bromide with ammonia	4	6
	(3)	Amination of β-(2-thienyl)acetone with ammonium formate	4	—
		Reduction of β-(2-thienyl)-2-nitropropene-1 with lithium aluminum hydride	3	32

[a] Based on thiophene as the starting material.

The yields ranged from 50 to 70% for the above reductions; the thienyl nitroölefins, having either the 5-position on the ring or the β-position on the side chain alkylated, giving slightly higher yields (65–70%) than the unsubstituted compound (63%), while β-(5-chloro-2-thienyl)ethylamine was formed in a lower yield (50%). As was expected, no dehalogenated product was obtained in the latter case (9).

Due to the fact that the amines readily absorb carbon dioxide from the air to

form the solid carbonates (1), the final distillations were carried out under nitrogen and the amines were analyzed as their hydrochlorides rather than in the uncombined state. Phenylthiourea derivatives were also prepared to further characterize the amines. The collected data on the compounds prepared are recorded in Table II.

A mixed melting point was taken of the hydrochloride of β-(2-thienyl)ethylamine prepared by the above method, with the one[2] obtained according to reference (1). There was no depression.

EXPERIMENTAL[3]

Preparation of intermediates. 2-Thenaldehyde and its alkylated and chlorinated derivatives were synthesized according to the previously described procedure (4). The thienyl nitroölefins were prepared as before (5) with the exceptions of 1-(2-thienyl)-2-nitropropene-1 and 1-(2-thienyl)-2-nitrobutene-1.

1-(2-Thienyl)-2-nitropropene-1. There were mixed together 20 g. (0.18 mole) of freshly distilled 2-thenaldehyde, 13.4 g. (0.18 mole) of freshly distilled nitroethane, and 1.56 g. (0.018 mole) of *n*-amylamine. The solution was stored in a dark place at room temperature. After one day an aqueous phase separated from the solution. At the end of 8 days there appeared a heavy deposit of crystals. After two weeks the mixture was taken up in hot ethyl alcohol and the solution was allowed to cool whereupon yellow crystals precipitated out. These were washed with 10 ml. of cold ethyl alcohol and dried. There were thus obtained 22.1 g. (73% yield) of 1-(2-thienyl)-2-nitropropene-1; m.p. 68.5°, which showed no depression when mixed with an authentic sample (5).

Anal. Calc'd for $C_7H_7NO_2S$: C, 49.69; H, 4.17; N, 8.28.

Found: C, 50.01; H, 3.89; N, 7.90.

1-(2-Thienyl)-2-nitrobutene-1. There were mixed together 20 g. (0.18 mole) of freshly distilled 2-thenaldehyde, 17.7 g. (0.18 mole) of freshly distilled 1-nitropropane, and 1.56 g. (0.018 mole) of *n*-amylamine. The solution was stored in a dark place at room temperature. After one day an aqueous phase separated from the solution but crystals failed to appear even after two weeks. At that time the reaction mixture was extracted with ether. The extract was washed with 6 *N* HCl, then with water and rectified after being dried over calcium sulfate. After a small pre-run of 1-nitropropane there was recovered 2.4 g. of 2-thenaldehyde b.p. 64–66°/4 mm. (88% conversion). Next, there was obtained 17.1 g. (52% yield) of 1-(2-thienyl)-2-nitrobutene-1, b.p. 120–122°/2.3 mm., m.p. 32°.

Anal. Calc'd for $C_8H_9NO_2S$: C, 52.44; H, 4.95; N, 7.65.

Found: C, 52.63; H, 4.72; N, 7.44.

Reduction of the thienyl nitroölefins. All of the reductions were carried out utilizing the same procedure. As an example, the preparation of β-(2-thienyl)ethylamine is given:

In a 2-liter 3-necked flask, fitted with a reflux condenser, a mercury-sealed stirrer, and a dropping-funnel, were placed 8.0 g. (0.21 mole, a 20% excess) of lithium aluminum hydride, dissolved in 300 ml. of absolute ether. A solution of 15.5 g. (0.1 mole) of ω-nitro-2-vinylthiophene in 400 ml. of absolute ether was added dropwise at such a rate as to cause gentle reflux. Shortly after the addition terminated, a few ml. of water was cautiously introduced to decompose the excess hydride. There was added 500 ml. of a 20% aqueous solution of sodium potassium tartrate. The etheral layer was separated and the aqueous layer extracted successively with two 100-ml. portions of ether. The combined extracts were dried over calcium sulfate and rectified, the vacuum-distillation bring carried out under nitrogen.

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[2] Courtesy of L. J. Oddo of this laboratory.

[3] The thiophene used in this investigation was obtained through the courtesy of Dr. G. A. Harrington of Socony-Vacuum Oil Company, and the nitroparaffins were placed at our disposal by the Commercial Solvents Corporation.

TABLE II

REDUCTION OF THIENYL NITROÖLEFINS WITH LITHIUM ALUMINUM HYDRIDE

STARTING MATERIAL	AMINE			HYDROCHLORIDE						PHENYLTHIOUREIDE				
	Product	Yield, %	B.P.[a] °C/MM.	M.P.,[a] °C.	Analysis						M.P.,[a] °C.	Analysis		
					Calc'd			Found				Calc'd		Found	
					C	H	N	C	H	N		C	H	C	H
ω-Nitro-2-vinylthiophene	β-(2-Thienyl)ethylamine	63	76–78/7.0[b]	200–202[c]	44.03	6.16	8.56	44.15	6.23	8.53	109.5–110[d]	59.59	5.38	59.25	5.16
1-(2-Thienyl)-2-nitropropene-1	β-(2-Thienyl)isopropylamine	65	62–65/1.5[e]	143–144.5[f]	47.31	6.81	7.88	47.10	6.59	8.19	98–99	60.83	5.83	60.65	5.91
1-(2-Thienyl)-2-nitrobutene-1	1-(2-Thienyl)-2-aminobutane	69	74–76/6.0	92–93	50.11	7.36	7.31	50.26	7.18	7.20	96.5–97	62.03	6.25	62.02	6.90
5-Methyl-2-(ω-nitrovinyl)thiophene	β-(5-Methyl-2-thienyl)ethylamine	67	79–81/5.5	180.5–182	47.31	6.81	7.88	47.30	6.71	7.92	119–120	60.83	5.83	61.00	6.02
5-Ethyl-2-(ω-nitrovinyl)-thiophene	β-(5-Ethyl-2-thienyl)-ethylamine	70	84–86/2.8	168–171	50.11	7.36	7.31	49.95	7.28	7.42	84–84.5	62.03	6.25	62.20	6.41
5-Propyl-2-(ω-nitrovinyl)thiophene	β-(5-Propyl-2-thienyl)-ethylamine	70	87–89/2.0	[g]	52.53	7.84	6.81	52.45	7.93	6.89	66–67	63.11	6.62	62.95	6.46
5-Chloro-2-(ω-nitrovinyl)-thiophene	β-(5-Chloro-2-thienyl)-ethylamine	50	70–74/1.2	215–217	36.37	4.58	7.07	36.20	4.44	7.17	87–88	52.61	4.41	52.50	4.58

[a] All melting and boiling points are uncorrected. [b] Reported (2) as 88–90°/13.0 mm. [c] Same as listed in ref. (1). [d] Same as recorded in ref. (11). [e] Reported as 94–96°/15.0 mm. (2). [f] Listed as 139–141° (2). [g] Starts to char at 140°. No definite m.p. was obtained.

In this way there was obtained 8 g. (63% yield) of β-(2-thienyl)ethylamine, b.p. 76–78°/7.0 mm.

Preparation of derivatives. The hydrochlorides were prepared by treating the amine, in absolute ether, with alcoholic hydrogen chloride. They were recrystallized by solution in warm, absolute alcohol, with the addition of absolute ether until the solution became cloudy, followed by boiling until the solution became clear, and subsequent cooling.

The phenylthioureides were prepared by treatment of the amines with an equal amount of phenylisothiocyanate. The reactants were shaken together for a few minutes, cooled, and washed successively with petroleum ether and 50% alcohol. They were recrystallized from 95% alcohol (10).

SUMMARY

1. Lithium aluminum hydride is shown to be an effective reducing agent for nitroölefins in the thiophene series.

2. The amine-catalyzed condensations of 2-thenaldehyde with nitroethane and 1-nitropropane are described.

3. A new and direct method is presented for the synthesis of β-(2-thienyl)-ethylamine and β-(2-thienyl)isopropylamine.

4. The following amines, together with their hydrochlorides and phenylthioureides, none of which is listed in the literature, are reported, *viz.*, β-(5-methyl-2-thienyl)-, β-(5-ethyl-2-thienyl)-, β-(5-propyl-2-thienyl)-, and β-(5-chloro-2-thienyl)-ethylamine and 1-(2-thienyl)-2-aminobutane.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY; YALE UNIVERSITY]

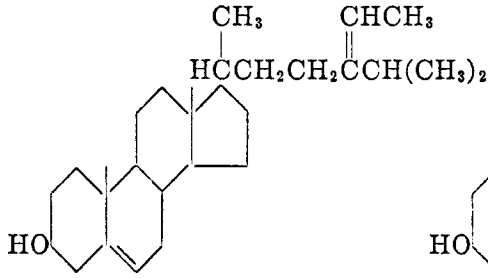
STEROLS OF ALGAE. I. THE OCCURRENCE OF CHONDRILLASTEROL IN *SCENEDESMUS OBLIQUUS*

WERNER BERGMANN AND ROBERT J. FEENEY

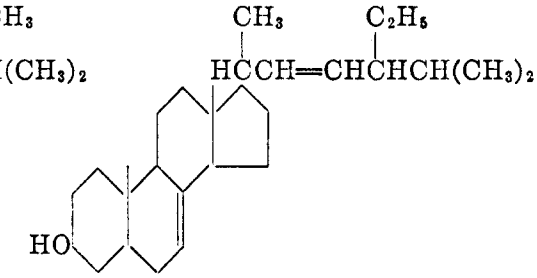
Received January 23, 1950

Fucosterol (I) is the only well characterized algal sterol (1) which has been described prior to the present publication. Ten years ago, in a comprehensive communication, Heilbron, *et al.* (2) reported the ubiquity of this sterol in the *Phaeophyceae* (marine brown algae), and its presence in a few species of algae belonging to other classes. The same authors also described the occurrence in *Chlorophyceae* (green algae) and some *Rhodophyceae* (red algae) of sterols of m.p. 128–137°, which afforded acetates of m.p. 128–134°. These melting points are significantly higher than those of fucosterol, m.p. 124°, and fucosteryl acetate, m.p. 119°, and reminiscent of those reported for sitosterol and its acetate. The authors therefore drew the conclusion that "*Chlorophyceae* approximate to the land plants since all members contain sitosterol".

During the past decade it has been shown that sitosterol as a rule consists of a more or less complex mixture of mono- and di-unsaturated sterols of the order C_{28} and C_{29}, and also that many impure invertebrate sterols show properties



I. Fucosterol



II. Chondrillasterol

similar to those of sitosterol. It appeared of interest therefore to reinvestigate the "sitosterols" of green algae, not only in order to establish their identity, but also their relationship to the general taxonomy of algae.

A study of the first green algae by the present authors has already led to results which were unexpected on the basis of Heilbron's earlier observations. The organism was *Scenedesmus obliquus* D^3, of which a substantial amount had been obtained through the courtesy of Dr. E. W. Fager of the University of Chicago. This alga yielded about 12% of acetone-benzene soluble material, which in turn afforded 17.5% of unsaponifiable matter. The latter contained large quantities of hydrocarbons and higher aliphatic alcohols which interfered with the smooth isolation of the sterol. It was eventually obtained by way of its benzoate. Surprisingly enough this sterol showed no resemblance to any of the sitosterol-like sterols. It was di-unsaturated and gave a strong Tortelli-Jaffe reaction. As shown in Table I, its physical properties and those of its derivatives

are those expected of a $\Delta^{7,22}$-stenol and are so much like those of chondrillasterol (II) (3) as to suggest the identity of the two sterols. Hydrogenation of the algal steryl acetate to α-chondrillastenyl acetate supports this suggestion. Chondrillasterol appears to occur in *Scenedesmus* to the practical exclusion of other sterols. It remains to be seen whether this sterol is typical for all green algae or whether it merely represents an exceptional case. Further studies along these lines are in progress in this laboratory.

EXPERIMENTAL

All melting points are corrected. All optical rotations were taken in a 1-dm. tube, the sample being dissolved in 3.06 cc. of chloroform.

Chondrillasteryl benzoate. A total of 820 g. of air-dried *Scenedesmus obliquus* D_3 was extracted with acetone for two days in a large Soxhlet apparatus. After evaporation of the acetone, the extract, which contained some water, was mixed with benzene, and the water was removed by co-distillation. A small amount of brown, water-soluble material remained undissolved. Evaporation of the benzene-solution gave 97 g. of a very viscous, dark green oil, corresponding to about 12% of the starting material. The oil was saponified, and the unsaponifiable matter isolated as described previously; yield, 17.0 g., corresponding to

TABLE I

COMPARISON OF SCENEDESMUS STEROL AND CHONDRILLASTEROL

DERIVATIVE	SCENEDESMUS		CHONDRILLA	
	M.P., °C.	$[\alpha]_D^{\circ}$	M.P., °C.	$[\alpha]_D^{\circ}$
Sterol	168–169	−2	168–169	−1.1
Acetate	174.5–175.5	−0.7	175–176	−1
Benzoate	194–195	+4	194–195	+3.9
α-Stenyl acetate	115	+7.9	111–112	+8.9

17.5% of the oil. Extraction of this fraction with boiling methanol, and cooling gave 4 g. of a waxy material. It was treated at 70° for 40 hours with a mixture of 20 cc. of pyridine and 3 cc. of benzoyl chloride. The mixture was then poured into 300 cc. of hot methanol. Upon cooling, 1.9 g. of chondrillasteryl benzoate was obtained (m.p. 187–191°). After four recrystallizations from dioxane it melted at 194–195°, $[\alpha]_D^{24}$ +3.9° (31.2 mg., α +0.04°). It did not show a depression of the melting point when mixed with authentic material.

Anal. Calc'd for $C_{36}H_{52}O_2$: C, 83.66; H, 10.14.

Found: C, 83.28; H, 10.27.

Chondrillasterol. The benzoate described above was saponified with alcoholic potassium hydroxide in the presence of some ether. The sterol was recrystallized twice from chloroform-methanol; m.p. 168–169°, $[\alpha]_D^{24}$ −2° (30.7 mg., α −0.02°). It did not show a depression of the melting point when mixed with authentic material.

Chondrillasteryl acetate. The acetate was prepared by refluxing the sterol with acetic anhydride. It was recrystallized three times from chloroform-methanol, m.p. 174.5–175.5°, $[\alpha]_D^{24}$ −0.7° (30.5 mg., α −0.007°). It did not give a depression of the melting point when mixed with authentic material.

Anal. Calc'd for $C_{31}H_{50}O_2$: C, 81.88; H, 10.14.

Found: C, 81.87; H, 10.54.

α-Chondrillastenyl acetate. The above acetate was hydrogenated at room temperature in glacial acetic acid with a platinum black catalyst. Absorption of hydrogen ceased after one mole had been rapidly consumed. The filtered solution was concentrated to a small volume

and the acetate precipitated by the addition of methanol. It was recrystallized twice from chloroform-methanol, m.p. 115°, $[\alpha]_D^{24}$ +7.9° (30.2 mg., α +0.08°).

SUMMARY

It has been shown that the sterol of the green alga, *Scenedesmus obliquus*, is identical with chondrillasterol.

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE AND THE WALKER CHEMICAL LABORATORIES OF THE RENSSELAER POLYTECHNIC INSTITUTE]

OXIDATIONS OF PENICILLIN ESTERS

CHESTER J. CAVALLITO AND JOHN H. HARLEY[1]

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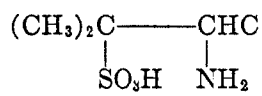
With few exceptions the preparation of derivatives of penicillins leads to products having no biological activity. One of the functional derivatives of penicillins which is claimed to have biological activity is the sulfone (1). Although the sulfone of methyl benzylpenicillin reputedly shows activity after hydrolysis of the ester group, or by *in vivo* assay, the corresponding sulfoxide is declared to be inert (2). In an investigation of oxidative degradations of penicillin esters with organic peracids, we have found that neither the mono- nor di-oxide[2] (sulfoxide and sulfone?) is active biologically by our testing procedures. The published activity of the sulfone (one-tenth that of the ester) (1) may have resulted from the presence of unoxidized ester with the sulfone. The stepwise preparation of the sulfone from ester through sulfoxide has not been described. Stepwise oxidations are described here for both the methyl and benzyl esters of benzylpenicillin.

In agreement with previous work, it has not been possible to isolate crystalline oxidation products of free penicillins. The methyl ester is known to yield a monoxide upon treatment with metaperiodate (2) and a dioxide upon oxidation with permanganate (3). The present work was initiated with the observation that treatment of the benzyl ester of benzylpenicillin with essentially anhydrous peracetic acid in acetonitrile yielded a crystalline product which was shown to be benzyl penicillaminate (I) which on catalytic hydrogenolysis yielded penicillaminic acid. When the oxidation was interrupted prior to separation of the penicillaminic ester, a crystalline compound was isolated from the reaction mixture which gave an analysis for a benzyl benzylpenicillin monoxide. Treatment of the isolated monoxide with peracetic acid led to formation of I. Oxidation of methyl benzylpenicillin with peracetic acid also yielded a monoxide which appeared to be identical with the monoxide prepared by oxidation with metaperiodate.[3] Perbenzoic acid could also be used for the oxidation.



I

An intermediate dioxide could not be isolated upon peracetic acid oxidation of monoxide to I. When the monoxide was oxidized with permanganate, the

[1] Work done at Rensselaer Polytechnic Institute. Present address; Chief, Analytical Laboratory, U. S. Atomic Energy Commission, P. O. Box 30, Ansonia Station, New York City.

[2] The terms "monoxide" and "dioxide" are used rather than "sulfoxide" and "sulfone" since rigorous proof is not available that the latter terms represent the true structures.

[3] The sulfoxide described in reference (2) was stated to be a hemihydrate and melted at 123°. Our preparations were anhydrous; m.p. 127° (corr.).

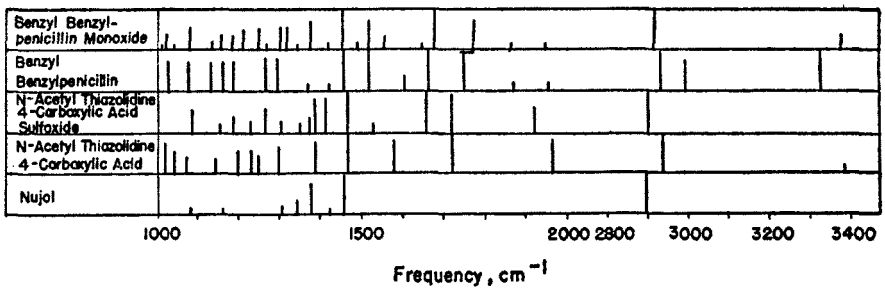
dioxide was obtained which upon treatment with peracetic acid also yielded I. Hydrogen peroxide had no effect on either the penicillin ester or its monoxide. Acetic acid had no effect on the penicillin esters in the time required for the oxidations described.

The various esters were tested for biological activity by suspension in rat blood serum, which hydrolyzed the ester group, followed by serial-dilution assay.[4] Both methyl and benzyl benzylpenicillin showed activity, while none of the oxidation products was active (less than $\frac{1}{10}$ unit per milligram). The same results were obtained by assay after mild alkaline hydrolysis of these compounds according to published procedures (1). Duplication of the described *in vivo* assay in mice was not attempted.

The monoxide obtained from benzyl benzylpenicillin was an easily crystallizable, sharply-melting product in contrast to the glassy starting ester. Ultraviolet absorption spectra show no evidence of penicillenate formation. The

TABLE I

Line Chart of Infrared Absorptions



oxides are neutral and show no basic groups by perchloric acid titration. In contrast, penicillin esters, at room temperatures, show the presence of one basic nitrogen in this titration. The basic nitrogen appears simultaneously with inactivation of the penicillin during titration. Mild alkaline hydrolysis of the monoxide utilizes from one to nearly two equivalents of alkali depending upon length of time of reaction. The monoxide did not react with iodine but one equivalent of iodine was reduced in the titration of a mild alkaline hydrolysis solution of the monoxide. The benzyl ester monoxide was unchanged after 16 hours refluxing in ethanol containing a trace of mercuric chloride.

The model compound N-acetylthiazolidine-4-carboxylic acid yielded the sulfoxide when treated with one mole of peracetic acid and the sulfone upon treatment with an excess. There was no evidence of cysteic acid formation.

Results of infrared absorption measurements of benzyl benzylpenicillin, its

[4] This method has proven to be quite reliable with penicillin esters. It appears to show *in vitro* activity wherever the activity appears *in vivo* since the latter activity of the esters depends on prior hydrolysis of the ester group by blood serum of the test animal. The *in in vitro* method also eliminates the factor of differences in rates of absorption of various esters which affect *in vivo* assays.

monoxide, and N-acetylthiazolidine-4-carboxylic acid and its sulfoxide are described as supplementary data in Table I. Until very recently (4) infrared absorption characteristics for the >SO bond were not available. The characteristic bond stretching vibration frequency for the sulfoxide group is given by Barnard, *et al.* (4) as 1055 cm^{-1}. The data in Table I show absorption bands at about 1080 cm^{-1} for both acetylthiazolidine-4-carboxylic acid sulfoxide and benzyl benzylpenicillin monoxide. However, benzyl benzylpenicillin absorbs in this region prior to its oxidation.

Attempts to isolate the products other than I obtained in oxidations with excess peracid have yielded glassy products difficult to characterize.

EXPERIMENTAL

Benzyl benzylpenicillinate monoxide. Method A. To 3 g. (7 millimoles) of benzyl benzylpenicillinate in 30 cc. of acetonitrile was added a solution of 14 millimoles of 70% peracetic acid in 10 cc. of acetonitrile; the mixture was kept at 5–10° for 30 minutes and then at 25° for 30 minutes. The solution was concentrated *in vacuo* to about 15 cc., then poured into aqueous sodium bicarbonate solution to yield a gummy precipitate which crystallized. The product was recrystallized from a dioxane-Skellysolve B solution as white plates, m.p. 146–147° (corr.), yield 2.1 g. or 68%.

Method B. The oxide was also obtained when a chloroform solution of perbenzoic acid was used in place of the peracetic acid. After the usual reaction period, the solution was shaken with aqueous sodium bicarbonate to remove acids and the chloroform evaporated to yield the oxide.

Anal. Calc'd for $C_{23}H_{24}N_2O_5S$; C, 62.71; H, 5.49; N, 6.36.
Found: C, 62.90; H, 5.38; N, 6.30.

A solution of 0.75 millimoles of the oxide and 3.8 millimoles of 90% hydrogen peroxide in 10 cc. of acetonitrile was allowed to stand at 25° for six hours. Upon dilution with water, the unchanged oxide was recovered.

Benzyl penicillaminate. To 482 mg. (1.1 millimoles) of the benzyl benzylpenicillinate monoxide in 25 cc. of acetonitrile was added 5 millimoles of peracetic acid in 5 cc. of acetonitrile. The solution was allowed to stand at 25°; crystals began to separate after two hours and separation was complete after about 24 hours with a yield of 375 mg. (60%) of benzyl penicillaminate, m.p. 245° dec.

Anal. Calc'd for $C_{12}H_{17}NO_5S$; C, 50.16; H, 5.96; N, 4.87; S, 11.16.
Found: C, 50.45; H, 6.14; N, 5.06; S, 11.01.

Potentiometric titration with 0.1 *N* alkali showed an equivalent weight of 209 between the points of inflection in the titration curve at *p*H 4.9 and 9.0; Calc'd mol. wt. is 197.

Catalytic hydrogenolysis of the compound in water with a palladium catalyst and evaporation of the solvent led to isolation of a crystalline acid, m.p. dec. slowly >270°. This product showed an identical potentiometric titration curve with a synthetic sample of penicillaminic acid.

Anal. Calc'd for $C_5H_{11}NO_5S$; C, 30.96; H, 5.52.
Found: C, 30.90; H, 5.62.

Methyl benzylpenicillinate monoxide. To one gram (3 millimoles) of methyl benzylpenicillinate (m.p. 97°) in 5 cc. of acetonitrile at 5–10° was added one cc. of 40% peracetic acid (5 millimoles) in 10 cc. of acetonitrile. The solution was kept at this temperature for 30 minutes and then allowed to warm to room temperature for 30 minutes. The mixture was poured into aqueous sodium bicarbonate solution and the oil which separated was extracted with chloroform. The chloroform extract was evaporated and the crystalline residue was recrystallized from either dioxane-Skellysolve B (or equivalent) or ethanol-water solutions and dried at 80°. Yield of white crystalline monoxide, 80%; m.p. 127° (corr.).

A preparation of methyl benzylpenicillinate sulfoxide from the ester by metaperiodate oxidation (2) yielded a compound with m.p. 127° and showed no depression of melting point when mixed with the peracetic acid oxidation product.

Anal. Calc'd for $C_{17}H_{20}N_2O_5S$; C, 56.03; H, 5.53.

Found: C, 56.07; H, 5.67.

Oxidation of benzyl benzylpenicillinate monoxide to a dioxide with permanganate. A solution of 17 cc. of 5% potassium permanganate in 80% acetic acid was shaken with one gram of benzyl benzylpenicillinate monoxide until solution was complete and the excess permanganate decolorized with 30% hydrogen peroxide [procedure used in the preparation of sulfone of methyl benzylpenicillinate (3)]. The mixture was poured into water, the precipitate was extracted with benzene, and the extract dried over sodium sulfate. Addition of Skellysolve B (or equivalent hydrocarbon) to the benzene solution yielded a precipitate which was dissolved in benzene and again precipitated. The product was dried *in vacuo* over paraffin to yield 350 mg. of white powder, m.p. 58–62°.

Anal. Calc'd for $C_{23}H_{24}N_2O_6S$; C, 60.51; H, 5.30.

Found: C, 60.73; H, 5.16.

A portion of the dioxide treated with excess peracetic acid in acetonitrile yielded crystalline benzyl penicillaminate.

Peracetic acid oxidation of 3-acetylthiazolidine-4-carboxylic acid. To a solution of 3.5 g. (0.02) mole) of 3-acetylthiazolidine-4-carboxylic acid (5) in 100 cc. of acetonitrile at 40° was added 0.02 mole of peracetic acid in 15 cc. of acetonitrile. After one hour the solution was concentrated under reduced pressure, diluted with water, and extracted with ethyl acetate. The extract was dried over sodium sulfate, evaporated to dryness, and the residue recrystallized from hot ethanol. The sulfoxide (about 50% yield) melted at 195–196°.

Anal. Calc'd for $C_6H_9NO_4S$; C, 37.68; H, 4.74.

Found: C, 37.73; H, 4.97.

When 0.1 mole of peracetic acid was used in the above preparation, the sulfone was obtained, m.p. 191–192°.[5]

Anal. Calc'd for $C_6H_9NO_5S$; C, 34.44; H, 4.33.

Found: C, 34.25; H, 4.20.

Reactions of benzyl benzylpenicillinate monoxide. A solution of 0.5 g. of oxide in 50 cc. of absolute ethanol containing 5 mg. of mercuric chloride was refluxed for 18 hours. A slight precipitate was filtered off and the unchanged oxide was recovered from solution.

To a solution of 215 mg. of the oxide in 10 cc. of dioxane and 5 cc. of water was added 10 cc. of 0.1 *N* sodium hydroxide in dropwise fashion while keeping record of the changes in *p*H. The solution was kept at *p*H 12 for one minute and then back-titrated with 0.1 *N* hydrochloric acid. The oxide utilized 1.5 equivalents of alkali during the hydrolysis; partial hydrolysis of the benzyl ester group apparently occurred. The neutralized hydrolysis solution was titrated with 0.1 *N* iodine solution. One equivalent of iodine was utilized. The original oxide did not react with iodine prior to hydrolysis.

Basicity of nitrogen in penicillins. Perchloric acid titration of sodium penicillins in acetic acid is known to demonstrate the presence of two basic groups (Na and N); esters show only one basic group. The titration of sodium penicillin with sulfuric acid in acetic anhydride with a Crystal Violet indicator also demonstrated two basic groups; the penicillin was inactivated by this treatment.

A solution of 100 mg. of potassium benzylpenicillin in 10 cc. of acetonitrile and 1 cc. of acetic acid was cooled to −20° to −10° and titrated with 0.1 *N* perchloric acid in acetic acid with Methyl Violet indicator. Rapid reaction occurred with one equivalent of acid and very slow reaction thereafter with a second equivalent. An aliquot of the titration mixture, diluted with *p*H 7 buffer and assayed, showed no inactivation of the penicillin after addition

[5] Ratner and Clarke (ref. 5) give m.p. 188–190° for the sulfoxide and m.p. 190° for the sulfone.

of the first equivalent of acid but nearly complete inactivation after the second. The first equivalent apparently reacted with the potassium.

Solutions of 100 mg. of methyl benzylpenicillin, benzyl benzylpenicillin, and the monoxide and dioxide of each in 10 cc. of acetic acid were titrated with perchloric acid in the usual manner. Only the first two reacted with one equivalent of perchloric acid; neither the monoxide nor dioxide showed the presence of basic nitrogen under these conditions.

Infrared absorption measurements. All samples were run in 0.025-mm. sections on a Perkin-Elmer Model 12B recording spectrophotometer. Solids were mulled in Nujol; benzyl benzylpenicillin was run without Nujol. In the high frequency region, a quartz prism was used to obtain greater dispersion than possible with the standard rock-salt prism. Only the data from the frequency sections from 1000 to 2000 and 2800 to 3400 cm^{-1} are given. The intensity of absorption at various wave numbers is denoted in the table by line charts.

Penicillin activity assays. The compounds were dissolved in a small volume of acetone, diluted with water and incubated with rat serum prior to assay by serial dilution techniques (6).

Acknowledgments. We are indebted to M. E. Auerbach, K. D. Fleischer and staff for microanalyses, to Mr. W. F. Warner for the biological assays, and to Dr. F. C. Nachod for aid in the physical-chemical aspects of the problem.

RENSSELAER, NEW YORK

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[CONTRIBUTION FROM THE STERLING-WINTHROP RESEARCH INSTITUTE]

ISOLATION OF VISNAGAN, THE AMORPHOUS CORONARY-DILATOR PRINCIPLE OF *AMMI VISNAGA*

CHESTER J. CAVALLITO AND HARRIET E. ROCKWELL[1]

Received February 6, 1950

A considerable amount of chemical and biological work has been reported within the past few years involving the crystalline principles of the seeds of *Ammi visnaga*. Only brief reports have appeared describing a crude amorphous fraction, designated as visnagan, which is claimed to have coronary-dilator properties (1, 2).[2]

Samaan described visnagan as a dark, oily liquid distilling with decomposition at 165° at 20 mm. and obtained in about 2% yield from the seeds. Similar material has been prepared which upon further purification has yielded a colorless, hard glass which did not distill at 10^{-6} mm. at 120°. This constitutes somewhat less than half of the crude visnagan preparation. Analyses on a number of preparations indicate a molecular formula of $C_{20}H_{27-28}O_7$ for visnagan. It formed no derivatives which would indicate the presence of hydroxyl, carbonyl or carboxyl groups and contains no methoxyl groups. Visnagan is optically active, $[\alpha]_D^{25}$ +30.5° ±0.5° (16 mg. per ml. in dioxane). Although existing as a hard glass at 25°, the principle is sufficiently fluid at 60° to allow a refractive index determination; n_D^{60} 1.5345. Mild alkaline hydrolysis of visnagan yields one acidic group, stronger hydrolysis yields nearly two. The principle reacts with one mole of iodine bromide (Hanus solution).

Ultraviolet absorption spectra[3] (Fig. 1) show an absorption maximum of $E_{1\,cm}^{1\%} = 308.2$ at λ 325 mμ and a minimum of $E_{1\,cm}^{1\%} = 63.8$ at λ264 mμ indicating the possible presence of an aromatic ring conjugated to another unsaturated system. Infrared absorption data[4] (Table I) suggest the presence of a *para*-substituted phenyl group, methyl groups, a bonded -OH group, and perhaps a strained ring carbonyl but no —COO-group.

[1] Present address: Smith, Kline, and French Laboratories, Philadelphia, Pa.

[2] Preliminary tests by Dr. F. P. Luduena of these laboratories indicate that visnagan is approximately of the order of activity of aminophylline in decreasing the depressor action of Pituitrin® on the dog heart. It appears to be approximately twice as active as khellin as a coronary dilator in perfusion experiments. Visnagan is quite insoluble in water but a turbid solution for intravenous administration in animals may be prepared by dissolving the material in a small volume of ethanol and diluting to about 0.5 mg. per ml. with water.

[3] The ultraviolet absorption spectrum was obtained with a Cary recording Spectrophotometer, Model 11, Serial 37, slow scanning speed, 50 slit schedule, 10.00-cm. quartz cells, and 95% ethanol as solvent. The data were plotted as molar extinction coefficients, using an average molecular weight figure of 403.

[4] Infrared absorption spectra were measured by Dr. John H. Harley at Rensselaer Polytechnic Institute with 0.025-mm. sections using a Perkin-Elmer Model 12B Recording Spectrophotometer. In the high frequency region, a quartz prism was used to obtain greater dispersion than would be possible with the standard rock-salt prism. The data obtained are represented in Table I with intensity of adsorption at various frequencies denoted by numbers ranging from 1 to 5, the higher numbers indicating more intense adsorption.

A crystalline impurity exists with crude visnagan which is difficult to separate completely and which may appear as crystals after long standing of the resin. This product melts slowly between 133–140°; the apparent formula is $C_{15}H_{12}O_5$. It forms a crystalline salt with hydrogen chloride in ether as do the *gamma*-chromone principles. Visnagan does not form an oxonium salt. The crystalline principle has no coronary-dilator properties.

EXPERIMENTAL

Isolation of visnagan. A concentrate containing visnagan was prepared essentially according to the procedure of Samaan (1). The oil was dissolved in ether and then diluted with a petroleum solvent (Skellysolve B) until no further precipitate of visnagan was formed.

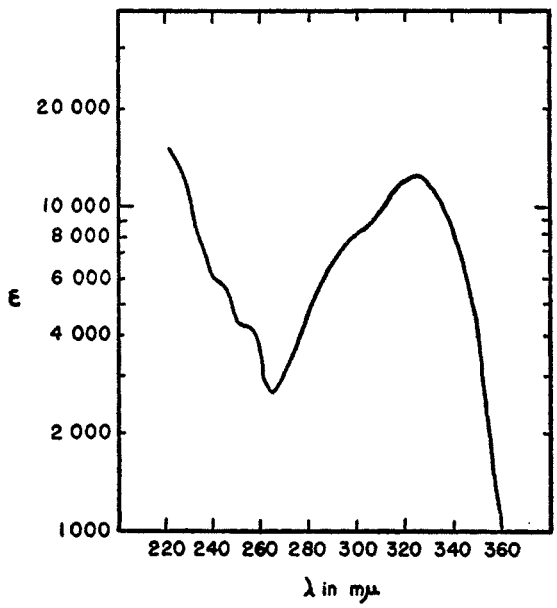

FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRUM OF VISNAGAN

This procedure was repeated several times and served to separate the soluble lipids from visnagan which is insoluble in petroleum solvents. The insoluble resin was dissolved in dry ether and ethereal hydrogen chloride was added. The crystalline precipitate (I) was filtered off and Skellysolve B was added slowly with shaking to the ether solution to precipitate a tacky, dark tar. The solution was decanted occasionally from the black tar and more Skellysolve added until the material which separated was a clear resin. The dark tar was discarded and the clear resin was completely precipitated from solution. The resin was dissolved in ether, diluted with Skellysolve B to the point of incipient turbidity, and then passed over a column of silica gel[5] previously wet with ether. Considerable visnagan and some crystalline impurity (I) appeared in the filtrate after development with ether. The column was eluted with an ethanol-ether solution and the slightly colored, hard glass-like visnagan was obtained upon evaporation of the eluate. The remainder of the color was removed by passing a dioxane solution of the resin over alumina (Brockmann, Merck) and evaporation of the filtrate.

[5] Activated, 28–200 mesh from the Davison Chemical Corporation.

Anal. Found: C, 65.65; H, 7.04; Another prep., C, 65.65; H, 6.68. Cryoscopic Mol. wt. determination in dioxane, 387.

Calc'd for $C_{22}H_{28}O_7$: C, 65.33; H, 6.98; Mol. wt. 404.4.

Calc'd for $C_{22}H_{26}O_7$: C, 65.66; H, 6.52; Mol. wt. 402.4.

Crystalline impurity from visnagan. The precipitate I obtained from the ethereal hydrogen chloride solution was treated with water to decompose the salt and the product was recrystallized about six times from water; m.p. 133–140° (corr.).

TABLE I

INFRARED ABSORPTION OF VISNAGAN

FREQUENCY, CM.$^{-1}$	INTENSITY	GROUP ASSIGNMENTS
666	–	—COO—
759	2	
774	3	*para*-substitution
840	5	
875	4	
889	3	usually phenyl
922	3	" "
948	1	" "
965	1	" "
991	1	" "
1007	5	
1028		
1042	4	—OH
1115	5	*para*-substitution
1144	5	
1185	3	*para*-substitution
1227	5	
1281	3	
1352	3	$-CH_3$
1373	4	$-CH_3$
1402	3	
1439	2	$-CH_3$
1462	3	$-CH_3$
1496	3	$-CH_3$, phenyl
1603	5	phenyl
1642	2	
1765	5	
2670	1	
2925	5	$-CH_3$
3460	2	bonded —OH

Anal. Found: C, 66.20; H, 4.33; Cryoscopic Mol. wt. in dioxane, 260.

Calc'd for $C_{15}H_{12}O_5$: C, 66.17; H, 4.44; Mol. wt., 272.3.

Tests for functional groups in visnagan. Visnagan in ethanol-water solution is neutral and does not react with 0.1 *N* NaOH at 25°; heating with a 0.1 *N* NaOH solution at 100° leads to formation of from one to two acidic groups depending upon length of time of heating (10 to 60 minutes).

Visnagan was recovered unchanged after treatment with phenylhydrazine or hydroxylamine under the usual conditions. *p*-Nitrobenzoyl chloride in pyridine did not react and no derivative with phenyl isocyanate could be obtained. Visnagan decolorized bromine water and reacted with one mole of iodine bromide in acetic acid.

Acknowledgments. We are indebted to M. E. Auerbach, K. Fleischer, and staff for microanalyses and to Dr. F. C. Nachod for ultraviolet absorption spectra.

SUMMARY

Visnagan, the amorphous coronary-dilator principle of *Ammi visnaga* seeds, has been obtained as a hard glass and assigned the tentative molecular formula of $C_{20}H_{26-28}O_7$.

RENSSELAER, NEW YORK

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

CYCLOPROPANES. IV. ATTEMPTED SYNTHESIS OF A NITROCYCLOPROPYL SULFONE (1)

LEE IRVIN SMITH AND HORACE R. DAVIS, JR.[1]

Received February 6, 1950

In a previous paper (2) a mechanism was proposed for the cleavage of 2-nitrocyclopropyl ketones by action of alkali, whereby 1,3-diketones or their derivatives result.

$$\begin{matrix} RCH{-}CHCOR' \\ \diagdown\diagup \\ CHNO_2 \end{matrix} \rightarrow RCH_2COCH_2COR' \text{ or } RCH_2C(OCH_3){=}CHCOR'$$

An essential feature of this mechanism was the requirement that the carbon atom adjacent to the one holding the nitro group be joined to an electron-attracting group, such as a ketone or ester group, for the nitrocyclopropylcarbinol (A) was found to be inert to the action of bases such as sodium methoxide.

$$\begin{matrix} (CH_3)_2C{-}{-}CHCHOHCH_3 \\ \diagdown\diagup \\ CHNO_2 \end{matrix} \qquad \begin{matrix} RCH{-}CHSO_2R' \\ \diagdown\diagup \\ CHNO_2 \end{matrix} \qquad RCH_2COCH_2SO_2R'$$

A B C

If the function of the carbonyl or ester group attached to the nitrocyclopropane ring is solely that of an electron-attracting group, then other electronegative groups should be able to perform the role of the carbonyl group and allow cleavage of the ring by action of alkalis. Kohler and Potter (3) have shown that sulfones are chemically similar to ketones when conjugated with an aliphatic double bond, and other workers also have demonstrated the electron-attracting properties of the sulfone group. Therefore, the synthesis of a nitrocyclopropyl sulfone, such as B, was undertaken; action of sodium methoxide upon such a substance should give the β-ketosulfone (C) if the analogy between the carbonyl and sulfone groups is valid. The primary purpose of the research was not achieved, for all the syntheses of the cyclopropyl sulfones failed at some critical step. However, the results obtained are interesting in themselves.

Two α,β unsaturated sulfones I and II, were prepared. Sulfone I, phenyl β-styryl sulfone, was prepared by the method described by Kohler and Potter (3) for preparation of *p*-tolyl β-styryl sulfone.

$RSO_2CH{=}CHR'$ $RSCH{=}CHR'$ $C_6H_5SO_2CH(C_6H_5)CH_2SO_2C_6H_5$ IV

I $R = R' = C_6H_5$ III $R = R' = C_6H_5$ $(C_6H_5SO_2)_2CHCH_2C_6H_5$ V

II $R = p\text{-}CH_3C_6H_4$; $R' = H$

[1] Abstracted from a thesis by Horace R. Davis, Jr., presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph. D. degree, July, 1949. National Research Council Predoctoral Fellow, 1946–1949.

Thiophenol was added to phenylacetylene, producing a mixture of stereoisomers of phenyl β-styryl sulfide (III). It was not possible to obtain the sulfide in a crystalline form, nor to separate from the mixture any pure stereoisomers, as was possible in the case of *p*-tolyl β-styryl sulfide (3). Most of the product distilled at 155–160°/1 mm., and was apparently a mixture of the *cis-trans* isomers of III, but there was also a small amount of a material boiling at a somewhat higher temperature, 175–185°/1 mm. The lower-boiling material, when subjected to the action of hydrogen peroxide in acetic acid, gave a crystalline sulfone (I), but the yield was only 65% and the remainder, an oil, was probably a mixture of the stereoisomers of I. The higher-boiling material was likewise converted into a sulfone by action of hydrogen peroxide in acetic acid. This sulfone, a white crystalline solid, was inert toward neutral permanganate, and gave analytical values consistent with those required for either of the two disulfones, IV or V. These would result from the oxidation of the respective disulfides obtained by adding a second molecule of thiophenol to III in the two possible ways. The disulfone was only slightly soluble in aqueous sodium hydroxide (10%) and from this, it would appear that IV is the more probable structure, for Shriner, Struck, and Jorison (4) have shown that phenyl benzyl sulfone is only slightly soluble in alkali, whereas *bis*-(benzenesulfonyl)methane is readily soluble.

p-Tolyl vinyl sulfone II was prepared *via* the following sequence (R = *p*-tolyl):

$$RSH + ClCH_2CH_2OH \xrightarrow{NaOC_2H_5} RSCH_2CH_2OH$$

$$\xrightarrow{HCl} RSCH_2CH_2Cl \xrightarrow{H_2O_2} RSO_2CH_2CH_2Cl \xrightarrow{Et_3N} II$$

The yield of II from *p*-thiocresol was 67%; the yield of *p*-tolyl β-chloroethyl sulfide was 93%. This synthesis of *p*-tolyl β-chloroethyl sulfide involved a modification of the procedure of Steinkopf, Herold, and Stöhr (5); the procedure of Buckley, Charlish, and Rose (6) was used for conversion of the sulfide to the sulfone.

Although the addition of nitromethane to α,β-unsaturated sulfones has been reported (6) the products were not derived by simple addition of the reagents, but were formed from one molecule of nitromethane and three molecules of the sulfone; the condensing agent was 30% aqueous potassium hydroxide. Kohler (7) reported that nitromethane gave an excellent yield of a 1:1 addition product with benzalacetophenone when slightly more than one mole of sodium methoxide in methanol was used as the condensing agent. Under these conditions, the sulfone I failed to react with nitromethane or with the dipotassium salt of nitroacetic acid; a substantial amount of I was recovered unchanged. When only a catalytic amount of sodium methoxide was used, and the reaction was carried out at room temperature for 36 hours, there was obtained, in 40% yield, a product inert to neutral permanganate, which had the composition corresponding to that of VIa. Other catalysts were also tried in attempts to bring about addition of nitromethane to I, but without success. These included triethylamine,

Triton-B,

$C_6H_5CH(R)CH_2SO_2C_6H_5$ VI $(p\text{-}CH_3C_6H_4SO_2CH_2CH_2)_2CHNO_2$ VIII

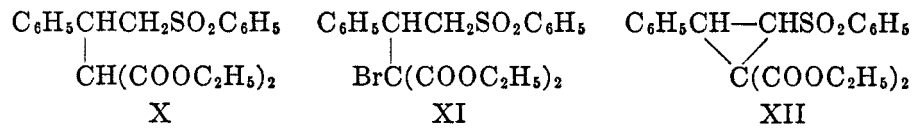
a. R = OCH_3; b. R = OC_2H_5; c. R = $N(CH_3)_2$

$p\text{-}CH_3C_6H_4SO_2CH_2CH_2CH_2NO_2$ VII $(p\text{-}CH_3C_6H_4SO_2CH_2CH_2)_3CNO_2$ IX

and the sodium derivative of nitromethane in dioxane or benzene. The failure of nitromethane to add to I was not a matter of steric hindrance, for other nucleophilic reagents—methanol, ethanol, dimethylamine, ethyl malonate—added easily.

On the other hand, nitromethane added readily to the sulfone II. Using the conditions described by Kohler (7) for addition of the nitro compound to benzalacetophenone, the sulfone II gave, in 91% yield, the *bis* derivative VIII, and none of the mono derivative VII. The *bis* derivative VIII was inert to neutral permanganate, and soluble in 10% aqueous sodium hydroxide. When VIII was heated for 30 minutes in any polar solvent (ethanol, methanol, acetone), it was converted in 84% yield into the *tris* derivative IX, a substance insoluble in aqueous alkali.

Since nitromethane could not be added to the sulfones I or II to give a simple 1:1 adduct, attention was turned to the addition of malonic ester to I in the hope of obtaining a substance which could be converted by known methods into a sulfonylcarboethoxycyclopropane. Solid sodio malonic ester was shaken with a solution of I in benzene (3), and an excellent yield of addition product X was obtained after acidification. This material reacted slowly with bromine under ultraviolet light.



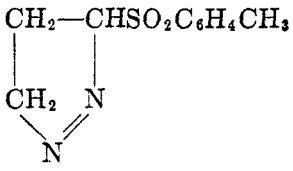
X XI XII

The same monobromo compound, XI was formed more rapidly, and in better yield, when the sodium derivative of X was brominated in benzene solution—a reaction which served to locate the bromine atom in XI.

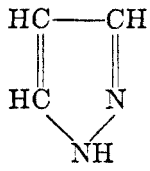
The bromo compound (XI) was inert to the action of fused potassium acetate in methanol, either at room temperature or at the boiling point of the solution. When XI was subjected to the action of 2,4,6-collidine at the boiling point (171–172°) for 25 minutes, bromine was removed, but the product was X and not the cyclopropane XII. Similarly, XI was reduced to X by action of triethylamine in ether at room temperature. In these reductions, ionic bromine was formed. Apparently, then, the sulfonyl group does not activate hydrogen atoms on the adjacent carbon atom sufficiently so that a cyclopropane ring may be closed by removal of the elements of hydrogen bromide, a reaction easy to bring about in the case of the analogous ketones.

Since the vinyl sulfone (II) was available, the synthesis of a sulfonyl cyclopropane (XV) *via* a pyrazoline was attempted (9). Diazomethane added readily to II in ether, to form the white, crystalline pyrazoline (XIII) in yields up to

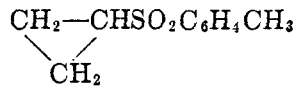
64%. In analogy with the work of von Auwers (8), this pyrazoline is written as the Δ_1-isomer. When the pyrazoline (XIII) was heated with platinized asbestos,



XIII



XIV



XV

only 32% of the calculated amount of nitrogen was evolved, whether or not a small amount of potassium hydroxide was included in the mixture. At 185°, pyrazole (XIV) distilled from the mixture, and was obtained in yields up to 53%. The pyrazole was identified by its physical constants and by the melting point of the picrate. The reaction thus represents a cleavage of *p*-toluenesulfinic acid, rather than nitrogen, from the pyrazoline (XIII). *p*-Toluenesulfinic acid was not isolated from the reaction mixture. When the evolution of nitrogen and distillation of pyrazole from the pyrolysis mixture ceased, the pyrolysis was continued in a vacuum. A small amount of yellow oil distilled at 275°/1.5 mm. (bath temperature); this oil solidified on standing overnight. The material was insoluble in water and dilute acid, was extremely soluble in all organic solvents, and was inert to neutral permanganate. After purification by adsorption on alumina, it melted at 41–43° (*p*-thiocresol, m.p., 43°; disulfide, m.p., 46°), but the analytical values were not concordant nor consistent with those required by a cyclopropyl sulfone or any other compound that would be expected as a product of the reaction. The amount of this material was too small for further investigation.

EXPERIMENTAL PART[2]

Phenyl β-styryl sulfone (I). Thiophenol (15.4 g., 0.014 mole) was added dropwise, with stirring and cooling, to phenylacetylene (14.3 g., 0.014 mole); the mixture was stirred at room temperature for one hour and then distilled under reduced pressure from a modified Claisen flask. After a small forerun, the main fraction (22.9 g., 77%) was collected at 155–160°/1 mm.; this was followed by a third fraction boiling at 175–185°/1 mm. (1.2 g.). The main fraction was dissolved in acetic acid (50 cc.) and aqueous hydrogen peroxide (30%, 30 g., 0.27 mole) was added. A heavy oil separated; the flask was shaken intermittently for two hours, when the oil dissolved. The mixture was allowed to stand overnight. Water (150 cc.) was added and the mixture was cooled. The product, separating as an oil, soon crystallized. The solid (15.9 g., 65%, m.p., 71–74°) was removed and dried in a vacuum over potassium hydroxide. The analytical sample, crystallized from aqueous methanol, melted at 74–75°.

Anal. Calc'd for $C_{14}H_{12}O_2S$: C, 68.83; H, 4.95.
Found: C, 68.88, H, 5.09.

1-Phenyl-1,2-dibenzenesulfonylethane (IV). The high-boiling fraction from the above distillation (1.2 g.) was dissolved in acetic acid (10 cc.), aqueous hydrogen peroxide (30%, 4 g.) was added, and the mixture was processed as described above for I, except that the mixture obtained by dilution with water (25 cc.) was extracted with benzene (10 cc.). The

[2] Microanalyses by R. W. Amidon, J. S. Buckley, Jr., and William Cummings.

benzene extract was filtered and the filtrate was diluted with petroleum ether (15 cc., b.p., 60–68°). The granular solid was removed, washed with petroleum ether, and crystallized from benzene-petroleum ether. It weighed 0.24 g.; m.p. 141.5–142.5°.

Anal. Calc'd for $C_{20}H_{18}O_4S_2$: C, 62.15; H, 4.69.
Found: C, 62.19; H, 4.89.

The sulfone I (2.44 g., 0.01 mole) and nitromethane (0.73 g., 0.012 mole) were dissolved in dry methanol (20 cc.), and a solution of sodium (0.3 g., 0.013 gram-atom) in dry methanol (5 cc.) was added rapidly. The temperature was maintained at 40–50° for 30 minutes; then acetic acid (0.8 g.) was added and the mixture was cooled. The white crystalline solid was removed and washed with dilute methanol. It weighed 1.95 g. (80%) and melted at 72–73°, alone or when mixed with authentic I. The sulfone I (1.22 g.) and the dipotassium salt of nitroacetic acid (1.8 g.) were heated to 40–50° in ethanol (10 cc.) and water (6 cc.) for a few minutes; the solution was then allowed to stand overnight. Addition of acetic acid (1 cc.) produced evolution of carbon dioxide. Water (10 cc.) was added and the solid was removed. It was unchanged I, m.p. and mixed m.p. 73–74°.

1-Phenyl-1-methoxy-2-benzenesulfonylethane (VIa). Nitromethane (0.73 g., 0.012 mole) and the sulfone I (2.44 g., 0.01 mole) were dissolved in dry methanol (20 cc.), and a solution of sodium (0.1 g., 0.003 mole) in dry methanol (5 cc.) was added. The solution was allowed to stand at room temperature for 36 hours after which it was acidified with hydrochloric acid (1 cc.) and diluted with water (25 cc.). The aqueous layer was decanted and the residual oil was dissolved in benzene (10 cc.). The solution was diluted with petroleum ether (15 cc., b.p. 60–68°) and cooled. The solid was removed, washed with petroleum ether, and dried. It weighed 1.1 g. (40%) and melted at 68–74°. The analytical sample, crystallized from aqueous methanol (75%), melted at 84.5–86°. The substance was inert toward permanganate, and contained no nitrogen.

Anal. Calc'd for $C_{15}H_{16}O_3S$: C, 65.19; H, 5.84.
Found: C, 65.48; H, 5.96.

1-Phenyl-1-dimethylamino-2-benzenesulfonylethane (VIc). The sulfone I (2.44 g., 0.01 mole) was dissolved in dry ethanol (10 cc.). Solid dimethylamine hydrochloride (0.89 g., 0.011 mole) was added, followed by a solution of sodium (0.23 g., 0.01 gram-atom) in dry ethanol (10 cc.). The mixture was allowed to stand at room temperature for 42 hours. Sodium chloride was removed, and the filtrate was cooled. The solid (0.9 g., 30%, m.p., 119–127°) was removed and dried. (Filtrate, see below.) It was almost completely soluble in dilute acid and only faintly unsaturated toward permanganate. A sample for analysis was prepared by dissolving the material in acid, filtering the solution, and neutralizing the filtrate. The solid was washed with water and crystallized successively from ethanol, benzene-petroleum ether, and methanol. It then melted at 133.5–134°.

Anal. Calc'd for $C_{16}H_{19}NO_2S$: C, 66.40; H, 6.62; N, 4.84.
Found: C, 66.29; H, 6.62; N, 4.76.

1-Phenyl-1-ethoxy-2-benzenesulfonyl ethane (VIb). The above filtrate remaining after removal of the crude dimethylamino compound was diluted with water (20 cc.) and cooled. The solid (1.81 g., 62%) was removed and dried in a vacuum. It melted at 88–90°; after crystallization from benzene-petroleum ether (1:2, b.p., 60–68°), and then from ethanol, the substance melted at 101–102°. It was not soluble in dilute acid, and was inert toward permanganate.

Anal. Calc'd for $C_{16}H_{18}O_3S$: C, 66.18; H, 6.25.
Found: C, 66.42; H, 6.36.

p-Tolyl vinyl sulfone (II). Sodium (7.6 g., 0.33 mole) was dissolved in ethanol (120 cc.) and *p*-thiocresol (40 g., 0.32 mole) was added to this solution, followed by addition of ethyl-

ene chlorohydrin (25.9 g., 0.32 mole) in four portions. The temperature was maintained at 45–55° for 30 minutes, then hydrochloric acid (200 cc.) was added and the mixture was heated on the steam-bath for 1½ hours, during which time a heavy yellow oil separated. Ethanol (75 cc.) was removed by distillation; the distillate was diluted with water and extracted twice with ether. The residue left after distillation of the ethanol was diluted with water (100 cc.) and extracted with ether. The extracts were combined with the extracts of the distillate and dried (sodium sulfate). The ether was removed and the residue was distilled under reduced pressure. *p*-Tolyl β-chloroethyl sulfide (55 g., 93%) was collected at 147–151°/22 mm. (This substance is a strong vesicant and proper precautions must be observed in handling it.) The sulfide was dissolved in acetic acid (150 cc.) and the solution was refluxed while aqueous hydrogen peroxide (30%, 200 g., 1.76 moles) was added. Refluxing was continued for two hours, then the mixture was cooled (5°), diluted with water (400 cc.), and kept at 5° for 30 minutes. The solid was removed, washed with water, and dried in a vacuum over potassium hydroxide. The sulfone was dissolved in ether (100 cc.) and a solution of triethylamine (60 cc.) in ether (100 cc.) was added. The white solid was removed, washed twice with ether (50 cc.), and the ether washings were combined with the filtrate. The ether was removed; the residual brown oil solidified when it was shaken with water. The solid was removed, washed with water, and crystallized from ethanol (150 cc.). The product (25 g.) melted at 65–66°; reported 66° (6). Additional material (14 g.) melting at 64–65° was obtained by diluting the mother liquor with water. The over-all yield for the four steps was 67%.

Bis-(2-p-toluenesulfonylethyl)nitromethane (VIII). The sulfone (II) (1.82 g., 0.01 mole) and nitromethane (0.73 g., 0.012 mole) were dissolved in dry methanol (20 cc.). The solution was warmed to 40° while a solution of sodium (0.3 g., 0.013 mole) in dry methanol (10 cc.) was added. The solution was maintained at 40–50° for 10 minutes, and was then acidified with acetic acid (1 cc.), cooled, diluted with water (3 cc.), and set aside at 0° for 2 hours. The solid was removed, washed with aqueous methanol (50%), and dried. It weighed 1.95 g. (91%) and melted at 121–131°. The analytical sample, crystallized twice from benzene-petroleum ether (1:2), melted at 134–137°. The substance was inert toward permanganate, and was soluble in aqueous sodium hydroxide (10%).

Anal. Calc'd for $C_{19}H_{23}NO_6S_2$: C, 53.63; H, 5.45; N, 3.29.
Found: C, 53.87; H, 5.55; N, 3.27.

Tris-(2-p-toluenesulfonylethyl)nitromethane (IX). The *bis*-compound (VIII) (0.45 g.) was warmed for 30 minutes in ethanol (40 cc.). The solution was cooled and the solid (0.36 g., m.p., 195–197°) was removed and crystallized from ethanol (100 cc.). It melted at 197–198°, and was insoluble in aqueous sodium hydroxide (10%).

Anal. Calc'd for $C_{28}H_{33}NO_8S_3$: C, 55.33; H, 5.47; N, 2.31.
Found: C, 55.42; H, 5.70; N, 2.36.

Ethyl 1-carboethoxy-2-phenyl-3-benzenesulfonylpropionate (X). A solution of the sulfone (I) (4.88 g., 0.02 mole) was added to a suspension of ethyl sodiomalonate (from ethyl malonate, 3.8 g., 0.024 mole and sodium, 0.5 g., 0.022 gram-atom) in benzene (20 cc.). The mixture was shaken for 24 hours, filtered, and the filtrate was washed with dilute hydrochloric acid and water. Removal of the benzene left an oil which solidified when cooled; weight, 7.85 g. (97%); m.p. 101–104°. After crystallization three times from ethanol, the substance melted at 110–110.5°.

Anal. Calc'd for $C_{21}H_{24}O_6S$: C, 62.36; H, 5.98.
Found: C, 62.60; H, 6.14.

Ethyl 1-carboethoxy-1-bromo-2-phenyl-3-benzenesulfonylpropionate (XI). *A*. Bromine (1.3 g., 0.008 mole) in carbon tetrachloride (20 cc.) was added to a solution of the malonic ester (X) (3.03 g., 0.0075 mole) in carbon tetrachloride (70 cc.). There was no evolution of hydro-

gen bromide when the solution was warmed, or when a drop of acetone was added. Evolution of hydrogen bromide began only after the solution was exposed to ultraviolet light; irradiation was continued for 6 hours. The solution was washed with aqueous sodium bisulfite and then with water, the solvent was removed, and the residue was crystallized from benzene-petroleum ether (1:2). The product (2.93 g., 81%) melted at 93–95°; after recrystallization from methanol, it melted at 96–97°.

Anal. Calc'd for $C_{21}H_{23}BrO_6S$: C, 52.18; H, 4.80.
Found: C, 52.14; H, 4.99.

B. A clear, filtered, benzene solution of the enolate of X was prepared as described above from sodium (0.76 g., 0.033 mole), ethyl malonate (5.90 g., 0.037 mole), and the sulfone (I) (7.32 g., 0.03 mole). To this was added a solution of bromine (5.27 g., 0.033 mole) in carbon tetrachloride (40 cc.). The color of the bromine rapidly faded. The solution was allowed to stand overnight and was then processed as described under A above. The product weighed 11.73 g. (81%) and melted at 93–96°, alone or when mixed with a sample prepared by method A.

The bromomalonate XI (1 g.) was dissolved in 2,4,6-collidine (10 cc.) and the solution was refluxed for 25 minutes. Within 5 minutes the solution became black and a granular solid was deposited. The solution was decanted from the solid material into benzene; the solid was washed with benzene and dissolved in water. This aqueous solution gave a strongly positive test for bromide ion. The combined benzene filtrates and washings were washed successively with dilute hydrochloric acid, aqueous sodium carbonate, and water. The benzene was removed and the residue was crystallized from benzene-petroleum ether (1:4). The white crystalline solid (0.5 g., 60%) melted at 98–103°. This material was deposited from benzene onto a column (18 × 110 mm.) of alumina (Alcoa, 80–200 mesh). A faint yellow band appeared in the middle of the column. The material was eluted with benzene-ether (4:1) until this band was within 15 mm. of the bottom of the column. The solvent was removed from the eluate and the residue was crystallized from benzene-petroleum ether (1:4). The product weighed 0.25 g. and melted at 109.5–110° alone or when mixed with authentic X. Essentially the same results were obtained in a duplication of this experiment, substituting triethylamine for the collidine. The bromomalonic ester XI (200 mg.) in methanol (5 cc.) was boiled with fused potassium acetate (0.5 g.) and then allowed to stand overnight. No potassium bromide was formed, and from the mixture only unchanged XI could be isolated.

3-p-Toluenesulfonylpyrazoline (XIII). Ethereal diazomethane [from N-nitrosomethylurea, 5 g., aqueous potassium hydroxide (40 cc., 40%), and ether, 50 cc.] was added to *p*-tolyl vinyl sulfone (II) (3.64 g., 0.02 mole) in ether (50 cc.). The solution was allowed to stand for 24 hours at room temperature; the ether was then removed under reduced pressure. The residue was crystallized from ether-petroleum ether (2:1). The product weighed 2.85 g. (64%) and melted at 86–93°. The analytical sample, crystallized twice from ether-petroleum ether, melted at 96–98°.

Anal. Calc'd for $C_{10}H_{12}N_2O_2S$: C, 53.55; H, 5.40; N, 12.49.
Found: C, 53.09; H, 5.60; N, 12.03.

The crude pyrazoline XIII (2 g., 0.01 mole, m.p., 86–93°) and platinized asbestos (0.1 g.) were placed in a 10-ml. flask connected to a receiver and immersed in a metal-bath. At 130°, nitrogen was evolved; the bath temperature was gradually raised to 275°. At 185° (thermometer in the reaction mixture) a clear white liquid distilled; the distillate solidified when cooled. This solid, pyrazole (XIV), weighed 0.32 g. (53%), melted at 68–69°, and formed a picrate melting at 161–162° (10). The volume of nitrogen evolved was 64 cc. (32%). When evolution of nitrogen and distillation of pyrazole ceased, the flask was heated at 275° (bath temperature) and under reduced pressure (1.5 mm.). The yellow, oily distillate crystallized on standing overnight at room temperature. The solid was dissolved in ether, the solution was washed with dilute hydrochloric acid, and dried (sodium sulfate). The solvent was

removed and the yellow oily residue was crystallized from petroleum ether (5 cc., b.p., 60–68°). The product weighed 75 mg. and melted at 39–41°. It was inert toward permanganate. The substance was dissolved in benzene-petroleum ether (10 cc., 1:1) and deposited on a column (8 × 60 mm.) of alumina (Alcoa, 80–200 mesh). The column was eluted with benzene-ether (5:1) and the solvent was removed from the eluate. The product, a yellow waxy solid, weighed 52 mg., and melted at 41–43°. The analytical values for this material were not concordant and did not agree with those required by the cyclopropane structure XV.

Anal. Calc'd for $C_{10}H_{12}O_2S$ (XV): C, 61.19; H, 6.17.
Calc'd for $C_{14}H_{14}S_2$(ditolyl disulfide) C, 68.3; H, 5.7.
Found: C, 68.69, 69.79; H, 6.44, 6.42.

SUMMARY

1. Two α,β-unsaturated sulfones, phenyl β-styryl sulfone (I) and *p*-tolyl vinyl sulfone (II) have been prepared.

2. Although nitromethane could not be added to phenyl-β-styryl sulfone (I) under a variety of conditions, this sulfone readily added methanol, ethanol, dimethylamine, and malonic ester.

3. Ethyl 1-carboethoxy-2-phenyl-3-benzenesulfonyl propionate (X), formed from the sulfone I and sodio ethyl malonate, was converted into the α-bromomalonic ester. No cyclopropane could be prepared from the bromo compound; potassium acetate was without action, and collidine or triethylamine merely removed the bromine atom reductively to give X.

4. Nitromethane reacted readily with *p*-tolyl vinyl sulfone (II), but the reaction involved two or three molecules of the sulfone. No 1:1 addition product could be obtained.

5. Action of diazomethane upon *p*-tolyl vinyl sulfone (II) gave 3-p-toluenesulfonylpyrazoline smoothly and in good yield, but pyrolysis of the pyrazoline gave pyrazole as the only pure product. No cyclopropyl sulfone could be obtained.

MINNEAPOLIS 14, MINN.

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

THE REACTION BETWEEN QUINONES AND METALLIC ENOLATES. XXV. TRIMETHYLQUINONE AND THE ENOLATES OF CYANOACETIC ESTER, CYANOACETAMIDE, BENZYL CYANIDE, OXALOACETIC ESTER, AND THE ACETAL OF DIACETYL (1)

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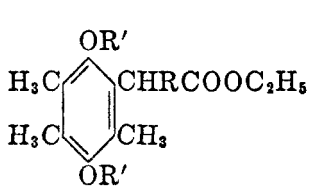
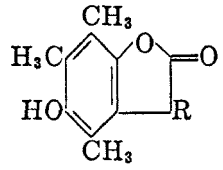
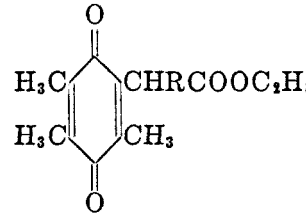
Received February 8, 1950

Previous work dealing with the reaction between trimethylquinone and various metallic enolates (2–7) has shown that the reaction involves a primary 1,4-addition to the open conjugated system in the quinone, to give a hydroquinone (I). Often the hydroquinone can be isolated only with difficulty; in these cases, the chief product of the reaction is one derived from the hydroquinone by ring closure. Thus, with the enolates of malonic ester, the products are the hydroquinone I and the isocoumaranone II derived from I by loss of the elements of ethanol; this reaction may or may not be accompanied by the loss of a carboethoxyl group.







I R = $COOC_2H_5$; R′ = H II R = $COOC_2H_5$ or H IV R = CN
III R = CN; R′ = H

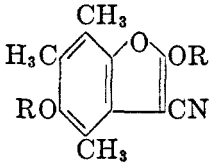
To explore further this reaction, and particularly to explore the structural features of the enolate which limit the reaction, a study has been made of the reaction between trimethylquinone and the enolates of cyanoacetic ester, cyanoacetamide, benzyl cyanide, oxaloacetic ester, and the mono acetal of diacetyl.

A. *Sodio ethyl cyanoacetate.* No pure product could be obtained when this enolate was condensed with trimethylquinone in ethanol, but in dry, peroxide-free dioxane, the hydroquinone III was obtained in small (up to 32%) yields. Although purple and red colors were developed during the reaction, the hydroquinone III was itself not colored. This is in contrast with the purplish-red *bis*-cyanoacetic ester addition product obtained by Wood, Colburn, Cox, and Garland (8) from cyanoacetic ester and the unsubstituted *p*-benzoquinone when ammonia was used as the condensing agent; this highly colored substance was shown by these authors to be quite analogous to III in structure.

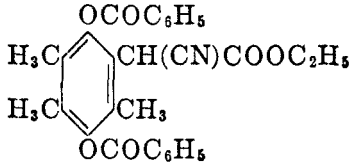
The hydroquinone III was converted, by action of ferric chloride, into the orange-yellow quinone IV. The hydroquinone was readily acetylated, but the

[1] Abstracted from a thesis by Wesley J. Dale, presented to the Graduate Faculty of the University of Minnesota, in partial fulfillment of the requirements for the Ph.D. degree, August, 1949. National Research Council Fellow, 1946–1949.

products were mixtures very difficult to separate into pure compounds. Action of acetic anhydride and pyridine upon III gave ill-defined results, but action of acetic anhydride and sulfuric acid produced the enol acetate of the acetoxyisocoumaranone V.



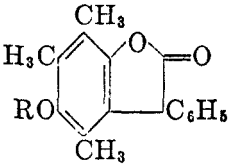
V R = Ac
VII R = C_6H_5CO



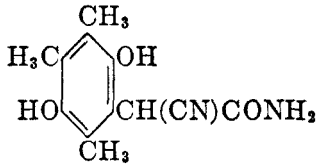
VI

Action of benzoyl chloride and pyridine upon III produced a mixture of the corresponding hydroquinone dibenzoate VI and the enol benzoate VII. When the hydroquinone III was subjected to the action of ethanol and sulfuric acid, the product was the known isocoumaranone II, R = H (2), formed by cyclization and elimination of the cyano group.

B. *Benzyl cyanide.* When the enolate of benzyl cyanide was condensed with trimethylquinone in methanol, the only product isolated (32%) was the hydroxyisocoumaranone VIII. This substance contained no nitrogen; the reaction therefore involved addition of the cyanide with subsequent hydrolysis of the nitrile group and elimination of water to give the cyclized product. The isocoumaranone VIII, when acetylated, gave only the monoacetate IX; no enol acetate was formed.

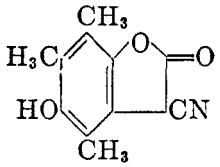


VIII R = H
IX R = Ac

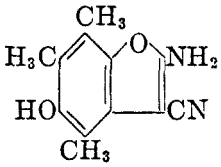


X

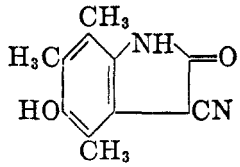
C. *Cyanoacetamide.* The enolate of cyanoacetamide would be expected to react with trimethylquinone to produce the hydroquinone X and/or a derivative of it formed by subsequent ring closure.



XI



XII



XIII

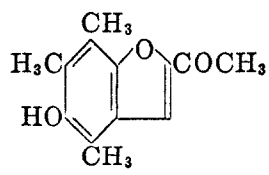
Excluding any products derived from X by hydrolysis of the cyano or amide groups, the further transformations of X would be expected to lead to the cyanoisocoumaranone XI (loss of ammonia) or, by loss of water, to the amino coumaron XII or to the hydroxyindolone XIII. The product of the reaction

between trimethylquinone and cyanoacetamide was a white substance melting at 240–245° which gave a positive Folin test. Action of acetic anhydride upon this product produced a diacetate, and action of benzoyl chloride produced a dibenzoate. The found analytical values, compared with those required by structures X, XI, and XII (XIII) and their respective diacetates and dibenzoates, are as follows:

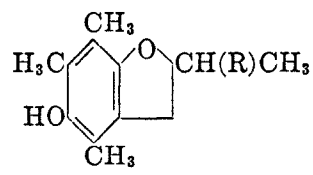
PARENT COMPOUNDS	C	H	N
X ($C_{12}H_{14}N_2O_3$)	61.52	6.02	11.96
XI ($C_{12}H_{11}NO_3$)	66.35	5.11	6.45
XII, XIII ($C_{12}H_{12}N_2O_2$)	66.65	5.60	12.96
Found:	66.69	5.77	12.73, 12.91
DIACETATES			
of X ($C_{16}H_{18}N_2O_5$)	60.37	5.70	8.80
of XI ($C_{16}H_{15}NO_5$)	63.80	5.02	4.65
of XII, XIII ($C_{16}H_{16}N_2O_4$)	63.99	5.38	9.33
Found:	63.67, 64.08	5.42, 5.46	9.24, 9.14
DIBENZOATES			
of X ($C_{28}H_{22}N_2O_5$)	70.58	5.02	6.33
of XI ($C_{26}H_{19}NO_5$)	72.50	4.65	3.39
of XII, XIII ($C_{26}H_{20}N_2O_4$)	73.57	4.75	6.60
Found:	73.53, 73.36	4.82, 5.03	6.63, 6.69

These data served to fix the course of the reactions quite definitely: the product is derived from one molecule each of the quinone and cyanoacetamide, followed by loss of water from the primary product X. Calculated upon this basis, the yield of recrystallized product was 74–83%. Structure XII was assigned to this product although the isomeric structure XIII cannot be entirely excluded.

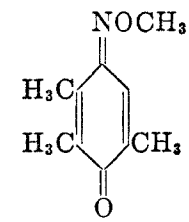
D. If the condensation between trimethylquinone and diacetyl or a suitable derivative of the diketone could be achieved, a route would be opened to coumarons of the type of XIV, and from these, by obvious methods, to coumarans of type XV.



XIV



XV



XVII

$CH_3COC(OCH_3)_2CH_3$

XVI

However, diacetyl itself does not undergo a base-catalyzed condensation with trimethylquinone, for the basic catalyst brings about self condensation of the diketone too rapidly. The mono acetal XVI of diacetyl is, however, stable toward sodium ethoxide and other bases. It appeared worth while to study the behavior of the enolate of XVI toward trimethylquinone, although Smith and Prichard (3) had found that the enolates of α,α-disubstituted acetoacetic esters could not be condensed with the quinone, even when the γ-hydrogen atoms were activated by the presence of a cyano or carbethoxyl group attached to the γ-carbon atom. Sodium ethoxide was without action upon XVI, and when sodium ethoxide was added to a solution of the quinone and XVI in ethanol, the only reaction was degradation of the quinone by action of the alkali. It was obvious, therefore, that a more powerful enolizing agent than sodium ethoxide would be necessary in order to convert XVI into its enolate. It was found that XVI was readily enolized by action of sodium amide (evolution of ammonia), but when trimethylquinone was added to the solution of the enolate, an intense green color developed and no condensation product could be obtained. This appearance of a green color in base-catalyzed reactions of trimethylquinone indicates degradation of the quinone by the base and is produced when the quinone alone is subjected to the action of bases. In all cases in which the quinone has been successfully condensed with an enolate, the colors of the reaction mixture have been brown, red, or purple—never green.

Isopropylmagnesium bromide reacted vigorously with XVI and a gas was evolved. However, when trimethylquinone was added to the solution of the enolate in ether or dioxane, a green color developed, and the only products were unchanged starting materials.

The acetal XVI was also converted into the enolate by action of powdered sodium at $-15°$. That XVI was in the form of the enolate was shown by hydrolysis of the enolate, by action of acid, to diacetyl and identification of the diketone as the dioxime, isolated in 66% yield. However, the sodium enolate of XVI, prepared in this manner, failed to condense with trimethylquinone. The reaction mixture developed the characteristic green color, and no pure product could be isolated from it.

In contrast with the quinone, the 1-monoxime methyl ether XVII (10) of the quinone is stable toward alkali. When the sodium enolate of XVI was added to a solution of XVII in ether, the reaction mixture did not develop the green color characteristic of unsuccessful condensations of the quinone, but became brownish-red and deposited a bluish-red solid. From this reaction mixture, acidic, neutral, and basic fractions were obtained, but no pure product could be isolated from any of these fractions.

E. When the attempts to condense trimethylquinone with the acetal XVI resulted in failure, attention was turned to ethyl oxalacetate, for successful condensation of trimethylquinone with the enolate of this substance would lead to a coumaron substituted in the hetero ring by carbethoxyl groups. These groups could then be manipulated so that coumarons and coumarans with various side chains could be synthesized. However, under none of the conditions tried, could any products other than dark, intractable tars, be obtained from

trimethylquinone and the enolate of oxalacetic ester. The conditions included use of the sodium enolate in dioxane or pyridine, and reaction of the quinone with the ester in the presence of a catalytic amount of piperidine. Under the latter conditions, there was no reaction at all and the starting materials were recovered completely.

EXPERIMENTAL PART[2]

A. *Ethyl 2,5-dihydroxy-3,4,6-trimethylphenyl-α-cyanoacetate.* (III). Trimethylquinone (15 g., 0.1 mole) in dry, peroxide-free dioxane (9) (20 cc.) was slowly (70 minutes) added dropwise and with stirring and cooling (15°) to a suspension of sodio ethyl cyanoacetate (from sodium, 2.3 g., and ethyl cyanoacetate 11.7 cc.) in dioxane (70 cc.). The purple suspension was stirred at 15° for an hour, then cooled to 5° while hydrochloric acid (9.5 cc.) was adedd dropwise. The orange-brown slurry was poured, slowly and with stirring, into ice and water (1 l.). The brown putty-like mass was removed, dissolved in ether, the solution was washed with water until the washings were neutral, and dried (sodium sulfate). The solvent was removed; the residue (26 g.), a syrup containing some solid, was triturated twice with hot petroleum ether (150 cc., b.p., 60–68°) to remove unchanged quinone. The residue wsa dissolved in ether and the solution was washed several times with aqueous sodium hydrosulfite, dried, and the solvent was removed. The dry residue (20 g.), crystalline and brick-red, was extracted six times with boiling (60–68°) petroleum ether (300 cc. each time) and the filtered (hot) extracts were combined and cooled (−15°) in a refrigerator overnight. The gray-white solid was removed and crystallized from aqueous ethanol (50%), when it melted at 155.5–156°. The Folin test was positive.

Anal. Calc'd for $C_{14}H_{17}NO_4$: C, 63.86; H, 6.51; N, 5.32.
Found: C, 63.54; H, 6.75; N, 5.36.

The hydroquinone III was recovered unchanged when a solution of it in sulfuric acid was warmed to 40°. When III (0.7 g.) was subjected to the action of 81% sulfuric acid at 100° for 3 hours, the only product was a black powder (0.2 g.).

The hydroquinone (1 g.) in ethanol (25 cc.) was refluxed with sulfuric acid (4 cc.) for 5 hours; the solution was poured into water, the solid (0.7 g.) was removed and crystallized successively from aqueous ethanol and benzene-petroleum ether. It then melted at 194.5–196°, and was the coumaron II, R = H (2).

2,5-Diacetoxy-3-cyano-4,6,7-trimethylcoumaron (V). A solution of the hydroquinone III (1 g.) in acetic anhydride (15 cc.) containing sulfuric acid (1 drop) was warmed for 2 hours, then poured into ice-water and allowed to stand for 4 hours. The solid was removed, dissolved in hot ethanol (45 cc.), and the solution was slowly cooled to room temperature. The white clusters weighed 0.09 g. (8%) and melted at 225–230°. After recrystallization twice from ethanol, the substance showed the same melting point.

Anal. Calc'd for $C_{16}H_{15}NO_5$: C, 63.87; H, 5.02; N, 4.65.
Found: C, 64.01; H, 5.25; N, 4.68.

The mother liquors, when diluted with water, deposited 1.2 g. of solid melting at 95–120°. This mixture could not be separated into pure materials by crystallization from ethanol; when chromatographed from benzene onto alumina, a small amount of material melting at 137–137.5° was obtained. The analytical values of this material did not correspond with those required by any reasonable structure derived from V. When V (0.4 g.) was acetylated by action of acetic anhydride (7 cc.) in pyridine (10 cc.), there was obtained a material melting at 135–138°, not identical with that of m.p. 137–137.5° above. After

[2] Microanalyses by Roger Amidon, Jay S. Buckley, and William Cummings.

crystallization several times from aqueous ethanol and benzene-petroleum ether, this material melted at 142–144.5°, but no reasonable structure could be written for it.

Anal. Found: C, 65.06; H, 6.62; N, 4.41.

Ethyl α-cyano-2,5-dibenzoyloxy-3,4,6-trimethylphenylacetate (VI). Benzoyl chloride (2 cc.) was added to a solution of the hydroquinone III (0.26 g.) in pyridine (8 cc.). The solution was boiled for 5 minutes, cooled, and poured into water (20 cc.). Ethanol was added until a yellow solid deposited; this solid was removed (see below) and the filtrate was diluted with water and set aside in a refrigerator. The white solid (0.32 g., m.p., 155–160°) was removed and crystallized from ethanol, when it still melted at 155–160°. It was then dissolved in benzene and the solution was passed through a column of alumina. The column was eluted with benzene (750 cc.), leaving a yellow band on the column. The eluate, on evaporation, left 0.14 g. of product melting at 171–175°. The analytical sample, crystallized from ethanol, melted at 178–179.5°.

Anal. Calc'd for $C_{26}H_{25}NO_6$: C, 71.32; H, 5.35; N, 2.97.
Found: C, 71.50; H, 5.61; N, 3.09.

2,5-Dibenzoyloxy-3-cyano-4,6,7-trimethylcoumaron (VII). The yellow solid (0.1 g.) obtained from the above preparation of VI was recrystallized several times from chloroform-ethanol, when it melted at 266–267.5°.

Anal. Calc'd for $C_{26}H_{19}NO_5$: C, 73.40; H, 4.50; N, 3.29.
Found: C, 73.65; H, 4.54; N, 3.23.

Ethyl 3,5,6-trimethylquinone-2-α-cyanoacetate (IV). A solution of the hydroquinone III (0.7 g.) in ethanol (15 cc.) was added to a solution of ferric chloride (5 g.) in water (5 cc.) and hydrochloric acid (4 drops). The solution, after standing for 90 minutes, deposited an orange-yellow solid. The solution was diluted with water (10 cc.) and set aside in a refrigerator. The product (0.34 g.) was removed, washed with water, and dried, when it melted at 230° (dec.). This material was dissolved in ether and the solution was passed through a column (1.4 × 13 cm.) of alumina (80–200 mesh). The filtrate was concentrated to 7 cc. and diluted with petroleum ether (b.p., 28–38°). The solid (m.p., 247–250°) was removed and crystallized three times from aqueous acetone, when it melted at 251.5–253° (dec.).

Anal. Calc'd for $C_{14}H_{15}NO_4$: C, 64.35; H, 5.79.
Found: C, 64.21; H, 5.65.

B. *3-Phenyl-4,6,7-trimethyl-5-hydroxyisocoumaranone* (VIII). Benzyl cyanide (12.7 cc., 0.11 mole) was added dropwise and with stirring to a solution of sodium methoxide in methanol (from sodium, 2.3 g., and methanol, 30 cc.). Stirring was continued for 10 minutes, and then, with continued stirring, a solution of trimethylquinone (15 g., 0.1 mole) in methanol (10 cc.) was added dropwise. The mixture was allowed to stand at room temperature for 2 days, and was then poured onto ice (200 g.) containing hydrochloric acid (10 cc.). The solid was removed, dissolved in ether, and the solution was filtered to remove a small amount (0.2 g.) of red material. The filtrate was washed with water until the washings were neutral, dried, and the solvent was removed. The dark residue (25.2 g.) was a brown, semi-solid mass. A portion (12.4 g.) was dissolved in hot benzene (60 cc.), the solution was boiled for one minute with Norit, filtered, and the filtrate was concentrated to 45 cc. and set aside for several days. The solid (4.2 g., 32%) was crystallized several times in an atmosphere of nitrogen from benzene-petroleum ether, when it melted at 152.5–157.5°. Solutions of VIII were sensitive to air.

Anal. Calc'd for $C_{17}H_{16}O_3$: C, 76.00; H, 6.00.
Found: C, 76.12; H, 6.08.

3-Phenyl-4,6,7-trimethyl-5-acetoxyisocoumaranone (IX). A solution of VIII (0.65 g.) in acetic anhydride (17 cc.) and sulfuric acid (1 drop) was heated to the boiling point, then

cooled and poured into water. The solid (0.8 g.) was removed, washed with water, and dried. It then melted at 205–206°; after several crystallizations from ethanol, it melted at 207–208°.

Anal. Calc'd for $C_{19}H_{18}O_4$: C, 73.52; H, 5.85.
Found: C, 73.60; H, 5.85.

C. *2-Amino-3-cyano-4,6,7-trimethyl-5-hydroxycoumaron* (XII) [or *3-Cyano-4,6,7-trimethyl-5-hydroxyindolone* (XIII)]. A solution of sodium methoxide (from sodium, 2.3 g., and methanol 60 cc.) was added, dropwise and with stirring, to a solution of cyanoacetamide (10.1 g., 0.12 mole) in methanol (30 cc.). To the clear solution of the enolate, a solution of trimethylquinone (15 g., 0.1 mole) in methanol (10 cc.) was added, dropwise and with stirring. During these operations, the reaction mixture was carefully protected from moisture. Heat evolved during the reaction was sufficient to cause the solution to reflux gently; after addition was complete, the mixture was stirred and refluxed for 20 minutes and was then allowed to stand overnight. The cooled (5°) mixture was stirred while hydrochloric acid (9.5 cc.) was added dropwise; the whole was then vigorously stirred into ice and water (1 l.), and allowed to stand for 3 hours. The solid (20.5 g.) was washed with water, dried, and dissolved in dioxane (200 cc.). The solution was filtered and the filtrate was cooled (10°). The crystalline product (16.9 g., 78%) was slightly pink, but could be obtained completely free of color by several crystallizations from dioxane. The pure substance melted at 240–245° (dec.) with previous darkening at 220–230°. The analytical values are given in the table.

Diacetate. A solution of XII (1.3 g) in acetic anhydride (10 cc.) and sulfuric acid (1 drop) was boiled for one minute and then poured into water. The solid was removed and crystallized several times from small volumes of ethanol, when it melted at 226–227.5°. The analytical values are given in the table.

Dibenzoate. A solution of XII (1 g.) and benzoyl chloride (2 cc.) in dry pyridine (6 cc.) was boiled for one minute, then cooled and poured into water. The solid was crystallized several times from large volumes of ethanol, when it melted at 238.5–241°. The analytical values are given in the table.

D. A solution of trimethylquinone (3 g.) and XVI (2.64 g.) in dry ethanol was added to a solution of sodium ethoxide (from sodium, 0.46 g., and ethanol, 5 cc.). The black reaction mixture was allowed to stand for 24 hours, then was poured onto ice and hydrochloric acid (5 cc.) and steam-distilled. The distillate contained a small amount of diacetyl; the residue was a black resin. Essentially the same results were obtained when the experiment was repeated and dioxane was substituted for ethanol.

A solution of XVI (6.9 g.) in benzene (25 cc.) was added to a solution of sodium amide (from sodium, 1.15 g., and liquid ammonia, 100 cc.) in benzene (75 cc.). The temperature rose, and ammonia was evolved. The solution was stirred for 20 minutes and then a solution of trimethylquinone (7.5 g.) in benzene (25 cc.) was added dropwise. A green color developed at once. The mixture was stirred and refluxed for 2 hours, then cooled and stirred with hydrochloric acid (10%, 100 cc.). The benzene layer was removed, washed with water, and dried. Removal of the solvent left an amorphous, brown, tarry resin, which resisted all attempts at crystallization. The same results were obtained where the experiment was repeated and dioxane was substituted for benzene.

A solution of XVI (2.9 g.) in ether (20 cc.) was added to a solution of isopropylmagnesium bromide (from magnesium, 0.54 g., isopropyl bromide, 2.5 g.) in ether (20 cc.). Evolution of gas occurred, and a voluminous white precipitate separated. The mixture was stirred while a solution of trimethylquinone (3 g.) in ether (20 cc.) was added; thereafter, the mixture was refluxed for 4 hours. A green color developed within 10 minutes after the quinone was added. The mixture was poured onto hydrochloric acid (5%, 75 cc.) and steam-distilled. The distillate contained trimethylquinone and diacetyl; the residual liquid in the distillation flask contained only traces of organic material. When the experiment was repeated and dioxane was substituted for ether, the results were the same except that a black resinous material remained in the distillation flask.

To a cooled (−15°) suspension of powdered sodium (0.9 g.) in ether (30 cc.), the acetal XVI (6.35 g.) was added in small portions. After 2 hours, the metal had dissolved; the cold solution was acidified with hydrochloric acid (5 cc. in water, 10 cc.). The solution was stirred vigorously at room temperature; the ether layer was removed and the aqueous layer was extracted three times with ether. The combined ether solutions were dried; hydroxylamine hydrochloride (13.3 g.) in water (100 cc.) was added, followed by addition of sodium carbonate (10.2 g.) in water (100 cc.). The mixture was shaken for 15–20 minutes, ether was removed by distillation, and the aqueous solution was concentrated and cooled. The solid (3.7 g., 66%) melted at 230–232°, alone or when mixed with an authentic specimen of dimethylglyoxime. To a solution of the enolate of XVI, prepared as described above, trimethylquinone (6 g.) in ether (20 cc.) was added dropwise. A green color developed at once; the mixture was stirred with aqueous hydrochloric acid (1:1); the ether layer was separated, dried, and the solvent was removed by distillation. The residue, when evaporatively distilled at 0.001 mm. and 100°, yielded a small amount of trimethylhydroquinone formed by reduction of the quinone. No other pure material could be isolated.

Results similar to the above were obtained when the monoxime methyl ether XVII was substituted for trimethylquinone in experiments involving the sodium enolate of XVI.

E. A solution of sodium ethoxide (from 1.4 g. of sodium) in ethanol (20 cc.) was diluted with dioxane (20 cc.). To this was added a solution of ethyl oxalacetate (11.5 cc.) in dioxane (25 cc.). To the suspension of the enolate was added, dropwise and with stirring, a solution of trimethylquinone (3 g.) in dioxane (15 cc.). The dark solution was allowed to stand at room temperature for one week, then was cooled (5°) and stirred while hydrochloric acid (5 cc.) was added dropwise. The solution was poured into ice-water (1 l.), neutralized with sodium bicarbonate, and set aside at room temperature overnight. The aqueous layer was removed by decantation and the oil was dissolved in ethyl acetate. This solution was extracted four times with 100-cc. portions of aqueous sodium bicarbonate (5%). Removal of the solvent from the organic layer left a residue (4.6 g.) of brown, viscous oil. The alkaline extracts were acidified and extracted with ethyl acetate. Removal of the solvent left another brown oil (3 g.). Both oils contained small amounts of crystalline material, a small amount of which was isolated from the oil insoluble in carbonate. This material melted at 183–184.5°, but the amount was too small for characterization. No other solid material could be isolated from either of the oils. Substantially the same results were obtained when the experiment was repeated and pyridine was substituted for dioxane. The neutral fraction weighed 4.3 g.; the acidic fraction weighed 3.5 g. Both were red-brown oils which could not be separated into any pure substances.

When trimethylquinone and oxalacetic ester were dissolved in ethanol containing a amall amount of piperidine, there was no reaction—no change in color occurred, and only unchanged starting materials were isolated from the solution.

SUMMARY

1. Trimethylquinone has been condensed with the enolates of several nitrogenous compounds. Ethyl cyanoacetate gave, as the primary product, the expected hydroquinone (III) formed by 1,4-addition of the enolate to the quinone. The hydroquinone has been converted into the quinone IV, the coumaron V, and several other derivatives.

2. Benzyl cyanide behaved in an analogous manner, although the primary addition product was not obtained. Instead, the primary product under the conditions used underwent ring closure to give an isocoumaranone VIII.

3. Cyanoacetamide gave a product derived from the primary hydroquinone by loss of water. This product appears to be the aminocyanocoumaron XII, although the isomeric structure XIII for the hydroxyindolone cannot be entirely excluded.

4. Two enolates of the monoacetal of diacetyl have been prepared, but neither of these enolates could be condensed with trimethylhydroquinone. The only products were black tars resulting from decomposition of the quinone itself.

5. The enolate of ethyl oxalacetate could not be condensed with trimethylquinone: again the only products were those resulting from decomposition of the quinone. Piperidine in catalytic amounts caused no reaction between ethyl oxalacetate and trimethylquinone.

MINNEAPOLIS 14, MINNESOTA

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[CONTRIBUTION NO. 207 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE, INC.]

THE SYNTHESIS OF KHELLIN DERIVATIVES

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Interest in the synthesis of khellin, one of the components of the Egyptian drug Ammi Visnaga, has recently been stimulated by the reports (1, 2) on its pharmacological activity and its clinical effectiveness.

The structure of khellin was established by Späth and Gruber (3). The recent synthesis of khellin by Baxter, Ramage, and Timson (6) and Clarke and Robertson (4), reported during the course of the work to be described, anticipate in general two of the approaches made by us. In view of these publications, we take opportunity to describe our work in as far as it differs in detail and to describe some related work.

2,5-Dimethoxyresorcinol on chloroacetylation gave 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I). This was cyclized to 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) which on treatment with acetonitrile according to Hoesch gave 5-acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III). On cyclizing, 3-keto-3(2H)-dihydro-6-acetylkhellin and 3-acetoxy-6-acetylkhellin wereformed.

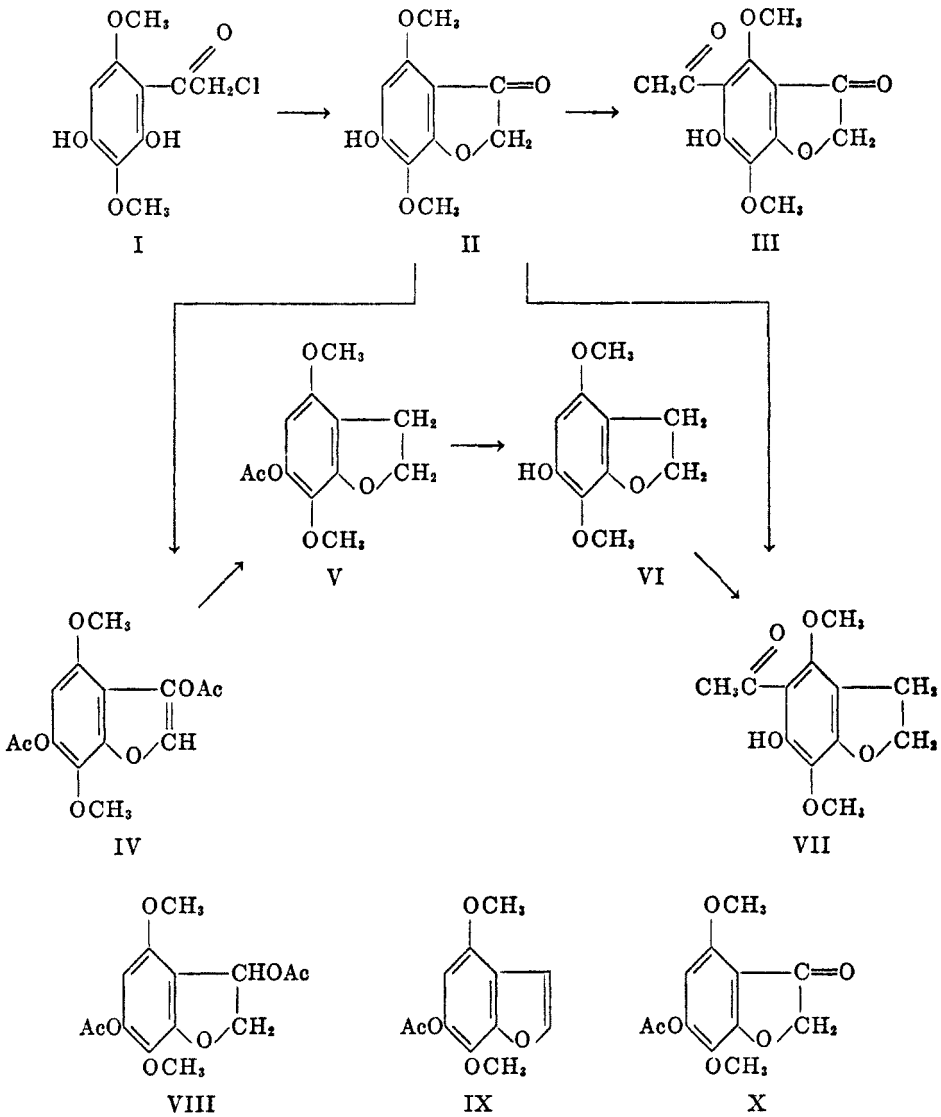
2,4-Dihydroxy-3,6-dimethoxyacetophenone on treatment with N-bromosuccinimide gave the bromo compound, 2,4-dihydroxy-3,6-dimethoxy-ω-bromoacetophenone. Although 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I) was cyclized to 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) according to the method of Späth and Pailer (7) or Shriner and Grosser (10), the bromo derivative was not cyclized by boiling water nor sodium acetate in aqueous alcohol. Fusion eliminated hydrogen bromide, but no identifiable compound was obtained.

Attempts to catalytically reduce II directly to VI with palladium-on-carbon, platinum oxide, or Raney nickel at various pressures and temperatures in different solvents failed, although reduction of closely related compounds using palladium-black in acetic acid has been reported (7).

In analogy with Gruber (8), compound II was acetylated to yield IV, and this on reduction was expected to yield an acetylated secondary alcohol VIII which in turn was expected to lose acetic acid on vacuum-distillation, yielding an intermediate IX which might be transformed into khellinone. The reduction did not occur under Gruber's conditions. However, using platinum oxide as a catalyst, 4,7-dimethoxy-3,6-diacetoxybenzofuran (IV) was reduced to 4,7-dimethoxy-6-acetoxydihydrobenzofuran (V). The identity of this compound was established by analysis, its failure to acetylate, and its deacetylation to 4,7-dimethoxy-6-hydroxydihydrobenzofuran (VI). On vacuum-distillation V was recovered unchanged. 4,7-Dimethoxy-6-acetoxydihydrobenzofuran (V) was expected by dehydrogenation to yield the corresponding 4,7-dimethoxy-6-acetoxybenzofuran (IX), and a similar reaction was reported during the course of this work by

Baxter, Ramage, and Timson (6). The latter workers prepared VI by reduction of 6-benzyloxy-4,7-dimethoxycoumarone, reporting the same melting point as

FIGURE 1



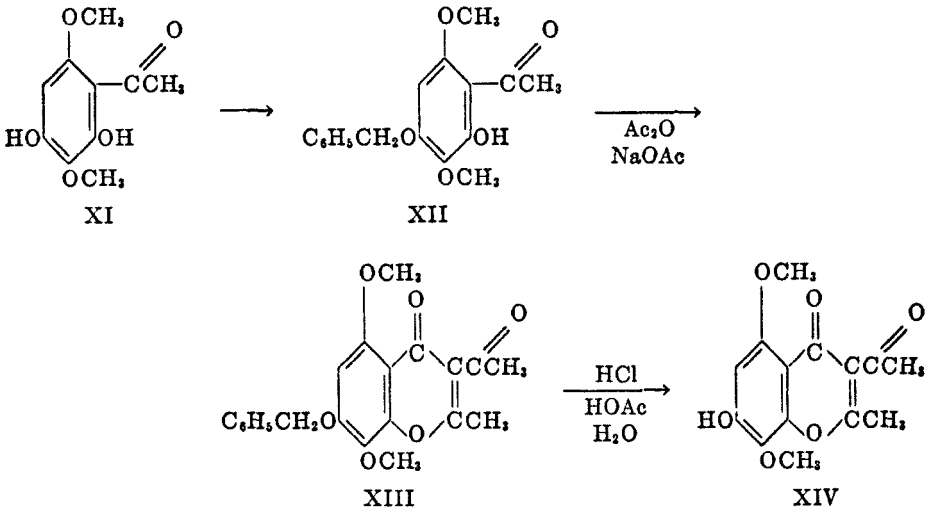
obtained in this work. This serves to confirm the unexpected reduction of IV to V.

Compounds analogous to 6-acetoxy-4,7-dimethoxy-3(2H)-benzofuranone (X) have been reported by Horning and Reisner (17) to be reduced to the dihydrobenzofuran type (V) using palladium-on-carbon. This suggests that the 3-acetoxy

group in IV is hydrolyzed, rearranged to the keto group, and reduced. However, proof of this mechanism is lacking because of the failure to synthesize X. Using the Horning and Reisner (17) method for obtaining monoacetates on 6-hydroxy-4,7-dimethoxy-3(2H)-benzofuranone (II) only the diacetoxy derivative (IV) was obtained.

In another approach to the synthesis of khellin, 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) was benzylated to give XII which on chromone ring closure with sodium acetate and acetic anhydride gave 2-methyl-3-acetyl-5,8-dimethoxy-7-benzyloxychromone (XIII). This on debenzylation with hydrochloric acid and water in acetic acid gave 2-methyl-3-acetyl-5,8-dimethoxy-7-hydroxychromone (XIV). This latter compound could not be made to undergo a Gattermann reaction to yield a 6-aldehydo derivative.

FIGURE 2



A Gattermann reaction on 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) (12) gave 3-acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde on which it was then hoped to build the furan and chromone rings by known procedures. Despite many attempts, however, the yield could not be brought above 17%. Similar difficulties were experienced by Gruber and Traub (9) on compounds of closely related structures. On these grounds this approach was not further pursued. Attempts to prepare 3-acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde by a Hoesch condensation on 2,4-dihydroxy-3,6-dimethoxybenzaldehyde failed.

In the benzylation (4, 5, 13) of 2,4-dihydroxy-3,6-dimethoxyacetophenone, 2-benzyloxy-4-hydroxy-3,6-dimethoxyacetophenone was also obtained. The acetylated derivative was isolated in the pure state. The formation of both monobenzyloxy compounds in the benzylation of 2,4-dihydroxy-3,6-dimethoxyacetophenone (XI) is in contrast to the selective benzylation of 2,4-dihydroxy-3,6-dimethoxybenzaldehyde described by Clarke and Robertson (4).

This latter publication, which appeared during the course of this work, also described the cyclization of ethyl (5-benzyloxy-3,6-dimethoxy-2-formylphenoxy) acetate in alcohol with sodium ethoxide to yield ethyl (6-benzyloxy-4,7-dimethoxybenzofuran)-2-carboxylate. In work along similar lines in this laboratory we had saponified this ester to obtain 5-benzyloxy-3,6-dimethoxy-2-formylphenoxyacetic acid (m.p. 151°) which was cyclized and simultaneously decarboxylated with sodium acetate and acetic anhydride to give 6-benzyloxy-4,7-dimethoxybenzofuran (m.p. 51°). This compound yields khellin by routes established by Baxter, Ramage, and Timson (6) and Späth and Gruber (3).

In an attempt to prepare other coumarin derivatives which might be of pharmacological interest, the condensation of 2,4-dihydroxy-3,6-dimethoxybenzaldehyde with acetic anhydride and sodium acetate gave a small quantity of the expected 7-acetoxy-5,8-dimethoxycoumarin and a larger quantity of 4,6-diacetoxy-2,5-dimethoxybenzaldehyde diacetate.

EXPERIMENTAL

1,2,3-Tribenzyloxybenzene. This compound was prepared from pyrogallol and benzyl chloride in 65–70% yields by the addition of potassium iodide to the reaction. The use of benzyl chloride alone was reported (11) to give a 32% yield.

2,6-Dibenzyloxy-p-benzoquinone. Tribenzyloxybenzene (500 g.) was dissolved in 4 l. of warm acetic acid in a 12-l. round-bottom flask, cooled to room temperature, and with stirring 24 g. of pulverized sodium nitrite and 200 ml. of nitric acid (d = 1.19) was added. The mushy mass was kept at 4° for 4 hours with occasional *vigorous* shaking. At this time an additional 200 ml. of nitric acid (d = 1.19) was added, the mixture shaken vigorously and allowed to stand at room temperature overnight. After filtration the mother liquor was diluted with water, when further precipitation of product occurred. The latter precipitate was sludged twice with acetone, using 100 ml. each time at room temperature to remove an unidentified, uncrystallized oil. The combined crystalline material consisted of a mixture of 2,6-dibenzyloxy-*p*-benzoquinone and 5-nitro-1,2,3-tribenzyloxybenzene.

5-Nitro-1,2,3-tribenzyloxybenzene and 2,6-dibenzyloxy-p-hydroquinone. The product from the oxidation of 500 g. of 1,2,3-tribenzyloxybenzene, consisting of a dry mixture of 5-nitro-1,2,3-tribenzyloxybenzene and 2,6-dibenzyloxy-*p*-hydroquinone, was dissolved with vigorous stirring in 1.8 l. of hot acetic acid, and then 500 ml. of water was added. The temperature was held at 70°, and to the suspension 400 ml. of a saturated solution of sodium hydrosulfite ($Na_2S_2O_4$, 200 g.) was added. The mixture was stirred for 15 minutes at 50°, during which time the suspension changed from a yellow to a light cream color, and then was filtered at 50°. The residue of practically pure 5-nitro-1,2,3-tribenzyloxybenzene was crystallized from acetone. M.p. 141–142° [previously reported 139° (11)]; yield, 165 g. (30%).

Anal. Calc'd for $C_{27}H_{23}NO_5$: C, 73.5; H, 5.3.
Found: C, 73.7; H, 5.3.

The aqueous-acetic acid filtrate was cooled and substantially pure 2,6-dibenzyloxy-*p*-hydroquinone crystallized. Yield, 116 g. (29%). Yields varied from 25–40%, based on 1,2,3-tribenzyloxybenzene used in the preceding step.

Pure hydroquinone was obtained as colorless needles by recrystallizing the crude product from 80% acetic acid-water solution containing a small quantity of sodium hydrosulfite. M.p. 116–117° in accordance with previous reports (11).

The nitro group of 5-nitro-1,2,3-tribenzyloxybenzene was arbitrarily assigned to the 5-position by Baker, Nodzu, and Robinson (11). This was confirmed. 5-Nitro-1,2,3-tribenzyloxybenzene (15 g.) was heated at 65–70° for 1 hour with 100 ml. of acetic acid and 40 ml. of hydrochloric acid (d = 1.19). The reaction mixture was evaporated to dryness at 50°

in vacuo, the residue dissolved in boiling water, decolorized with Norit, and on cooling yellow needles crystallized. M.p. 203–204° [5-nitropyrogallol, reported m.p. 205° (14, 15)].

The 4-nitropyrogallol has the reported m.p. 162° (16).

1,3-Dibenzyloxy-2,5-dimethoxybenzene. This compound was prepared from 2,6-dibenzyloxy-*p*-hydroquinone in 75–95% yields in a 4-hour methylation, using sodium hydroxide and dimethyl sulfate at reflux temperatures. The previous procedure (11) required a low-temperature, 9-hour reaction.

2,5-Dimethoxyresorcinol. 1,3-Dibenzyloxy-2,5-dimethoxybenzene (11) (25.0 g.) was treated with hydrogen at 50 p.s.i. in 150 cc. of methanol, using 2 cc. of concentrated hydrochloric acid and 5.0 g. of 10% palladium charcoal at 50° until a quantitative uptake of hydrogen occurred. The catalyst was filtered off and the methanol removed by distillation. On triturating the residual oil with a little water, a white crystalline dihydrate was obtained, m.p. 62–63°. A quantitative yield was obtained. The compound has been previously prepared by acid hydrolysis (11).

2,4-Dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I). 2,5-Dimethoxyresorcinol (8.6 g.) was reacted in a modified Hoesch synthesis with 8 ml. of chloroacetonitrile and 4 g. of freshly fused zinc chloride in 200 ml. of dry ether at room temperature. Dry hydrogen chloride gas was bubbled through the reaction for 4 hours while the reaction mixture was continuously stirred. The reaction was allowed to stand overnight at room temperature. The ether layer was decanted from the oily precipitate; the oily residue was washed with ether and stirred into water. The water solution was kept at 80° for ½ hour. The crystalline acetophenone derivative separated to a major extent and after cooling was recovered by filtration. Ether extraction of the mother liquor gave a further small quantity of the compound. The 2,4-dihydroxy-3,6-dimethoxy-ω-chloroacetophenone could be recrystallized from boiling water, or after decolorization by carbon in acetone or ether, upon the addition of petroleum ether crystallized in creamy white needles. Yield, 6.3 g. (52%); m.p. 148–149°.

Anal. Calc'd for $C_{10}H_{11}ClO_5$: C, 48.8; H, 4.5.

Found: C, 48.9; H, 4.6.

4,7-Dimethoxy-6-hydroxy-3(2H)-benzofuranone (II). 2,4-Dihydroxy-3,6-dimethoxy-ω-chloroacetophenone (I) (6.2 g.) was refluxed for 20 hours in 250 ml. of 95% ethanol solution with 20 g. of sodium acetate (10). The reaction mixture was concentrated to dryness at 50° under a vacuum, and the residue extracted several times with boiling acetone. After decolorization and with the addition of petroleum ether the furanone crystallized in colorless needles. Yield, 3.1 g. (59%); m.p. 177–178°.

Anal. Calc'd for $C_{10}H_{10}O_5$: C, 57.1; H, 4.8; CH_3O, 29.5.

Found: C, 57.1; H, 5.1; CH_3O 28.2.

5-Acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III). 4,7-Dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) (1.5 g.) was reacted in a Hoesch condensation with acetonitrile. On hydrolysis of the imino complex a yellow precipitate was obtained. This was dissolved in acetone, decolorized with carbon, and precipitated with petroleum ether. Yield, 0.8 g. (44%) of poorly crystallized, yellowish scales; m.p. 80–84°.

Anal. Calc'd for $C_{12}H_{12}O_6$: CH_3O, 24.6. Found: CH_3O, 24.8.

3-Keto-3(2H)-dihydro-6-acetylkhellin or (6-acetyl-3(2H)-4,9-dimethoxy-7-methyl-5-furo[3.2-g][1]-benzopyran-3,5-dione). 5-Acetyl-4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (III) (0.5 g.), 100 ml. of acetic anhydride, and 6 g. of freshly fused sodium acetate were heated in an oil-bath at 180° for 60 hours. After the removal of the excess anhydride the residue was treated with water, and the aqueous suspension was then extracted several times with ether. The ether extract was decolorized with carbon and diluted with petroleum ether when a yellow, crystalline product separated. This was extracted with 5% acetic acid to remove ash, washed with water, and dried. Yield, 200 mg. (32%); m.p. 145–146° (vacuum tube).

Anal. Calc'd for $C_{16}H_{14}O_7$: C, 60.4; H, 4.5; CH_3O, 19.5.

Found: C, 60.3; H, 4.8; CH_3O, 19.0.

3-Acetoxy-6-acetylkhellin or (3-acetoxy-6-acetyl-4,9-dimethoxy-7-methyl-5-furo[3.2-g][1]-

benzopyran-5-one). The mother liquor from the crystallization of 3-keto-3(2H)-dihydro-6-acetylkhellin gave 100 mg. of material on evaporation. Extraction of this residue with boiling hexane (60–72°) gave 3-acetoxy-6-acetylkhellin which crystallized in yellow needles. M.p. 118–120° (vacuum tube); yield, 60 mg.

Anal. Calc'd for $C_{18}H_{16}O_6$: C, 60.0; H, 4.5; CH_3O, 17.2.

Found: C, 60.6; H, 4.5; CH_3O, 16.8.

3,6-Diacetoxy-4,7-dimethoxybenzofuran (IV). Two grams of 4,7-dimethoxy-6-hydroxy-3(2H)-benzofuranone (II) was refluxed with 50 ml. of acetic anhydride and 5 ml. of acetyl-chloride. The reaction mixture was concentrated to dryness, water added, the mixture extracted with ether, and the extract concentrated to an oil. This was crystallized from acetone-petroleum ether or from petroleum ether. Yield, 1.95 g. (70%); m.p. 108–109°.

Anal. Calc'd for $C_{14}H_{14}O_7$: C, 57.2; H, 4.8; CH_3O, 21.1; CH_3CO, 29.4.

Found: C, 57.5; H, 5.0; CH_3O, 21.7; CH_3CO, 29.6.

6-Acetoxy-4,7-dimethoxydihydrobenzofuran (V). 3,6-diacetoxy-4,7-dimethoxybenzofuran (IV) (2.0 g.) in acetic acid was reduced at 50 p.s.i. with hydrogen at 30° using a platinum oxide catalyst. The theoretical amount of hydrogen required to saturate the double bond in the furan ring was taken up in 1 hour. The catalyst was removed and the product concentrated to an oil. This was crystallized from ethanol-petroleum ether, and on recrystallizing twice from the same solvents, fine, colorless needles were obtained, m.p. 89–90°. Mixed melting point with the starting compound, m.p. 108–109°, gave a depression, m.p. 72–78°. Yield, 0.4 g. (23%). In the experiments the yield varied from 0–40%.

Anal. Calc'd for $C_{12}H_{14}O_5$: C, 56.3; H, 6.2; CH_3O, 24.2; CH_3CO, 16.8.

Found: C, 56.6; H, 5.8; CH_3O, 24.4; CH_3CO, 16.1.

4,7-Dimethoxy-6-hydroxydihydrobenzofuran (VI). 6-Acetoxy-4,7-dimethoxy-3-hydroxydihydrobenzofuran (V) (0.8 g.) was saponified in 50 ml. of ethanol with 10 ml. of 5% sodium hydroxide solution at 70° for 3 hours. The recovered product was crystallized from acetone and petroleum ether. Yield, 0.5 g. (82%); m.p. 114–115° [reported m.p. 114° (6)].

Anal. Calc'd for $C_{10}H_{12}O_4$: C, 61.2; H, 6.2; CH_3O, 31.6.

Found: C, 61.3; H, 6.2; CH_3O, 30.7.

Acetylation of 4,7-dimethoxy-6-hydroxydihydrobenzofuran (VI) gave the 6-acetoxy-4,7-dimethoxydihydrobenzofuran monohydrate (V); m.p. 88–89°.

5-Acetyl-6-hydroxy-4,7-dimethoxydihydrobenzofuran (VII). 4,7-Dimethoxy-6-hydroxydihydrobenzofuran (VI) (200 mg.) was reacted in a Hoesch condensation with acetonitrile. The imino complex was hydrolyzed with water at 80° for 1 hour. On cooling, a yellow, crystalline compound separated which was recrystallized from acetone and petroleum ether. Yield, 120 mg. (50%); m.p. 104–104.5° [reported m.p. 105° (6)].

Anal. Calc'd for $C_{12}H_{14}O_5$: CH_3O, 26.1. Found: CH_3O, 25.9.

2-Benzyloxy-4-hydroxy-3,6-dimethoxyacetophenone and 4-benzyloxy-2-hydroxy-3,6-dimethoxyacetophenone (XII). 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (10.8 g.), 21.5 g. of powdered potassium carbonate, and 6.5 g. of benzyl bromide were refluxed in 120 ml. of dry acetone for 1½ hours. The reaction was filtered and the acetone solution concentrated to dryness. A small quantity of water was added and the oily residue crystallized. It was washed with water and dried. Crude yield, 10.5 g. (68%); m.p. 103–105°. Purification and recrystallization from acetone and petroleum ether gave colorless needles with m.p. 105–107°. The mixture could not be separated.

Anal. Calc'd for $C_{17}H_{18}O_5$: C, 67.5; H, 6.0.

Found: C, 68.0; H, 6.2.

2-Benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone and 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII). The mixture of benzyloxyhydroxydimethoxyacetophenones (10.6 g.), obtained in the preceding experiment, was refluxed at 170° (oil-bath) with 400 ml. of acetic anhydride and 50 g. of fused sodium acetate for 70 hours. The excess anhydride was removed under a vacuum, water was added to the residue, the mixture was extracted with ethyl acetate, and the extract concentrated to an oil. This slowly crystallized from ethyl acetate containing an excess of petroleum ether. Crude yield, 11.0 g.

A 6.5-g. sample of the crude mixture obtained above was extracted three times with 100-

ml. portions of hot hexane (60–72°). The first extract, 1.5 g. of 2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone, was repeatedly decolorized in ethyl acetate solution and crystallized from hot petroleum ether as colorless needles. M.p. 113–114°.

Anal. Calc'd for *2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone* $C_{19}H_{20}O_6$: C, 66.1; H, 5.8; CH_3O, 18.1.

Found: C, 65.9; H, 5.6; CH_3O, 18.1.

The second extract, 2.5 g., was a mixture and was not investigated further.

The third extract, 1.0 g., was taken up in hot petroleum ether, decolorized with carbon, and cooled. The pale yellow crystals obtained were washed several times with ethyl ether to yield almost colorless plates. Yield, 0.4 g. of 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII); m.p. 149–150°.

Anal. Calc'd for *3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone* (*XIII*) $C_{21}H_{20}O_6$: C, 68.4; H, 5.5; CH_3O, 16.8.

Found: C, 68.0; H, 5.6; CH:O, 16.8.

3-Acetyl-5,8-dimethoxy-7-hydroxy-2-methylchromone (XIV). Due to the difficulty of separation, 1.0 g. of the crude mixture of 2-benzyloxy-4-acetoxy-3,6-dimethoxyacetophenone and 3-acetyl-7-benzyloxy-5,8-dimethoxy-2-methylchromone (XIII) was treated with 25 ml. of acetic acid and 7 ml. of concentrated hydrochloric acid at 70–80° for 1 hour. The reaction mixture was concentrated to dryness under a vacuum and the residue taken up in ethyl acetate. The addition of petroleum ether caused crystallization of a mixed product. The chromone was less soluble in ethyl acetate at 25° than the debenzylated by-product. Repeated extractions of the mixed crystals with cold ethyl acetate and final recrystallization from hot ethyl acetate and petroleum ether gave colorless plates of the chromone (XIV). Yield, 100 mg.; m.p. 219–220°.

Anal. Calc'd for $C_{14}H_{14}O_6$: C, 60.4; H, 5.0; CH_3O, 22.3.

Found: C, 60.4; H, 4.8; CH_3O, 21.6.

7-Acetoxy-5,8-dimethoxycoumarin. 2,4-Dihydroxy-3,6-dimethoxybenzaldehyde (10 g.), fused sodium acetate (15 g.), and 150 ml. of acetic anhydride were refluxed for 16 hours at an oil-bath temperature of 180°. The excess anhydride was evaporated off *in vacuo*, and the residue was treated with 0.5% sodium hydroxide solution. The resulting solid (8 g.) was dissolved in ethanol; after decolorizing, the solution gave three crystalline fractions.

Fraction (A) was identified as the *coumarin*, m.p. 181–183°, which was recrystallized twice from ethanol. Yield, 2.3 g. (18%); m.p. 186–186.5°.

Anal. Calc'd for $C_{13}H_{12}O_6$: C, 59.1; H, 4.6; CH_3O, 23.5.

Found: C, 59.1; H, 4.5; CH_3O, 22.9.

4,6-Diacetoxy-2,5-dimethoxybenzaldehyde diacetate. Fraction (B) in the preceding synthesis was recrystallized from ethanol. Yield, 1.6 g. (8%); m.p. 131–131.5°.

Anal. Calc'd for $C_{17}H_{20}O_{10}$: C, 53.2; H, 5.2; CH_3O, 16.2; CH_3CO, 44.7.

Found: C, 53.6; H, 5.2; CH_3O, 16.2; CH_3CO, 45.8.

Fraction (C) was impure fraction (B), 4.2 g. (22%).

3-Acetyl-2,5-dimethoxy-4,6-dihydroxybenzaldehyde. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (3.0 g.), zinc cyanide (6.0 g.), and potassium chloride (0.45 g.) were suspended in 100 ml. of dry ether. Anhydrous aluminum chloride (6 g.) in 150 ml. of dry ether was added. Dry hydrogen chloride gas was passed in for 4 hours and the product worked up as for (I). A small quantity crystallized from water. Recrystallization from ether-petroleum ether gave colorless needles. Yield, 0.6 g. (17%); m.p. 86–87°. Yields varied from 0–17%, and replacement of part of the ether by ethyl acetate did not increase the yield.

Anal. Calc'd for $C_{11}H_{12}O_6$: C, 55.0; H, 5.0.

Found: C, 55.1; H, 5.6.

2,4-Diacetoxy-3,6-dimethoxyacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (5.0 g.), acetic anhydride (100 ml.), and sodium acetate (10.0 g.) were heated together in an oil-bath (180°) for 2 hours. The reaction mixture was cooled, poured into water, and after 4 hours extracted with ether. The ether extract deposited two compounds on concentration. One was a yellow, amorphous material which was very soluble in ether. The

solid mixture was washed with cold ether, and the residue was a white, crystalline product which was recrystallized from petroleum ether. Yield, 0.7 g. (10%); m.p. 79–80°.

Anal. Calc'd for $C_{14}H_{16}O_7$: C, 56.8; H, 5.4; CH_3O, 20.9.
Found: C, 57.0; H, 5.8; CH_3O, 20.0.

This compound did not give a reliable acetyl analysis.

2,4-Dicarboxymethoxy-3,6-dimethoxyacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (3.0 g.), ethyl monobromoacetate (3.0 g.), and potassium carbonate (5.0 g.) in 50 ml. of acetone were refluxed for 3 hours and filtered. The residue was extracted with boiling acetone and concentrated *in vacuo* to an oil. The oil was purified by exhaustive precipitation successively from ether-petroleum ether and ethyl acetate. The final precipitate was heated with 5% sodium hydroxide solution and acidified with hydrochloric acid. The purified oil was then crystallized as colorless masses from ethyl acetate-ethyl alcohol by the addition of petroleum ether. Yield, 0.48 g. (10%); m.p. 96°; resolidifies and remelts 143–150° with decomposition.

Anal. Calc'd for $C_{14}H_{16}O_9 + \frac{1}{2}\ C_2H_5OH$: C, 51.2; H, 5.4; apparent CH_3O, 20.9.
Found: C, 51.4; H, 5.2; apparent CH_3O, 21.1, 20.7.

2,4-Dihydroxy-3,6-dimethoxy-ω-bromoacetophenone. 2,4-Dihydroxy-3,6-dimethoxyacetophenone (XI) (4.0 g.) and N-bromosuccinimide (4.0 g.) were refluxed in 100 ml. of carbon tetrachloride for 2 hours. The reaction mixture was concentrated to dryness *in vacuo*, dissolved in ethanol, and poured into an excess of water. The alcohol was distilled off, and the product crystallized directly from water. It was decolorized in acetone solution and recrystallized from water, m.p. 158–159°; from acetone and an excess of petroleum ether, m.p. 159–160°; yield, 3.5 g. (64%).

Anal. Calc'd for $C_{10}H_{11}BrO_5$: C, 41.3; H, 3.8; CH_3O, 21.3.
Found: C, 41.5; H, 3.7; CH_3O, 21.1.

2,4-Dihydroxy-3,6-dimethoxypropiophenone. This compound was obtained in 63% yield from a Hoesch condensation, using propionitrile (15.0 ml.) and 2,5-dimethoxyresorcinol (12.0 g.), m.p. 126–127°.

Anal. Calc'd for $C_{11}H_{14}O_5$: C, 58.4; H, 6.2; CH_3O, 27.4.
Found: C, 58.0; H, 6.2; CH_3O, 26.3.

3,4,5-Tribenzyloxyaniline hydrochloride. 5-Nitro-1,2,3-tribenzyloxybenzene (50.0 g.) was added to 200 ml. of boiling ethanol, and 50 ml. of a saturated solution of sodium hydrosulfite ($Na_2S_2O_4$) was added. The suspension was then boiled ½ hour with stirring and filtered into water containing concentrated hydrochloric acid. The hydrochloride crystallized as colorless needles and was recrystallized by solution in boiling ethanol, decolorization with carbon, and filtration into 50 ml. of concentrated hydrochloric acid. Yield, 33.5 g. (66%); m.p. 165–169°.

Anal. Calc'd for $C_{27}H_{25}NO_3 \cdot HCl$: C, 72.3; H, 5.8; N, 3.2.
Found: C, 72.1; H, 5.9; N, 3.3.

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SUMMARY

Two new analogs of khellin, 3-keto-3(2H)-dihydro-6-acetylkhellin and 3-acetoxy-6-acetylkhellin, some new benzofuranones, dihydrobenzofurans, and some new chromones have been prepared.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

BRANCHED-CHAIN FATTY ACIDS. XV. SYNTHESES OF DIMETHYL-OCTADECANOIC ACIDS. FURTHER STUDY OF THE CADMIUM REACTION AND OF THE HUANG-MINLON REDUCTION

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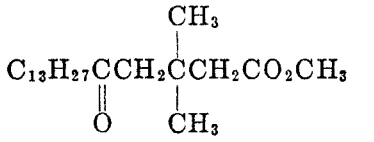
In order to permit further study of the effect of *alpha* and *beta* substituents on the rate of amide hydrolysis (1), 2,2-dimethyl- and 3,3-dimethyl-octadecanoic acid have been prepared, and a second synthesis of 2,3-dimethyloctadecanoic acid (2) has been investigated.

2,2-Dimethyloctadecanoic acid has previously been prepared by two groups of investigators. Buu-Hoï and Cagniant (3) prepared the amide by alkylation of isobutyrophenone with hexadecyl bromide, and cleavage of the resultant ketone with sodium amide. Hydrolysis yielded the acid, m.p. 50–51°. Birch and Robinson (4), who prepared the acid similarly except that stearophenone was dialkylated with methyl iodide, reported m.p. 42°. Later, Polgar, Robinson, and Seijo (5) prepared the acid by alkylation of methyl 2-methyloctadecanoate, and reported m.p. 48–49°. We have prepared this acid by dimethylation of octadecanenitrile, using lithium diethylamide according to Ziegler and Ohlinger (6). Hydrolysis of the disubstituted nitrile yielded acid of m.p. 51–55°. Although this value is higher than reported by the previous workers it was raised slowly by recrystallization, and no material of a constant m.p. was obtained in this way. Since introduction of the second methyl group is slow and difficult, it was suspected that the 2,2-dimethyloctadecanoic acid was contaminated with 2-methyloctadecanoic acid which would be essentially impossible to remove by crystallization or distillation. Since it has previously been shown (1) that 2,3-dimethyloctadecanamide is hydrolyzed much more slowly than the 2-methyl amide, and 3-methyloctadecanamide is hydrolyzed more slowly than the 2-methyl isomer, our crude 2,2-dimethyloctadecanamide was saponified and evolution of ammonia followed as previously described (1). When the rate of ammonia evolution indicated essentially complete hydrolysis of an amide initially hydrolyzing more rapidly, the saponification was interrupted and the mixture of amide and acid was separated by the use of Amberlite IRA-400 ion-exchange resin.[1] Recrystallization of the amide passing through the anion exchange resin yielded material of m.p. 85.5–86.0°, a value higher than previously reported (3, 4). Hydrolysis of the amide with potassium hydroxide in diethylene glycol yielded acid of m.p. 57.1–58.0°. It appears, then, that the 2,2-dimethyloctadecanoic acid prepared by Robinson and co-workers (4, 5) contained large

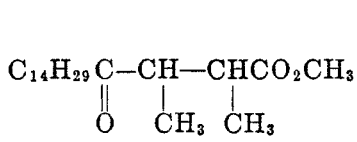
[1] Separation of fatty acids from neutral material has been traditionally difficult and tedious. Not only do the soaps cause stable emulsions but they also dissolve neutral material and the whole remains in the aqueous phase. Introduction of the strong anion exchange resins has rendered this separation very simple and rapid, and greatly facilitates the obtaining of pure samples of fatty acids. We are indebted to the Resinous Products Division, Rohm and Haas Company, for supplying us with samples of Amberlite IRA-400.

quantities of 2-methyloctadecanoic acid, but this could hardly have been the impurity which lowered the m.p. of the sample prepared by Buu-Hoï and Cagniant (3), for the latter workers alkylated isobutyrophenone with hexadecyl bromide. This is of interest, since the sample of 2,2-dimethyloctadecanoic acid prepared by the French workers was reported as producing typical tubercular lesions on injection in animals, whereas the sample prepared by the English workers did not (5). It is apparent that samples of fatty acids used for biological testing should be purified with great care, and it seems probable that deductions which have been based on such tests might well be subjected to further scrutiny.

3,3-Dimethyl- and 2,3-dimethyl-octadecanoic acid were prepared by reduction of keto esters, I and II, respectively. The keto esters were prepared from appropriate cadmium reagents (7) and ester acid chlorides. The ester acid



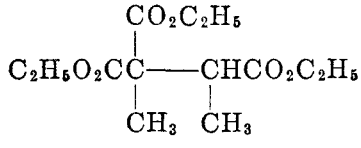
I



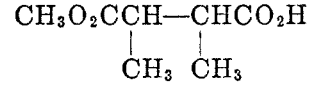
II

chloride needed for the preparation of ester I is that of β,β-dimethylglutaric acid, and this acid was readily obtained by hypohalite oxidation of dimedone according to Walker and Wood (8). No complications were encountered in converting this dibasic acid to the anhydride, the half ester, and the ester acid chloride.

The ester acid chloride needed for the preparation of ester II is that of α,α'-dimethylsuccinic acid. Of the various methods which have been used for the preparation of this acid, probably the most promising is that of Bone and Sprankling (9), who alkylated ethyl cyanoacetate first with ethyl α-bromopropionate, then with methyl iodide to yield diethyl α-cyano-α,α'-dimethylsuccinate. Hydrolysis and decarboxylation yielded the desired acid. In the present work, a similar but somewhat shorter path was used, in that diethyl methylmalonate was alkylated with ethyl α-bromopropionate to yield the triester, III.



III



IV

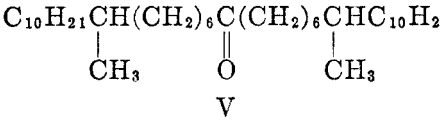
When this alkylation was carried out in ethanol, using sodium ethoxide as the metalating agent, the yield was only 45% but when potassium *tert*-butoxide in *tert*-butyl alcohol was used as the metalating agent the yield was increased to 85%. The crude dimethylsuccinic acid, obtained by hydrolysis and decarboxylation of ester III, was converted to the anhydride and this was allowed to react with excess methanol to yield the half ester, IV, but this half ester appeared to revert to anhydride on standing or on heating for distillation. For

synthesis of keto ester II, the crude, undistilled half ester IV was converted to the acid chloride below 40°, and this was used directly for reaction with di-*n*-tetradecylcadmium.

The present preparation of 2,3-dimethyloctadecanoic acid was undertaken in an effort to improve the very low yield obtained in the earlier preparation (2), but the present synthesis is only a slight improvement, for reduction of the keto ester II has not been accomplished in yields greater than 26%. Since ester I, exhibiting a similar amount of steric hindrance, was reduced in good yield by the Huang-Minlon procedure (10), the difficulty in reducing ester II appears to be associated with the γ-position of the keto group. Previously, it has been reported (11) that reduction of methyl 4-keto-8-methyloctadecanoate gave only 36% yield, and in the present work further study of this γ-keto ester has raised the yield to only 48%. Reduction of methyl 4-ketoöctadecanoate yields 75% of nearly pure stearic acid, and reduction of methyl 4-keto-8-methyltetradecanoate (12) has given a 68% yield. Thus, the best yields obtained by us for reduction of γ-keto esters are comparable with the lowest yields obtained for reduction of other types, and presence of steric hindrance in the γ-keto esters leads to much lower yields. A very highly hindered δ-keto ester has been reduced by this method in 41.5% yield (13).

The low yields obtained in the reduction of γ-keto esters are accompanied by considerable residues from distillation of the reduced esters. When the heating period for reduction of ester II was extended, in an effort to improve the yield, the yield was lowered and the distillation residue was larger. The distillation residues from several preparations were investigated in hopes of discovering the cause of the low and variable yields received in these reductions, and some findings of general interest may be reported.

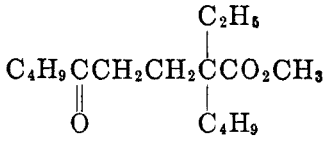
When the stearic acid obtained by reduction of methyl 4-ketoöctadecanoate was separated from neutral material by use of Amberlite IRA-400, the crude acid eluted from the column melted at 66–68.5°, and one crystallization gave an 85% recovery of pure stearic acid, m.p. 68.9–69.5°. Thus, the by-products are nearly entirely neutral material. From the distillation residues after reduction of methyl 4-keto-8-methyloctadecanoate there was isolated a hydrocarbon, $C_{37}H_{76}$, presumably 11,25-dimethylpentatriacontane resulting from reduction of the ketone V. The ketone would be formed during heating of the initial product,



V

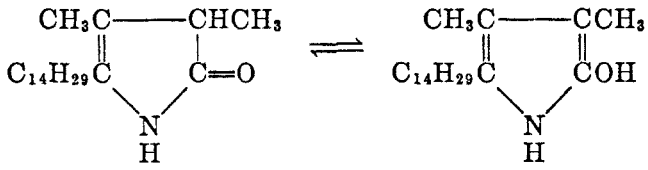
8-methyloctadecanoic acid, with alkali, as is done in this type of reduction. One of us (13) has previously recommended for aliphatic keto acids a longer heating period and higher temperature than originally used by Huang-Minlon (10). This suggestion resulted from the fact that keto ester VI was reduced in 90% yield under the more drastic conditions. It is now apparent that the high yield in this instance is dependent on the fact that the keto in ester VI is unhindered

but the acid group is highly hindered, the most favorable possible combination of circumstances for this type of reduction. The conditions originally proposed by Huang-Minlon are adequate in the aliphatic series for reduction of all but highly hindered keto groups, and more drastic conditions result in lower yield or less pure product.



VI

Since it is known (14) that γ-keto acids give a cyclic hydrazide with hydrazine, it was suspected that the difficulty in reducing the γ-keto acids might be associated with an abnormal reaction of this intermediate, although the cyclic hydrazide from levulinic acid decomposes normally on heating with sodium ethoxide, to give valeric acid (14). Steric hindrance might prevent normal hydrolysis of the hydrazide, and permit side reactions to become more significant. From distillation residues after reduction of keto ester II, there was isolated a solid compound containing nitrogen and giving an analysis in agreement with the formula, $C_{20}H_{37}NO$. The unsaturated lactam or pyrollone shown in formula VII has such a composition, and the possibility of this structure is supported



VII

by the report (15) that hydrazones may be reduced to amines under certain conditions. Carrière (16) has prepared pyrrolones by saponification of unsaturated γ-amino esters with concentrated potassium hydroxide, and Almström (17) has prepared pyrrolones directly from γ-keto acids and aniline. Compound VII was saponified little, if any, by heating for 46 hours with alcoholic potassium hydroxide, but the structure indicated would be expected to be highly hindered.

In some runs during the preparation of keto esters I and II, very low yields (5–15%) were obtained in the cadmium reaction. It has been established that the low yields were caused by thermal cracking of the dialkylcadmium reagent by heating on a steam-bath. This difficulty is less pronounced with lower molecular weight alkyls, but in all cases the residue, obtained after ether is distilled from the cadmium reagent, should not be heated; instead benzene should be added and the reaction with the acid chloride completed at once. It seems highly probable that the erratic yields obtained from cadmium reactions in various laboratories have been caused by too much heating of the cadmium reagent after distillation of ether. Prolonged boiling in ether appears to cause little, if any, cracking of cadmium reagents from primary alkyls. The principal product

of reactions in which the cadmium reagent has been overheated is a hydrocarbon corresponding to the alkyl radical, and this has been shown by hydrogenation to be an approximately equimolar mixture of alkane and alkene. This would result from disproportionation of the radicals initially formed by cracking of the organometallic reagent.

EXPERIMENTAL

All melting points are corrected, and all boiling points are uncorrected. Analyses were performed by the Microanalytical Division of the Department of Chemistry and Chemical Engineering of the University of California. Unless otherwise specified, all distillations were through a 65-cm. Podbielniak type column which had a simple tantalum wire spiral and a partial reflux head.

2,2-Dimethyloctadecanoic acid. Of various modifications of this preparation which were investigated, the following appears best. To 485 ml. of 0.652 molar phenyllithium (0.315 mole), prepared as described by Rapoport and Williams (18), in an atmosphere of nitrogen, there was added during 40 minutes, with stirring and cooling in ice, 32 ml. (0.32 mole) of diethylamine in 50 ml. of ether. Immediately after addition was complete, the Gilman test (19) was negative. Approximately half of this solution of lithium diethylamide was removed and stored under nitrogen. To the remaining half there was added without cooling a solution of 31.9 g. (0.12 mole) of octadecanenitrile (fractionated, b.p. 180–182° at 2 mm.) in 50 ml. of ether, during 30 minutes. After the first five minutes a white precipitate began to separate and the Gilman test had become positive. After addition was complete, stirring was continued at room temperature for one hour.

To the solution of the lithium derivative of octadecanenitrile, cooled in an ice-bath, there was added dropwise with stirring a cold solution of 19 g. (0.20 mole) of methyl bromide in 25 ml. of ether. The Gilman test was negative as soon as addition was complete.

To the reaction mixture there was next added dropwise the other half of the lithium diethylamide. After stirring at room temperature for two hours, addition of a second 19 g. of methyl bromide was made, with cooling. After stirring had been continued for 30 minutes at room temperature and 45 minutes under reflux, the reaction mixture was washed with water, 2 *N* hydrochloric acid, and saturated aqueous sodium chloride solution. Ether was removed by distillation, the last traces at reduced pressure.

The crude nitrile was dissolved in 375 ml. of concentrated sulfuric acid, and the solution was stirred for 20 minutes in an oil-bath at 100°. The cooled solution was poured into 2.5 liters of ice and water, and the precipitated amide, obtained in nearly quantitative yield, was filtered, washed, and dried. The crude amide was heated in a steel flask in 600 ml. of 95% ethanol containing 33 g. of potassium hydroxide, the flask being fitted with a reflux-distillation head of the type described by Cason and Wolfhagen (1). Ammonia evolution was followed as described by these authors. At the end of 80-hours heating under reflux, 44% of the theoretical amount of ammonia had been titrated, and the rate of ammonia evolution had dropped to less than one half the initial value of about 1% per hour. At this point, most of the alcohol was distilled, the reaction mixture was diluted with water and acidified, and the mixture of amide and acid was extracted with ether. The wet ether solution was passed through a column of 225 g. (wet weight) of Amberlite IRA-400 which had previously been washed with alkali and then with water until the eluate was neutral. The eluate was passed through the column a second time, then the column was washed with two 100-ml. portions of ether, the second portion leaving only 0.2 g. of residue on evaporation. Removal of ether from the total eluate left a residue of 21.1 g. of amide, m.p. 80–84°. After two crystallizations from methanol and two from hexane there was obtained 14.8 g. (39% yield from octadecanenitrile) of *pure 2,2-dimethyloctadecanamide*, m.p. 85.5–86.0° [literature, m.p. 81° (4), 85° (3)].

Elution of the ion-exchange column with a mixture of ether, methanol, and aqueous hydrochloric acid yielded 15.3 g. of mixed acid which was not further investigated.

A 5-g. sample of the amide was hydrolyzed by heating for four hours at a bath temperature of 210–220° with a mixture of 30 ml. of diethylene glycol and 3.6 g. of potassium hydroxide. The theoretical amount of ammonia was titrated. Dilution with water and acidification of the cooled reaction mixture gave a quantitative yield of crude acid which was esterified by heating under reflux for six hours with 25 equivalents of methanol containing 10% by weight of concentrated sulfuric acid. Distillation gave 4.7 g. (88% from amide) of *methyl 2,2-dimethyloctadecanoate*, b.p. 172–172.5° (3 mm.) For analysis, there was used a center cut, n_D^{24} 1.4438.

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.
Found: C, 77.22; H, 12.93.

By hydrolysis of the ester and three crystallizations from acetone, there was obtained *2,2-dimethyloctadecanoic acid*, m.p. 57.1–58.0°.

Anal. Calc'd for $C_{20}H_{40}O_2$: Equiv. wt., 312.5. Found: Equiv. wt., 314.0.

The *p-bromoanilide* was prepared as has been described (13). After crystallization from benzene, there was obtained a 67% yield of fine needles, m.p. 84.9–85.4°.

Anal. Calc'd for $C_{26}H_{44}BrNO$: N, 3.00. Found: N, 2.90.

2,2-Dimethyloctadecanenitrile was isolated from a dimethylation of octadecanenitrile carried out similarly to that described above. The crude nitrile obtained from the reaction was distilled, b.p. 175–180° (1.6 mm.), and the distillate was crystallized repeatedly from methanol until there was isolated a small yield of colorless blades of constant m.p. 37.0–38.6°.

Anal. Calc'd for $C_{20}H_{39}N$: N, 4.77. Found: N, 4.68.

The quantity of nitrile thus isolated was too small to make this method of purification practical, but the purity of the final product was established by conversion of a sample to the amide by use of concentrated sulfuric acid, as described above. After crystallization from hexane, the amide so obtained melted at 85.5–86.0°, in agreement with the best sample obtained by the purification method described above.

Methyl hydrogen β,β-dimethylglutarate. β,β-Dimethylglutaric anhydride was prepared by heating 72 g. (0.45 mole) of β,β-dimethylglutaric acid[2] (8) with three mole-equivalents of acetyl chloride on a steam-bath for 90 minutes. The reaction mixture was treated with about 30 ml. of petroleum ether (b.p. 30–70°) and allowed to crystallize. After cooling in an ice-bath, there was collected 51.1 g. of anhydride, m.p. 126.0–126.5°, not raised by further crystallization [literature (20), m.p. 124°]. By evaporation of the mother liquor and recrystallization of the residue from anhydrous ether, there was obtained an additional 10.7 g. of anhydride in three crops, the least pure melting at 123–125°; total yield, 61.8 g. (97%).

The half ester was best prepared by heating under reflux for five hours a mixture of 21.6 g. (0.152 mole) of the anhydride and 18.5 ml. (0.45 mole) of methanol. Distillation yielded 5 g. of diester (distilling principally at 81° at 6 mm.) and 21.2 g. (80%) of half ester, b.p. 126–127° (4.5 mm.).

Anal. Calc'd for $C_8H_{14}O_4$: Equiv. wt., 174.2. Found: Equiv. wt., 172.8.

When an attempt was made to prepare this half ester as has been described for methyl hydrogen succinate (21), much anhydride remained unreacted on account of steric hindrance. It is best to use excess methanol and an adequate heating time in order to insure reaction of all anhydride, for diester is readily separable from half ester by distillation whereas anhydride is not.

γ-Carbomethoxy-β,β-dimethylbutyryl chloride was prepared by allowing 56.8 g. (0.326 mole) of the above-described half ester to stand overnight with 77.6 g. (0.65 mole) of thionyl

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[2] We are indebted to Mr. Charles N. Whiteside for preparation of this acid.

chloride. On distillation there was obtained 57.8 g. (92%) of ester acid chloride, b.p. 75–76° (3 mm.).

Anal. Calc'd for $C_8H_{13}ClO_3$: Equiv. wt., 96.3. Found: Equiv. wt., 96.2.

Methyl 3,3-dimethyl-5-ketoöctadecanoate (I). A Grignard reagent was prepared in an atmosphere of nitrogen in the usual manner from 4.9 g. (0.2 mole) of magnesium turnings and 52.7 g. (0.2 mole) of *n*-tridecyl bromide (22), and this was converted to the cadmium reagent with 29.2 g. (0.16 mole) of anhydrous cadmium chloride. Ether was distilled until distillation on a steam-bath became slow, then 65 ml. of benzene was added immediately, and an additional 10 ml. of distillate was collected. This mixture was cooled to about 20°, and then there was added in one portion to the stirred mixture a solution of 19.3 g. (0.1 mole) of γ-carbomethoxy-β,β-dimethylbutyryl chloride in 70 ml. of benzene. The temperature of the mixture rose rapidly to 40° and was maintained at 38–40° for about 80 minutes, cooling being necessary during the first 20 minutes. The temperature was then raised to 65° during one hour, after which time the mixture was worked up as usual (7). On distillation, there was obtained 14.5 g. of fore-run consisting mostly of *tridecane*, b.p. 115° (15.5 mm.), and 30.1 g. (88%) of *keto ester* I, b.p. 191–193° (2.5 mm.), n_D^{25} 1.4490.

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.
Found: C, 74.06; H, 11.85.

In a run similar to that described above, the cadmium reagent remaining after distillation of ether was heated on a steam-bath for about 75 minutes in order to remove as much ether as possible. When the reaction products were distilled, there was less than 10% of keto ester and 28.8 g. of material distilling largely at about 111° (13 mm.). This was shown to be a mixture of *tridecane* and *tridecene* in the following manner.

The material was redistilled and a center cut taken, b.p. 116.5–117° (17.5 mm.), n_D^{22} 1.4292. On hydrogenation of a 5-g. sample of this material with commerical platinum oxide catalyst, there was absorbed 347 ml. of hydrogen (corrected to 0° and for hydrogen absorbed by catalyst). This corresponds to 56% of alkene in the sample. The hydrocarbon recovered after hydrogenation had b.p. 120–121° (21 mm.), n_D^{22} 1.4256. From the literature (23, 24), for tridecane, b.p. 114° (15 mm.), 130° (30 mm.), n_D^{20} 1.4266; for tridecene, n_D^{20} 1.4340. Thus, the calculation of tridecene in the original sample, from index of refraction, gives 54%, in good agreement with the value obtained by hydrogenation.

3,3-Dimethyl-5-ketoöctadecanoic acid, obtained by saponification of its ester, after two crystallizations from hexane and one from acetone, melted at 48.5–48.9°.

Anal. Calc'd for $C_{20}H_{38}O_3$: C, 73.57; H, 11.73; Equiv. wt., 326.5.
Found: C, 73.75; H, 11.64; Equiv. wt., 325.7.

Methyl 3,3-dimethyloctadecanoate. A 47.3-g. sample of keto ester I was reduced as described by Huang-Minlon (10) except that the final heating period was for seven hours at 218–221°. The crude acid, obtained by dilution with water and acidification of the cooled reaction mixture, was esterified by heating with 25 equivalents of methanol containing 10% by weight of sulfuric acid. Distillation yielded 35.6 g. (78.5% from keto ester) of reduced ester, b.p. 176.5–180° (2.5 mm.). For analysis, there was used a center cut, b.p. 178° (2.5 mm.), n_D^{21} 1.4475.

Anal. Calc'd for $C_{21}H_{42}O_2$: C, 77.24; H, 12.97.
Found: C, 77.81; H, 12.91.

3,3-Dimethyloctadecanoic acid was obtained by saponification of 32.8 g. of the ester. After one crystallization from acetone, there was obtained 28.1 g. (89.5%) of m.p. 41.9–43.8°, and after two further crystallizations there was obtained 24.7 g. with constant m.p. 44.0–44.8°.

Anal. Calc'd for $C_{20}H_{40}O_2$: Equiv. wt., 312.5. Found: Equiv. wt., 313.3.

The *amide*, prepared essentially as described previously (2), after four crystallizations from methanol, had the constant m.p. 57.8–58.5°.

Anal. Calc'd for $C_{20}H_{41}NO$: N, 4.50. Found: N, 4.41.

The *p-bromoanilide*, prepared by the usual procedure (13), was crystallized three times from methanol to give platelets with the constant m.p. 89.4–89.7°.

Anal. Calc'd for $C_{26}H_{44}BrNO$: N, 3.00. Found: N, 3.07.

Diethyl α-carbethoxy-α,α'-dimethylsuccinate (III). In 1200 ml. of *tert*-butyl alcohol (distilled from sodium) was dissolved 35.8 g. (0.92 mole) of potassium, and to the cooled solution there was rapidly added 163.8 g. (0.94 mole) of diethyl methylmalonate (prepared from ethyl oxalpropionate). To this mixture there was added with stirring, during about five minutes, 140.8 g. (0.78 mole) of ethyl α-bromopropionate, and the mixture was heated under reflux for two hours. After most of the alcohol had been distilled from the mixture, with stirring, the residue was shaken out with water and benzene. From the benzene extract there was obtained 181.2 g. (85%) of *triester* III, b.p. 151–152° (12 mm.) [literature (25), b.p. 190° (50–60 mm.), 279° (760 mm.)]. In a 5-mole run, the yield was 80%.

α,α'-Dimethylsuccinic anhydride. Triester III (162 g.) was hydrolyzed by heating under reflux, with stirring, with a mixture of 450 ml. of water and 450 ml. of concentrated hydrochloric acid until the mixture had become homogeneous (usually 4–6 hours). The reaction mixture was then distilled to dryness, and the residue was decarboxylated by heating at 180–200° for about one hour. The crude acid was heated on the steam-bath for one hour with 120 ml. of acetic anhydride. Distillation of the mixture gave 52.1 g. (68.5%) of anhydride, b.p. 95–98° (5 mm.), which set to a semi-solid on standing. No effort was made to separate this mixture of stereoisomers (26).

Methyl 4-keto-2,3-dimethyloctadecanoate (II). This preparation was carried out essentially as described for preparation of the isomeric ester, I, starting with 55.4 g. (0.2 mole) of *n*-tetradecyl bromide. For preparation of the required ester acid chloride, 12.8 g. (0.1 mole) of α,α'-dimethylsuccinic anhydride was heated under reflux for two hours with 5 ml. of methanol, excess methanol was removed in a vacuum, and the residual crude half ester was allowed to stand overnight with 25 ml. of thionyl chloride. Excess thionyl chloride was removed at reduced pressure, and from the residue were distilled at reduced pressure two 25-ml. portions of benzene. The residual acid chloride was used for the cadmium reaction. The yield of *keto ester* II was 22.0 g. (64.5%), b.p. 196–197° (3 mm.).

Anal. Calc'd for $C_{21}H_{40}O_3$: C, 74.07; H, 11.84.
Found: C, 73.67; H, 11.53.

2,3-Dimethyloctadecanoic acid. A 15.7-g. sample of keto ester II was reduced by the modified Huang-Minlon procedure previously described (13), and the crude reaction product was esterified by heating for five hours with 40 ml. of methanol and 3 ml. of concentrated sulfuric acid. Distillation yielded 3.9 g. (26%) of discolored methyl 2,3-dimethyloctadecanoate, b.p. 181–184° (3 mm.). In another run, which was carried out in an atmosphere of nitrogen, the heating period at 210–220° was extended to 30 hours, and the yield was only 12%.

A total of 5.9 g. of ester was saponified with alcoholic potassium hydroxide. After the acid had been crystallized three times from acetone, there was obtained 0.37 g. of one racemic form, m.p. 64.5–64.7°. The best sample previously obtained (2) melted at 63.0–64.0°, and a mixture of the two samples melted at 63.3–64.2°.

Investigation of the Huang-Minlon reduction. A. *Reduction of methyl 4-ketooctadecanoate* (5.0 g.) was carried out as described by Huang-Minlon (10), using potassium hydroxide and diethylene glycol. The final heating period was for 5 hours at 195–200°. After the cooled reaction mixture had been diluted with water and acidified it was extracted with ether, and the wet ether extract was passed through a column of the basic form of Amberlite IRA-400. The column was washed with 400 ml. of ether, then the acid was eluted with a mixture

of 200 ml. of ether, 80 ml. of 95% alcohol, and 40 ml. of concentrated hydrochloric acid. The column was washed with an additional 150 ml. of ether. After removal of hydrochloric acid from the eluate by washing with water, the solvent was evaporated to dryness to yield 3.4 g. (75%) of stearic acid, m.p. 66–68.5°. One crystallization from acetone gave 2.85 g. of acid, m.p. 68.9–69.5°.

The material originally passing through the ion-exchange column weighed 0.58 g. and was shown by titration to be neutral.

When a similar run was made, except that the heating period was 7 hours at 215–220°, the same yield of crude acid was obtained, but the m.p. was 59–67°, and two crystallizations were required to yield pure stearic acid.

B. About 20 g. of *residues* from distillation of the ester from several reductions of *methyl 4-keto-8-methyloctadecanoate* were distilled in a von Braun flask to yield 6.4 g. of greenish-yellow material, b.p. 160–230° (1 mm.), which began to crystallize after standing several days. After repeated crystallization from ethanol, hexane, and acetone, there were obtained clusters of small needles with the constant m.p. 41.5–41.7°. The analysis is in agreement with that for *11,25-dimethylpentatriacontane.*

Anal. Calc'd for $C_{37}H_{76}$: C, 85.29; H, 14.71.
Found: C, 85.41; H, 14.70.

C. From *reduction* of 7.2 g. of *ester II* and esterification of the product, there was obtained 1.5 g. of semi-solid, b.p. 200–220° (0.5 mm.). After repeated crystallization from acetone and hexane there was obtained 0.1 g. of colorless needles with the constant m.p. 70.8–72.2°. The analysis is in agreement with the structure indicated in *formula VII.*

Anal. Calc'd for $C_{20}H_{37}NO$: C, 78.11; H, 12.12; N, 4.55.
Found: C, 78.32; H, 12.37; N, 4.58.

A 0.1-g. sample of this substance of m.p. 64–68° was refluxed for 46 hours in 10% alcoholic potassium hydroxide. On dilution of the alkaline solution there separated a solid of m.p. 62–67°, and acidification of the alkaline filtrate gave only a barely perceptible trace of oil which did not solidify.

SUMMARY

Syntheses have been developed for 2,3-dimethyl-, 2,2-dimethyl-, and 3,3-dimethyl-octadecanoic acid. Of these acids, the last-mentioned has not been previously prepared, and the second has not been previously prepared in a pure state.

A further study has been made of side reactions occurring in the cadmium reaction for preparation of ketones and in the Huang-Minlon modification of the Wolff-Kishner reduction.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

ADDITION OF HYDROGEN CHLORIDE TO *p*-BENZOQUINONES. FAILURE OF ACETYL CHLORIDE TO REACT WITH *p*-BENZOQUINONE

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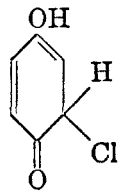
There have appeared numerous reports (1) of the preparation of halogenated *p*-benzoquinones by oxidation of halohydroquinones obtained from the reaction of halogen acid with *p*-benzoquinones. These reports are conflicting in several respects, especially as regards the ease with which a pure haloquinone may be isolated. There is also an uncertainty as to whether the reaction is best carried out with aqueous halogen acid or with anhydrous hydrogen halide in dry chloroform or other solvent. In addition, no structures have been assigned to some of the products obtained (1). The present investigation was undertaken in an effort to clarify this situation and to determine the general utility of this method of preparation of halogenated *p*-benzoquinones.

Clark (2) has suggested that the reaction of a halogen acid with quinone proceeds by way of initial oxidation of the halogen acid, to give hydroquinone and halogen, followed by substitution of halogen in the hydroquinone; however, his data appear not to support this suggestion. It seems more reasonable to assume that halogen acid adds in a 1,4-manner to quinones, as has been demonstrated (3, 4) to be the mechanism of the reaction of numerous other reagents with quinones. Tautomerism of the addition product (I) gives the halohydroquinone, which may be oxidized by the starting quinone. The resultant haloquin-



I

one may add halogen acid, thus giving rise to dihalohydroquinone. Although numerous investigators (5–8) have reported preparation of haloquinones by oxidation of hydroquinones obtained in this manner, and have mentioned no difficulty with separation of more highly halogenated products, others (9-11) have reported that separation of the more highly halogenated quinones was difficult. Since it has been reported (8) that the reduction potential of hydroquinone is just slightly higher than that of chlorohydroquinone, some dihalohydroquinone would be expected.

In the present work, there has been studied the addition of hydrogen chloride to *p*-benzoquinone, *p*-toluquinone, 3-chloro-, 5-chloro-, and 6-chloro-toluquinone,

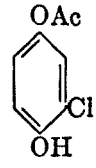
and addition of hydrogen bromide to 6-bromotoluquinone. From the results obtained, it seems safe to state that polyhalogenated quinones are always obtained and that the separation of these less-soluble compounds from the monohalogenated products is usually exceedingly difficult, if at all possible. The structures tentatively assigned (1) to certain of the compounds obtained by addition of halogen acids to halotoluquinones should be disregarded, for most of the compounds in question were probably not pure. Work is now in progress on synthesis, by unequivocal methods, of the dichlorotoluquinones.

The only satisfactory preparation which has been encountered by us is that which we first investigated, 5-chlorotoluquinone (12). In contrast with the report of Clark (2), we were not able to isolate pure chlorohydroquinone from the addition of hydrogen chloride to quinone. The best sample obtainable by us from this reaction melted at 100.9–101.9°, which is in agreement with the value of 101–102° reported by Conant and Fieser (8), but well below the melting point of 106.0–106.8° which was obtained by us for chlorohydroquinone prepared by reduction of an authentic sample of chloroquinone. For this purpose, chloroquinone was prepared by electrolytic reduction of *o*-nitrochlorobenzene and oxidation of the resultant 2-chloro-4-hydroxyaniline. It was also possible to isolate pure chloroquinone after oxidation of the impure chlorohydroquinone.

It has been frequently reported (1) that when halogen acid is added to a quinone already substituted with an *ortho, para*-director the hydroquinone obtained bears the substituents in the 2,5-relationship. It is also a fact that numerous similar reactions (13) have always yielded 2,5-disubstituted hydroquinones. It should be mentioned, however, that a few investigators (2, 14–16) have claimed the presence of small amounts of the 2,6-isomer. One report (14) of the isolation of 2,3-dichlorohydroquinone from the reaction of hydrogen chloride with chloroquinone could not be confirmed by Hollander (15). It seems generally agreed that the 2,5-isomer is the chief product, and difficulty with separating other isomers is definitely minor in comparison with separating more highly halogenated products.

From our data, no conclusion may be reached as to whether addition is best carried out in aqueous medium or in a dry organic solvent such as chloroform. For example, addition to toluquinone is best carried out in aqueous hydrochloric acid, whereas with benzoquinone best results are obtained in chloroform solvent.

Since preparation of halogenated hydroquinones by addition of halogen acids to quinones is of such limited and uncertain scope, the reported (17–20) addition of acetyl chloride to quinones appears an attractive route to the same compounds. If such an addition to benzoquinone should occur, the initial addition product



II

would be the monoacetyl chlorohydroquinone, II, which would not be oxidized, in anhydrous medium, to the quinone; hence, there would be no difficulty with introduction of additional halogen atoms. This course of the reaction seems inconsistent with one report (20) that both mono- and di-chloro derivatives of diacetyl hydroquinone were obtained. Actually, we have found that carefully purified acetyl chloride in dry equipment does not react with quinone, but vigorous reaction ensues on addition of acetic acid. Thus, initial attack is by hydrogen ion on the quinone oxygen, and this reaction is no different from a normal addition of hydrogen chloride to quinone except that the hydroquinone is acetylated in the reaction medium. The latter reaction furnishes adequate hydrogen chloride so that only catalytic amounts of acid are necessary to initiate the addition reaction by establishing equilibrium with acetic anhydride and hydrogen chloride. A mixture of the mono- and di-halogenated derivatives was obtained.

EXPERIMENTAL

All melting points are corrected. Analyses are by the Microanalytical Division of the Department of Chemistry and Chemical Engineering of the University of California.

6-Bromotoluquinone was prepared by the general procedure described for 6-chlorotoluquinone (12) except that the oxidation in a 1-mole run was carried out in two liters of 70% aqueous acetic acid. The yield of steam-distilled quinone was 127 g. (63%), which after one crystallization from 60% aqueous alcohol melted at 91–93.5°. The best sample obtained by further crystallization melted at 93.6–93.9°.

3-, 5-, and 6-chlorotoluquinones were the samples previously described (12).

Chloroquinone. *o*-Chloronitrobenzene (11.2 g., 0.07 mole) was reduced electrolytically by the procedure previously described (12), using a current density of 0.8 amp./sq. dec. and 1.5 equivs. of current, but a nickel cathode was used instead of platinum. The aminophenol was oxidized with dichromate as previously described, and steam-distillation gave 4.1 g. (40%) of chloroquinone, m.p. 54–56°. After two crystallizations from 75% aqueous ethanol, the m.p. became constant at 55.3–56.3° [literature (22), m.p. 56–56.5°]. Reduction with sodium hydrosulfite in aqueous solution, followed by ether extraction and two crystallizations from chloroform gave *chlorohydroquinone* of the constant m.p. 106.0–106.8°. Reductive acetylation (21), followed by four crystallizations from hexane, gave *diacetyl chlorohydroquinone* of the constant m.p. 70.7–71.5° [literature (22), m.p. 70.5°].

Additions of halogen acid in aqueous medium were carried out essentially as described (12) for the addition of hydrogen chloride to toluquinone, except that longer periods of standing were required in some cases before the solution became light-colored.

For the reactions in chloroform, hydrogen chloride from a cylinder was passed into a 7% solution of dry quinone in chloroform (dried over phosphorus pentoxide) until the black quinhydrone had changed to nearly white hydroquinone. Time of reaction was usually 1–2 hours. Similar results were obtained on cooling the reaction in an ice-bath or allowing it to warm to about 35°. The product was obtained either by filtration of the cold solution or evaporation of the solvent.

Oxidation of the hydroquinones was with ferric ion, as previously described (12), and the steam-distilled quinones were crystallized from hexane or 50% aqueous ethanol.

Since similar procedures were used in all instances, only the results are cited below.

Quinone plus hydrogen chloride in chloroform. Repeated crystallization of the hydroquinone from chloroform failed to yield material melting above 100.9–101.9°. Chloroquinone was obtained in 69% over-all yield, m.p. 52–55°, raised by two crystallizations to 55.3–56.3°, not depressed on mixing with the authentic sample described above. Reduction of this sample of chloroquinone with sodium hydrosulfite yielded chlorohydroquinone of m.p. 105.5–106.3°.

Quinone plus aqueous hydrochloric acid. After oxidation and fractional steam-distillation, followed by repeated crystallization, the best material from two runs melted respectively at 51–65° and 52–56°. Top fractions from the crystallizations melted up to 110° and higher.

Toluquinone plus hydrogen chloride in chloroform. After oxidation, steam-distillation, and repeated crystallization, the best samples from three runs melted respectively at 94–104°, 95–105.5°, and 101–103.7°.

Toluquinone plus aqueous hydrochloric acid. Use of the procedure previously described (12) gave a 75% yield of steam-distilled 5-chlorotoluquinone, m.p. 101–104°, raised by one crystallization to 103.7–104.8°.

3-Chlorotoluquinone plus aqueous hydrochloric acid. Systematic crystallization of the hydroquinone from water yielded only fractions with melting points such as 145–156°. From several runs, after fractional steam-distillation and systematic crystallizations (8–12 times), there were obtained fractions of quinone melting at 98.5–100° or near there. Analysis showed: Cl, 37.08, 36.80. (Calc'd for dichlorotoluquinone, $C_7H_4Cl_2O_2$: Cl, 37.12. This sample showed a depressed m.p. of 97.7–98.9° when mixed with an authentic sample of 3,5-dichlorotoluquinone of m.p. 103.3–103.8°. Classification of this substance as a mixture of isomers or as 3,6-dichlorotoluquinone must await synthesis of the latter compound by an unequivocal method.

5-Chlorotoluquinone plus aqueous hydrochloric acid. After oxidation, steam-distillation, and repeated crystallizations, the best samples from two runs melted respectively at 85–89° and 84–88.7°. Top fractions melting as high as 200–225° were obtained. A combination of several fractions melting in the range, 85–120°, was fractionally steam-distilled through a 65-cm. Vigreux column with heated jacket and partial reflux head, to yield four fractions, the last melting at 83–136° and the first melting at 85–95° and giving a chlorine analysis of 39.48, 38.81 %. Kehrmann, Silva, and Keleti (11) reported a quinone melting at 85–86° as obtainable from this reaction.

6-Chlorotoluquinone plus aqueous hydrochloric acid. From one run there was obtained a best fraction of quinone of m.p. 85–97°, chlorine content, 39.48, 39.77%. From another run in which the hydroquinone was repeatedly crystallized before oxidation, a quinone sample was obtained which melted at 78.2–78.6°, chlorine content, 39.85, 40.21%. Previously (11) there has been reported as isolated from this reaction a quinone of m.p. 76°.

6-Bromotoluquinone plus aqueous hydrobromic acid, followed by oxidation, steam-distillation, and repeated crystallization, gave material of m.p. 87–97°.

Reaction of acetyl chloride with quinone. Acetyl chloride (8 g.), purified by distillation from dimethylaniline, was mixed at 25° with 5.4 g. of dry quinone in a carefully dried apparatus. The mixture darkened slowly, but with no evolution of heat or hydrogen chloride, even after heating under reflux for two hours, and insoluble quinone remained. On addition of 1 ml. of glacial acetic acid at 25°, there immediately ensued a vigorous exothermic reaction with evolution of hydrogen chloride, and during about 10 minutes the color changed through red to light yellow. After removal of solvent and one crystallization from 75% aqueous ethanol, material of m.p. 62–65° was obtained, and further crystallization from ethanol, hexane or aqueous acetic acid gave the same material. Several runs gave similar results. Hydrolysis and oxidation yielded a quinone mixture of m.p. 52–95°. Fractional steam-distillation, followed by recrystallization, gave a quinone of m.p. 159–161°, the m.p. reported by Ling (23) for 2,5-dichloroquinone.

Slow evaporation of a hexane solution of the mixed diacetyl hydroquinones gave a mixture of large flat tablets and fine needles. Hand-picking of the tablets, followed by recrystallization, gave diacetyl chlorohydroquinone of m.p. 68.3–69.3°, no depression on mixing with the authentic sample described above.

SUMMARY

In contrast with numerous previous reports, it has been shown that addition of halogen acids to *p*-benzoquinones is not a satisfactory general preparation of pure halogenated hydroquinones.

It has been shown that *p*-benzoquinone does not react with acetyl chloride, but that reaction with hydrogen chloride occurs on addition of small amounts of acid to the reaction mixture.

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THE PREPARATION AND RELATIVE REACTIVITIES OF MANY-MEMBERED CYCLIC DISULFIDES

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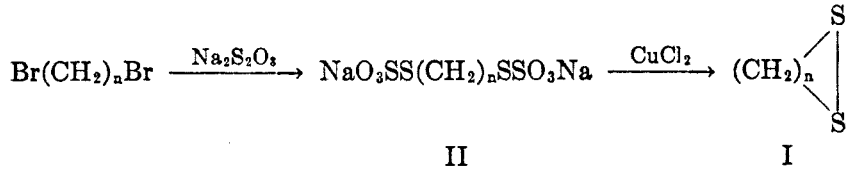
It has recently been shown that cyclic 1,2-disulfides (I) can be opened catalytically to rubbery disulfide polymers without any substantial volume change (1). The resulting interest in rings of this type has led to the present search for an improved synthetic method.

Davis and Fettes have shown that steam-distillation of a polymeric disulfide latex results in the slow removal of the cyclic monomer (2). This is the only method previously reported by which a series of cyclic disulfides of many ring members might be successfully prepared. In the present work, attempts to cyclize polymethylene Bunte salts (II) by oxidation with iodine or hydrogen peroxide in aqueous or aqueous-alcoholic solution failed in every case (3, 4). The only products that were obtained were polymeric disulfides. This result was not changed by decreasing the concentration of the reactant (Bunte salt). It was discovered, however, that these salts react with aqueous cupric chloride to produce molecular complexes (from II when n = 2, 3, 4 or 5) or clear aqueous solutions (from II when n = 6, 7, 8, 9 or 10), from which the desired cyclic disulfides can



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be isolated by steam-distillation. The constitution of the yellow or orange molecular complexes could not be determined, nor is the nature of the reaction involved clearly understood. It is significant that ferric and stannic chlorides are as effective in producing dibenzyl disulfide from sodium benzylthiosulfate as is cupric chloride. Zinc chloride is approximately 50% as effective. These observations would indicate that oxidation is not a necessary part of the reaction. The action of the metal cation may consist in an electrophilic attack on the bivalent sulfur atom, thereby weakening the vulnerable sulfur-sulfur bond.

The cyclic disulfides prepared are listed in Table I together with analytical data and an indication of their relative reactivities in the sense of ring opening and polymer formation. The relative yields are roughly comparable to those generally obtained from other cyclization reactions (5). It is presumed that this comparison will remain valid, and that the yields will increase as ring size is increased beyond twelve atoms. The increase in yield which results upon replacement of a methylene group by an oxygen atom is clearly visible in the case of 1,4,5-oxadithiepane and, again, is in conformity with investigations on other

ring systems (5). 1,3-Dioxa-6,7-dithionane is somewhat soluble in water and this may account for the lower yield of this substance.

TABLE I

ANALYTICAL DATA AND RELATIVE REACTIVITIES OF CYCLIC DISULFIDES, R—S—S

NO ATOMS IN RING	R	YIELD, %	REACTIVITY (1 = least reactive)	B.P., °C.	MOLECULAR WEIGHT		S	
					Calc'd	Found	Calc'd	Found[a]
4	$-(CH_2)_2-$	trace	6	-	-	-[b]	-	-[b]
5	$-(CH_2)_3-$	60	5+	-	106	150.5[c]	60.4	60.0
6	$-(CH_2)_4-$	22	5	*Ca.* 60 at 5 mm.	120	130	53.4	52.9
7	$-(CH_2)_5-$	13	1	57–60 at 5 mm.	134	136.5	47.8	47.4
8	$-(CH_2)_6-$	4	5	-	148	153	-	-[d]
9	$-(CH_2)_7-$	2	1	*Ca.* 70 at 5 mm.	162	169	39.5	38.8
10	$-(CH_2)_8-$	3	5	-	176	168	36.4	36.7[e]
11	$-(CH_2)_9-$	0.2	1	-	-	-[f]	-	-[f]
12	$-(CH_2)_{10}-$	2–3	5+	-	-	-[g]	31.4	31.5
7	$-(CH_2)_2-O-(CH_2)_2-$	50	4	55–56 at 3 mm.	136	133	47.1	46.4
9	$-(CH_2)_2-O-CH_2-O-(CH_2)_2-$	1.0	1	*Ca.* 70 at 5 mm.	-	-[h]	38.6	38.3

[a] Sulfur analyses were done by the method of Cheyney, *Ind. Eng. Chem., Anal. Ed.*, **13**, 238 (1941), except where otherwise noted. [b] Less than 1 mg. of polymeric material was obtained from 0.2 moles of reactant. [c] Trimethylene disulfide could not be isolated as the monomeric oil. Its molecular weight was determined by passing the uncondensed steam mixture through benzene. The monomeric material is stable in benzene solution. The freezing-point of an aliquot of the benzene solution was determined and the solute weighed after evaporation to the polymeric residue. [d] Hexamethylene disulfide polymerized to a sticky rubber on standing. This material could not be further purified, and the commercial analysis proved unsatisfactory. [e] This analysis was done commercially. [f] The trace of oil obtained was too small to be readily purified. The commercial analysis proved unsatisfactory. [g] Decamethylene disulfide polymerized almost spontaneously. [h] The trace of oil obtained was too small for a molecular weight determination.

The chemical reactivity of these cyclic disulfides can be estimated by the readiness with which their rings are opened to form linear polymers. All the

rings listed in Table I polymerize within a few hours in contact with a trace of aluminum chloride (1). The five- and twelve-membered rings are obtained as oils which immediately become viscous and polymeric when the solvent is removed. The six-, eight- and ten-membered rings and the cyclic ether disulfide are stable if they are separated directly from the distillate; if they are extracted from the distillate with ether they polymerize slowly on standing when the solvent has been removed. The seven-, nine-, and eleven-membered rings and the 1,3-dioxa-6,7-dithionane are stable indefinitely even after treatment with ether. The action of ether is presumed to be due to the presence of peroxides.

The ease with which the five- and six-membered rings are opened is unexpected. These rings should resemble cyclopentane and cyclohexane in structure, for the C—S—S angle is very nearly tetrahedral, 107 ± 3° (6). The S—S bond distance, 2.05 Å, is considerably larger than the C—C distance, but construction of the disulfide models indicates that this is not sufficient to induce much strain into the ring. It is believed that the relative reactivities of the cyclic disulfides may be taken as evidence for restricted rotation about the S—S bond.

Quantum-mechanical calculations have shown that in the hydrogen peroxide molecule the O—O bond presents its valencies at an azimuthal angle of about 100°, and that a very real energy barrier must be surpassed to permit rotation from this angle (7). It appears that rotation to an azimuthal angle of 180° (*trans*-) requires an activation of about 4000 calories and that rotation to the *cis*-form requires about 12,000 calories (8). It seems very reasonable for one to assume that a similar situation exists with the hydrogen persulfide molecule. Dipole moment measurements have been made on many molecules containing a S—S single bond (9), but this technique cannot distinguish between a freely rotating S—S bond and one restricted at an azimuthal angle of nearly 90°. Electron diffraction studies of hydrogen persulfide and dimethyl disulfide were unable to present any evidence for or against restricted rotation (6). Similar studies on sulfur monochloride indicate that an azimuthal angle of 97° may exist in this case (10).

If the assumption of restricted rotation about a S—S single bond may be accepted, the relative reactivities observed for the cyclic disulfides are more easily explained. On this basis the five-membered ring must be highly strained. Its formation requires rotation of the bond to an azimuthal angle of nearly 0° and this is the most unstable position in which this bond could be held. The largest azimuthal angle possible for the six-membered ring disulfide is about 70° as shown by molecular models. The strain involved in this ring must therefore be small. Larger rings do not require any large deviation from an angle of about 100° and so should be quite strainless. The alternation in reactivity found in this range may be due to a compression of the domain required for the methylene groups, an idea which is frequently used to explain the instability of rings of eight to twelve members of various types (11). A study of the models of cyclic disulfides indicates that a fixed azimuthal angle of 100° for the S—S bond may result in a very slight increase in the domain available for the methylene groups in the nine- and eleven-membered rings relative to that available in the eight-, ten-, and twelve-membered rings.

EXPERIMENTAL

Preparation of Bunte salts. Solutions of 125 grams (0.5 mole) of sodium thiosulfate pentahydrate in 250 cc. of water and 0.2 mole of the polymethylene dihalide in 250 cc. of alcohol were mixed and the mixture refluxed on the water-bath until it became homogeneous. The alcohol was then removed by low-temperature distillation. The cyclization reaction could be run directly on the aqueous-alcoholic solution, the alcohol being removed from the steam distillate; however, it was found to be more convenient to remove it from the Bunte salt solution.

Preparation of cyclic disulfides. In a 5-liter flask was placed 255 grams (1.5 moles) of cupric chloride dihydrate in 500 cc. of water. Steam which had been preheated to 150° was passed through this solution and the Bunte salt solution (0.2 to 0.4 molar) was added dropwise over a period of about two hours. Distillation was stopped when the condensate became clear. Any subnatant oil was separated from the distillate which was then extracted with ether. The extracts were combined, dried over calcium chloride, and the solvent removed. The products were then distilled under reduced pressure in those cases in which they were sufficiently plentiful and sufficiently stable. The presence of the disulfide bond and the absence of mercaptan and thiocarbonyl groups in the product were demonstrated in each case by tests with Grote's solution (12).

Although the method just outlined gives the largest yields of those disulfides having more than seven ring members, it is apparently inferior for the smaller rings. These were best prepared by the direct solution of solid cupric chloride in the hot (80°) Bunte salt solution. After standing for several hours, preferably overnight, a voluminous precipitate of a molecular complex separated. The solution was then steam-distilled, and the distillate worked up as before.

SUMMARY

A new method for the synthesis of cyclic disulfides is described. The relative reactivity of the rings is discussed, and an explanation is offered to account for the ease of opening of the five- and six-membered disulfide rings.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF QUEENS COLLEGE]

PYROLYSES OF *cis*-PHENYLDIBENZOYLETHYLENE, ITS OXIMES, AND SOME RELATED HETEROCYCLIC COMPOUNDS

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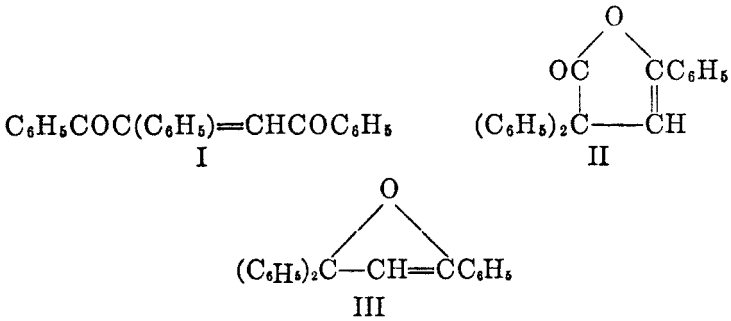
Received March 13, 1950

In this article are presented a number of observations made incidentally to a study of the oximes of *cis*-phenyldibenzoylethylene (1). In part these observations serve to correct some erroneous reports of long standing, in part they are new; collectively their application to analogously constituted compounds may be useful.

cis-Phenyldibenzoylethylene, its oximes, and the pyrroles and the 1,2,6-oxazines derived from the oximes undergo a variety of striking reactions on pyrolysis. These reactions include ring closure and ring opening as well as ring enlargement and contraction. *cis*-Phenyldibenzoylethylene (I) on pyrolysis undergoes ring closure to form triphenylcrotolactone (II) as Japp and Klingemann (2) reported many years ago. They also reported that the lactone on further heating lost carbon monoxide to furnish a product for which they suggested formula III.

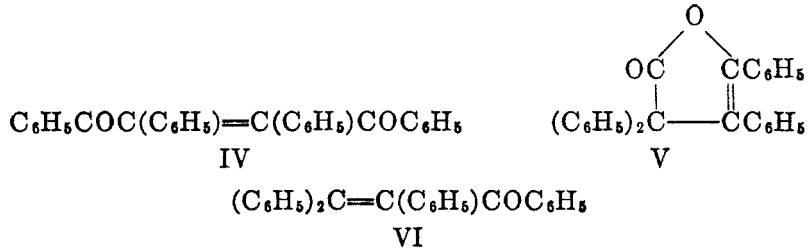


$C_6H_5COC(C_6H_5)=CHCOC_6H_5$ (I)

(II)

(III)

The physical properties of the pyrolysis product correspond, however, with those of β-phenylbenzalacetophenone, $(C_6H_5)_2C=CHCOC_6H_5$, and the suggestion was made in Beilstein's "*Handbuch*" that this final product might be β-phenylbenzalacetophenone (3). We have confirmed the correctness of this suggestion by a direct comparison of the pyrolysis product and the unsaturated ketone. This result brings the pyrolysis of *cis*-phenyldibenzoylethylene into line with that of dibenzoylstilbene (IV) which furnishes tetraphenylcrotolactone (V) and then diphenylbenzalactetophenone (VI) (2).

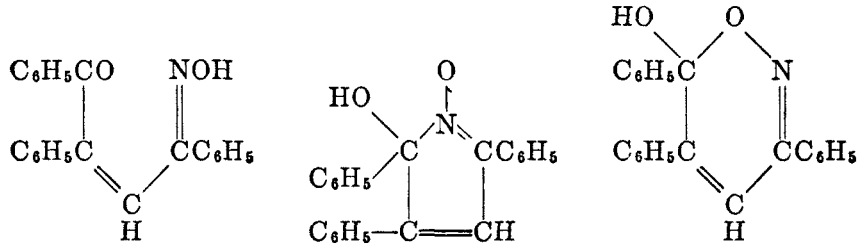


$C_6H_5COC(C_6H_5)=C(C_6H_5)COC_6H_5$ (IV)

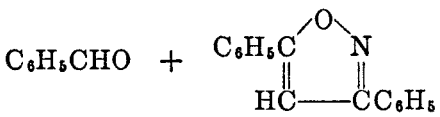
(V)

$(C_6H_5)_2C=C(C_6H_5)COC_6H_5$ (VI)

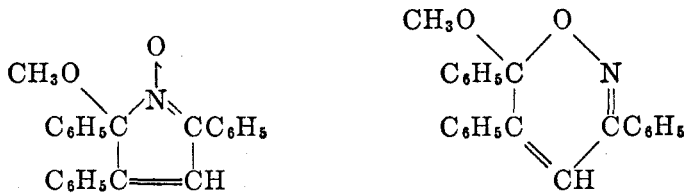
The pyrolysis of *cis*-phenyldibenzoylethylene monoxime (VII) and its cyclic isomer (the nitrone VIII) was also described many years ago; the single pyrolysis product reported was benzonitrile (4). This was evidently the result of a faulty identification for both the oxime and the nitrone furnish benzaldehyde and 3,5-diphenylisoxazole on pyrolysis.



VII VIII IX

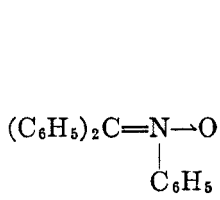


The same pyrolysis products, benzaldehyde and 3,5-diphenylisoxazole, are also obtained by heating the hydroxy-1,2,6-oxazine, IX. It seems reasonable to assume that the oxime on heating is converted *via* the nitrone to the hydroxy-1,2,6-oxazine which then undergoes thermal cleavage. The assumption that the nitrone, VIII, undergoes thermal ring enlargement to the hydroxy-1,2,6-oxazine, IX, is supported by the observation that the methoxy nitrone, X, does undergo an exactly comparable ring enlargement to furnish the thermally-stable methoxy-1,2,6-oxazine, XI, on pyrolysis.

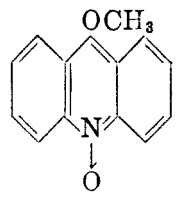


X XI

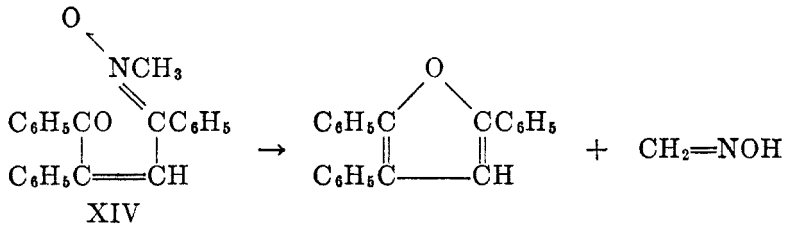
The ring enlargement of the pyrrole nitrone, X, to the 1,2,6-oxazine, XI, is a new type of thermal behavior for nitrones. The open-chain nitrone, XII, yields benzaldehyde, nitrosobenzene, and azobenzene on pyrolysis (5), while the cyclic nitrone, XIII, furnishes acridone and formaldehyde (6). The open-chain nitrone, XIV, obtained from phenyldibenzoylethylene, undergoes ring closure on pyrolysis to yield triphenylfuran and, presumably, polymeric formaldoxime.



XII



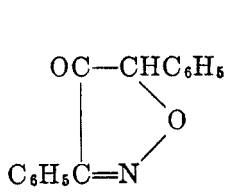
XIII



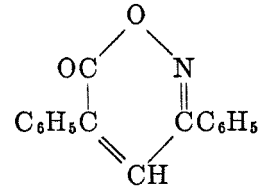
XIV

These three nitrones whose behavior on pyrolysis is known are not strictly comparable with the nitrone, X, for in this latter compound the group which shifts from nitrogen to oxygen during pyrolysis is both a benzyl and an allyl group. By analogy with the behavior of the nitrone, X, one would expect that open-chain nitrones with a benzyl or allyl group attached to nitrogen would undergo thermal pyrolysis to oxime O-ethers. Information on this point is not available in the literature, but Dr. A. C. Cope has informed us that he and Dr. A. C. Haven have found this type of rearrangement does take place.

In contrast to the novelty of the ring enlargement just described, the loss of a ring carbon atom as part of a carbonyl group, exemplified by the pyrolysis of the lactones, II and V, and the hydroxy-1,2,6-oxazine, IX, seems to be of some generality. Carbonyl bridges in diene adducts are frequently lost as carbon monoxide on heating (7), the isoxazolone, XV, loses carbon monoxide and yields benzaldehyde and benzonitrile (8), and the 1,2,6-oxazine, XVI, on heating in acetyl chloride loses carbon monoxide and furnishes 3,5-diphenylisoxazole (9).



XV



XVI

EXPERIMENTAL

Pyrolysis of cis-phenyldibenzoylethylene (10). Since the original description of this pyrolysis was lacking in details, some preliminary experiments were necessary. The diketone distills without change at 2 mm. At 25–30 mm. the diketone furnishes principally triphenylcrotolactone (II) (2) contaminated with a small amount of the *trans*-isomer of the diketone.

When triphenylcrotolactone was distilled at 150–160 mm., there was a noticeable evolution of gas and the distillate consisted of a mixture of β-phenylbenzalacetophenone and unchanged lactone. The lactone was removed by boiling with alcoholic potassium hydroxide and the β-phenylbenzalacetophenone, after crystallization from ethanol, was identified by a mixed melting point with an authentic specimen and by conversion to the oxime (11) and a mixed melting point with an authentic specimen of that material.

The remaining pyrolyses can for the most part be summarily described. They were carried out with 0.5–1.0-g. samples of material heated in Späth bulbs or test tubes in an air-bath and in the vacuum furnished by an effective oil-pump. Benzaldehyde, obtained from *cis*-phenyldibenzoylethylene monoxime (VII) (1a) and its cyclic isomers the nitrone, VIII, (1a) and the hydroxy-1,2,6-oxazine, IX, (1c) was condensed in a cold trap and identified by conversion to the phenylhydrazone and a mixed melting point with a known sample. 3,5-Diphenylisoxazole obtained from the same three pyrolyses was identified by comparison with a sample prepared from dibenzoylmethane and hydroxylamine (12). Triphenylfuran (13) obtained by pyrolysis of the open-chain nitrone, XIV, (1c) was also identified by comparison with an authentic sample.

The conversion of the methoxynitrone, X, (1a) to the methoxy-1,2,6-oxazine, (1c) XI, was studied with larger amounts of material as the pyrolysis is the most efficient method of preparing the methoxy-1,2,6-oxazine. When the methoxynitrone, X, is heated at a pressure less than 1 mm. the material distills at 215–220° and the product is the methoxy-1,2,6-oxazine, XI. From 4 g. of the nitrone, 3.8 g. of the 1,2,6-oxazine was obtained. The same conversion can also be effected without distillation. The nitrone in a distilling flask is heated in a vacuum until the solid melts and the liquid begins to boil. When the vigorous boiling ceases the product in the flask is the methoxy-1,2,6-oxazine.

SUMMARY

This article describes the behavior on pyrolysis of *cis*-phenyldibenzoylethylene, its oximes, and the heterocyclic compounds derived from these oximes.

FLUSHING, N.Y.

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[CONTRIBUTION FROM THE EATON LABORATORIES, INC.]

THE REDUCTION OF SOME ALIPHATIC *beta*-AMINO ALDEHYDES

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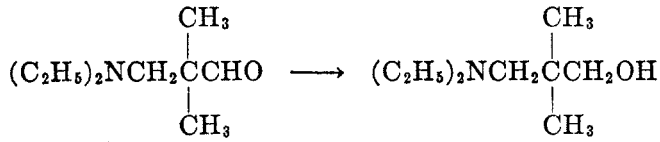
We have sought methods of reducing 2,2-dimethyl-3-diethylaminopropionaldehyde (I) to the corresponding amino alcohol which would be less cumbersome than the acid and sodium amalgam used by Mannich, *et al.* (1, 1a, 1b).



I

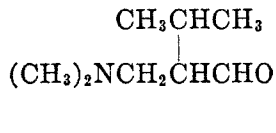
The mild conditions of the Meerwein-Ponndorf-Verley reduction, employing an aluminum alkoxide in alcohol, were thought to be attractive. The use of lithium aluminum hydride was also investigated following the report of Nystrom and Brown (2) that *p*-dimethylaminobenzaldehyde could be smoothly reduced to the amino alcohol with this reagent. After this work was completed a patent was issued to Wenner (3) which disclosed the reduction of *beta-tertiary*-aminoalkyl aldehydes by catalytic (Raney nickel) hydrogenation of the hydrochlorides. This method of Wenner, described in more detail in a later paper (3a), would appear to be more economical of time and chemicals. However, it requires the use of heated pressure-hydrogenation equipment (10–40 atmospheres), which is not always convenient, particularly on a small scale. Further, it has not been applied to *beta*-amino aldehydes bearing an α-hydrogen.

No report of an aluminum alkoxide reduction of an amino aldehyde could be found in the literature. Bersin (4), in his excellent review of this reaction, notes that the number of successful aluminum alkoxide reductions of compounds containing basic nitrogen atoms is not great and that the known cases are amino ketones. Harradence, *et al.* (5, 6) have reduced some saturated alicyclic *beta*-amino ketones, such as 2-morpholinomethylcyclohexanone, by this method. However, these authors encountered complete deamination with 2-morpholinomethylcyclopentanone under the customary conditions of the Meerwein-Ponndorf-Verley reduction. Work (7) reported failure in the case of 1,12-*bis*-diethylamino- and 1,12-*bis*-piperidino-dodeca-2,11-dione. He concluded that for ready reduction of *alpha*-amino ketones with aluminum alkoxide the carbonyl group must be conjugated with an aromatic system.

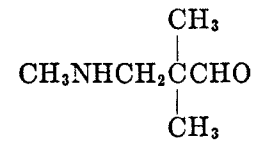
We subjected 2,2-dimethyl-3-diethylaminopropionaldehyde (I), as the free base, to the standard reduction with aluminum isopropoxide in isopropanol. The detection of acetone in the distillate indicated reduction occurred, and an 81–91% yield of 2,2-dimethyl-3-diethylamino-1-propanol was isolated. This alcohol was identified by its boiling point and the melting points of the *p*-nitro-

benzoate hydrochloride and *p*-aminobenzoate hydrochloride, which were in agreement with the constants reported by Mannich, *et al.* (1, 1b).

It was thought that success with this particular aldehyde might be due to the absence of hydrogen on the *alpha*-carbon atom with the resultant freedom from losses by aldol condensation. To determine this point a *beta*-amino aldehyde bearing an *alpha*-hydrogen, 2-isopropyl-3-dimethylaminopropionaldehyde (II) (1, 1a) was treated with aluminum isopropoxide. The corresponding alcohol was obtained in 66% yield. Thus the *alpha*-hydrogen seems to have little influence on the course of the reduction.



II



III

It was of interest to explore the influence of a *secondary*-amino group on the aluminum isopropoxide reduction of an aliphatic *beta*-amino aldehyde. Burger and Deinet (8) had observed that in the case of some 2-benzofuryl aminomethyl ketones the monobenzylaminomethyl ketone was reduced almost as satisfactorily as the dibenzylaminomethyl compound. They also reduced 2-benzofuryl methylaminomethyl ketone, but reported no yield. We observed that 2,2-dimethyl-3-methylaminopropionaldehyde (III) (9), when reduced (as the free base) with aluminum isopropoxide, gave an 8–27% yield of the corresponding alcohol.

The greater success of Burger, *et al.* (8) with an *alpha-secondary*-amino ketone may be due in part to their use of the amine hydrochloride. Drake and Goldman (10) have proposed that salt formation suppresses the basic character of the amine and allows the successful reduction of some amino ketones. However, the closely related *tertiary*-amino aldehyde (I) would be expected to have a basic strength at least as great as the *secondary*-amino aldehyde (III), yet I is reduced quite smoothly in the form of the free base, in contrast to III. Thus the acidic nature of the catalyst causing the formation of a complex with the amine of the type $R_3N{:}AlR'_3$, with the resultant removal of the catalyst and amine from the sphere of action, as proposed by Woodward, Wendler, and Brutschy (11), would not seem to be the cause of the low yield in the reduction of III. Supporting this was the absence of any precipitate in the reduction mixtures.

It is probable that the reduced yield with the *secondary*-amine is due to its lesser stability. With the three amino aldehydes investigated some deamination occurred in each case, as observed by the presence of volatile amines in the distillate. This was especially prominent with the *secondary*-amino aldehyde, III. Harradence, *et al.* (5) had observed deamination in the case of one *beta*-amino ketone.

These three saturated aliphatic *beta*-amino aldehydes were also reduced with lithium aluminum hydride by the method of Nystrom and Brown (2). The

tertiary-amino aldehydes, I and II, reacted smoothly and gave good yields of the alcohols. The *secondary*-amino aldehyde, III, gave almost as good a yield, but required a large excess of reducing agent. The alcohols prepared with lithium aluminum hydride were identical with those produced by the aluminum isopropoxide reduction.

EXPERIMENTAL

2,2-Dimethyl-3-diethylamino-1-propanol (1, 1b). *I A.* 2,2-Dimethyl-3-diethylaminopropionaldehyde (I) (prepared by the method of Mannich, *et al.* (1, 1a)), of b.p. 118–123° (103–104 mm.), 11.6 g. (0.074 mole), and 15.1 g. (3 equivalents) of freshly prepared, crude aluminum isopropoxide in 118 ml. of anhydrous isopropanol were slowly distilled to remove the acetone formed. An electrically-heated, 45-cm. column packed with glass helices was used to effect the separation. After 145 minutes the acetone test was negative. The brown reaction mixture was reduced to ⅓ the original volume by distillation at 100 mm., and the residue was shaken with five volumes of cold 10% sodium hydroxide solution. The crude amino alcohol, which appeared as an oily layer, was separated and the aqueous portion was extracted with ether. The ether extract and the crude oil were combined, dried with potassium hydroxide pellets, and fractionally distilled (Vigreux column) *in vacuo*. The 2,2-dimethyl-3-diethylamino-1-propanol was obtained as a colorless liquid of b.p. 90.0–90.5° (12 mm.) 10.0 g. (84.7%). Numerous reductions gave yields ranging from 81 to 91%. This material yielded a *p*-nitrobenzoate hydrochloride of m.p. 159–160°, and a *p*-aminobenzoate hydrochloride of m.p. 196–197°; Mannich (1b) reported melting points for these derivatives of 160° and 195–196°, respectively, and a boiling range of 90–91° (12 mm.) for this amino alcohol.

I B. Twenty grams (0.127 mole) of 2,2-dimethyl-3-diethylaminopropionaldehyde (I) in 190 ml. of absolute ether were added during 30 minutes to a solution of 1.5 g. of 90+% lithium aluminum hydride dissolved in 70 ml. of absolute ether. The mixture refluxed spontaneously and was stirred one-half hour after the addition was completed. It was then poured over 100 g. of ice, the aluminum salts were dissolved by adding 60 ml. of 10% sodium hydroxide, and the ether layer was separated. The aqueous portion was re-extracted with ether, and after drying the combined extracts with sodium hydroxide pellets, the ether was removed by distillation. The residue was distilled at reduced pressure to yield 17.5 g. (86.4%) of amino alcohol, b.p. 82–88° (8–12 mm.). This material gave a *p*-nitrobenzoate hydrochloride of m.p. 159–160°.

2-Dimethylaminomethyl-3-methyl-1-butanol (1, 1a). *II A.* This was prepared by the same procedure as in *I A* starting with 2-isopropyl-3-dimethylaminopropionaldehyde (II) of b.p. 57–58° (11 mm.). This amino aldehyde was prepared by the method of Mannich, *et al.* (1, 1a), who reported the boiling point variously as 63–66° (13 mm.) (1) and 66–68° (12 mm.) (1a). Fifteen grams of II (0.105 mole), 22.4 g. of distilled aluminum isopropoxide, and 115 g. of isopropanol were fractionally distilled during 80 minutes to remove acetone; working up as above gave 10.1 g. (66.3%) of amino alcohol of b.p. 82.0–83.5° (14–15 mm.). Mannich, *et al.* in reference (1) reported b.p. 80° (13 mm.). This gave a *p*-nitrobenzoate hydrochloride of m.p. 175–176°; Mannich, *et al.* reported variously, 176° (1) and 174° (1b).

II B. This amino aldehyde (II) was reduced with lithium aluminum hydride in the same manner as *I B* above. Yield 86.4%, b.p. 83–85° (14–16 mm.); *p*-nitrobenzoate hydrochloride, m.p. 175.0–175.5°.

2,2-Dimethyl-3-methylamino-1-propanol (9). *III A.* Twenty grams (0.174 mole) of 2,2-dimethyl-3-methylaminopropionaldehyde (III) of b.p. 48.0–50.5° (12–13 mm.) [prepared by the method of Mannich and Wieder (9), who reported b.p. 48° (12 mm.)] were reduced with three equivalents of distilled aluminum isopropoxide as described in *I A* above. Acetone was produced continuously but considerable quantities of some volatile amine were evolved. When the reduction was arbitrarily stopped after 190 minutes a 12% yield of crude

amino alcohol of b.p. 68–90° (9–11 mm.) was obtained. Mannich, *et al.* (9) reported a b.p. of 75–77° (12 mm.). Increasing the time of reduction to 335 minutes decreased the yield to 8%; whereas decreasing the reaction time to 125 minutes increased the yield to 27%. Shorter reduction times were not investigated. This crude alcohol gave a *p*-nitrobenzoate hydrochloride in good yield; m.p. 206–208°. Mannich (9) reported m.p. 207° for this ester.

III B. This *secondary*-amino aldehyde (III) was reduced quite smoothly to the corresponding alcohol as in *I B* above except that a large excess (5 equivalents) of lithium aluminum hydride was employed; yield, 72%; b.p. 70–82° (11–12 mm.).

SUMMARY

1. Three saturated aliphatic *beta*-amino aldehydes, 2,2-dimethyl-3-diethylaminopropionaldehyde, 2-isopropyl-3-dimethylaminopropionaldehyde, and 2,2-dimethyl-3-methylaminopropionaldehyde, have been successfully reduced to the corresponding alcohols by the action of aluminum isopropoxide and isopropanol on the free bases.

2. The presence of a hydrogen atom on the carbon atom *alpha* to the carbonyl group does not appear to affect the reduction.

3. *Tertiary*-amino groups cause little interference, but *secondary*-amino groups markedly reduce the yield, in the Meerwein-Ponndorf-Verley reduction of *beta*-amino aldehydes.

4. Lithium aluminum hydride reduced these three aliphatic *beta*-amino aldehydes in good yield.

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[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

α,β-DIAMINOBUTYRIC ACIDS, AMIDES, AND ESTERS[1]

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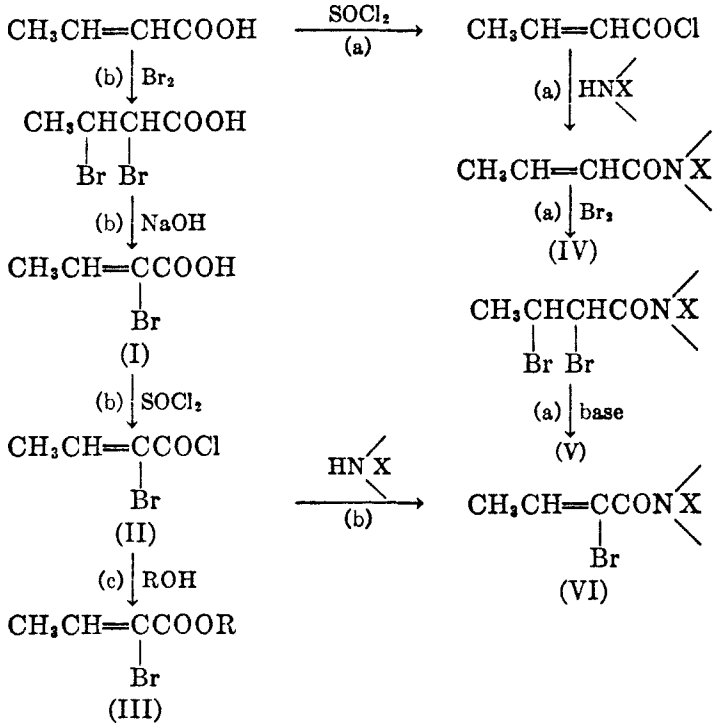
Previous to the present investigations no studies of the reactions of amines with α-halo-α,β-unsaturated amides or acids had been reported. In a series of two papers Roberts (1) showed that α-haloethylcinnamates and crotonates both react with piperidine or dimethylamine to give the corresponding α,β-diamino esters. Later Moureu (2) showed that α,β-dibromoethylbutyrate reacted with piperidine *via* the α-bromoethylcrotonate to form the α,β-dipiperidinoethylbutyrate.

It was the main purpose of the present studies to compare the reactions of amines with the α-bromo-α,β-unsaturated acids, amides, and esters, with the similar investigations which have been made of the α-bromo-α,β-unsaturated ketones (3). It was realized that these new types of amino acids, amides and esters might prove of interest for pharmacological screening.

There were two obvious routes, (a) or (b) to the synthesis of the required α-bromocrotonamides, starting with crotonic acid.



[1] Abstracted from the Ph.D. thesis of Floy Pelletier (1950); Smith, Kline, and French Laboratories Research Fellow, 1947–1950.

The feasibility of route (a) was established by carrying out the indicated reactions for the preparation of compounds (IV), (V), and (VI) where $-N\langle X$ was the morpholino group. In contrast to the related cinnamamide dibromides studied in an earlier investigation (4), these α,β-dibromobutyramides (V) readily lost hydrogen bromide to produce (VI) in a manner analogous to the behavior of the α,β-dibromo ketones which give the α-bromo-α,β-unsaturated ketones. The cinnamamide dibromides show a considerable tendency to lose bromine to reform the cinnamamides.

Although it was found that the over-all yields of the α-bromocrotonamides (VI) by either method (a) or (b) were of the same order, method (b) had the

TABLE I

PHYSICAL AND ANALYTICAL DATA OF α-BROMOCROTONAMIDES

α-BROMOCROTON-	B.P., °C.	YIELD, %	FORMULA	ANALYSES					
				CARBON		HYDROGEN		NITROGEN	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
piperidide[a]	105–107 (1 mm.)	81	$C_9H_{14}BrNO$	46.55	46.34	6.04	5.83	6.04	6.08
morpholide	110–112[b] (1 mm.)	70	$C_8H_{12}BrNO_2$	41.04	41.32	5.13	5.12	5.98	5.82
β'-naphthalamide	[c]	96	$C_{14}H_{12}BrNO$	57.80	57.57	4.14	4.09	4.83	4.88
p-ethoxyanilide	[d]	87	$C_{12}H_{14}BrNO_2$	50.71	50.70	4.97	5.01	4.93	5.20
N-diethylamide[e]	111 (1.2 mm.)	76	$C_8H_{14}BrNO$	43.64	43.84	6.41	6.32	6.36	6.15
N-dimethylamide[f]	120 (18 mm.)	85	$C_6H_{10}BrNO$	37.61	37.41	5.25	5.08	7.29	6.99

[a] n_D^{20} 1.5311. [b] M.p., 60–62°. [c] M.p., 78–79°. [d] M.p., 100–105°. [e] n_D^{20} 1.4990. [f] n_D^{23} 1.5138.

obvious advantage of involving the syntheses of the required α-bromocrotonic acid (I) and the versatile new reagent, α-bromocrotonyl chloride (II) needed for the other studies. This latter reagent could obviously be used to prepare the required α-bromocrotonic acid esters (III) as well as the amides (VI). Route (b) was therefore chosen for the preparation of the α-bromocrotonamides listed in Table I. The various α-bromocrotonates (III) which were prepared from α-bromocrotonyl chloride (II) by reaction (c) are to be found in Table II.

The only α,β-diaminobutyric acid to be found in the literature was the parent compound itself which had been prepared first by Neuberg (5) from α,β-dibromobutyric acid and ammonium carbonate. Using dimethylamine and piperidine, respectively, along with α-bromocrotonic acid (I) and heating the mixtures to

60° for several hours, the α,β-diaminobutyric acids were obtained in good yields. The dipiperidino acid was fractionally recrystallized to give the two possible racemates. We also obtained the higher-melting racemate, m.p. 212°, in considerably lower yields by either acidic or alkaline hydrolysis of the known ethyl-α,β-dipiperidinobutyrate (1, 2).

Several attempts to convert the high-melting racemate of α,β-dipiperidinobutyric acid into the corresponding α,β-dipiperidinobutyryl chloride were un-

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR α-BROMOCROTONATES

R IN α-BROMOCROTONATE ESTERS	B.P., °C. MM.	YIELD, %	FORMULA	ANALYSES			
				C		H	
				Calc'd	Found	Calc'd	Found
Benzyl	141 (20)	51	$C_{11}H_{11}BrO_2$	51.79	52.15	4.35	4.53
Benzohydryl	[a]	71	$C_{17}H_{15}BrO_2$	61.64	61.37	4.56	4.51
γ'-Di-N-butylamino-propyl	142 (0.3)	72	$C_{15}H_{28}BrNO_2$	—	—	—	—
β'-Diethylaminoethyl	125 (2.5)	85	$C_{10}H_{18}BrNO_2$	—	—	—	—

[a] M.p., 48–49°.

TABLE III

PHYSICAL AND ANALYTICAL DATA FOR α,β-DIAMINOBUTYRATES

DIAMINOBUTYRATES	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
				C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
α,β-Dipiperidinobutyrate									
Benzyl	100–101	86	$C_{21}H_{32}N_2O_2$	73.21	73.48	9.36	9.43	8.15	8.30
Benzohydryl	115–117	80	$C_{27}H_{36}N_2O_2$	77.10	76.86	8.62	8.35	6.66	6.91
α,β-*Bis*-dimethylamino-butyrate	79–80								
γ'-Dibutylaminopropyl	[b]	80	$C_{19}H_{41}N_3O_2$	66.42	66.36	12.03	11.86	12.23	12.09
β'-Diethylaminoethyl	[c]	75	$C_{14}H_{31}N_3O_2$	61.49	61.49	11.43	11.14	—	—

[a] Isomers separated by fractional crystallization from alcohol-water solvent. [b] B.p., 137°/0.04 mm.; n_D^{20} 1.4531. [c] B.p., 120°/0.6 mm.; n_D^{20} 1.4551.

successful. Using thionyl chloride and such solvents as pyridine or chloroform or ether, and either the diamino acid or its dihydrochloride, only tars resulted. These results are similar to those experienced by Emil Fischer (6) who tried unsuccessfully to prepare an acid chloride of a diamino acid.

Using dimethylamine and piperidine, the various α,β-diaminocrotonates listed in Table III were readily prepared from the corresponding α-bromocrotonates (III). The reactions proceeded rapidly in benzene or ether solution at room temperature.

The α-bromocrotonamides (VI) were found to react quite slowly even with piperidine in benzene solution at reflux temperature. Moreover the yields of the α,β-dipiperidinobutyramides were very low (8–10%). Using a polar solvent such as absolute alcohol the reactions were more rapid and the yields of the α,β-diaminobutyramides were increased. See Table IV. The basic strength and the steric requirements of the secondary amines used in these reactions had to be considered. The best amines studied in the order of their effectiveness were piperidine, dimethylamine, and morpholine. This is also the order of their basic strengths. The steric requirements of these three bases are similar. Diethylamine, which is of the same order of basic strength as piperidine, reacted with α-bromo-N-(*p*-phenetyl)crotonamide to give apparently only the α-amino-α,β-unsatu-

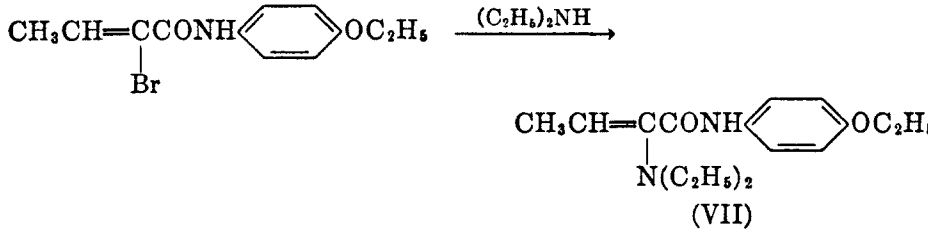
TABLE IV

PHYSICAL AND ANALYTICAL DATA FOR α,β-DIAMINOBUTYRAMIDES

DIAMINOAMIDES	M.P., °C.	YIELD, %	FORMULA	ANALYSES					
				C		H		N	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
Butyrpiperidide									
α,β-Dipiperidino	95–96.5	48	$C_{19}H_{35}N_3O$	71.02	71.05	10.90	10.78	13.08	12.93
α,β-Dimorpholino	126–127	25.5	$C_{17}H_{31}N_3O_3$	62.80	62.86	9.53	9.61	12.92	13.17
α,β-*Bis*-dimethyl-amino[a]	63–65	28	$C_{13}H_{27}N_3O$	64.68	64.98	11.28	11.12	17.45	17.64
α,β-Dipiperidinobutyr-morpholide	115–116	50	$C_{18}H_{33}N_3O_2$	66.83	66.74	10.28	10.35	12.99	13.24
p-ethoxyanilide	178–179	30	$C_{22}H_{35}N_3O_2$	70.73	70.56	9.44	9.20	11.25	11.25
	139–141	59	$C_{22}H_{35}N_3O_2$	70.73	70.50	9.44	9.67	11.25	11.20

[a] In using dimethylamine the reaction was carried out in a pressure bomb or sealed tube to allow the reaction mixture to be heated to 60°.

rated amide (VII). The structure of this compound was not studied. The steric requirements of the diethylamino group in such reactions are greater than those



(VII)

of the above mentioned secondary amines. Similar results were previously obtained when diethylamine was used in the reaction with an α-bromo-α,β-unsaturated ketone (7).

Several attempts were made to obtain the suspected intermediate α-bromo-β-aminobutyramides by adding one mole of the amine to the α-bromo-α,β-

unsaturated amide. Apparently the speed of this initial reaction was considerably slower than the subsequent reactions which led to the formation of the α,β-diaminobutyramides, the only products isolated from such experiments. Also the high solubility of these intermediates in the usual organic solvents probably helped to prevent their isolation.

It seems probable that all of these α-bromo-α,β-unsaturated carbonyl compounds react with amines according to the mechanisms previously outlined for the ketone series (3, 8).

EXPERIMENTAL[2]

Crotonmorpholide. One equivalent of crotonyl chloride was dissolved in benzene and cooled. A cold benzene solution containing two equivalents of morpholine was slowly added. The morpholine hydrochloride was removed by filtration and the product recovered by vacuum-distillation, b.p. 147° (18 mm.), m.p. 54–55°, recrystallized from low-boiling petroleum ether; yield 80%.

Anal. Calc'd for $C_8H_{13}NO_2$: C, 61.91; H, 8.44; N, 9.03.

Found: C, 62.24; H, 8.15; N, 9.22.

α,β-Dibromobutyrmorpholide. When bromine was added to crotonmorpholide in carbon tetrachloride solution, a 90% yield of a colorless solid resulted which was recrystallized from 50% ethyl alcohol, m.p. 122–123°.

Anal. Calc'd for $C_8H_{13}Br_2NO_2$: N, 4.44; Br, 50.74.

Found: N, 4.31; Br, 50.91.

When a sample of this dibromide was heated at reflux temperature for six hours with four equivalents of morpholine in absolute alcohol a 90% yield of the *α-bromocrotonmorpholide* resulted; b.p. 110–114° (1 mm.), m.p. 60–61°. This product was identical with that listed in Table I which was prepared from α-bromocrotonyl chloride.

α-Bromocrotonic acid. The *cis-trans* mixed acid was prepared by a modification of the method reported by James (9). Two equivalents of potassium hydroxide were dissolved in water and cooled to about 5°. A one-molar equivalent of solid α,β-dibromobutyric acid was slowly added with stirring. The reaction mixture was heated on the steam-bath for 15 minutes, then cooled and acidified with hydrochloric acid. The white crystalline product which separated on cooling was purified by recrystallization from petroleum ether (b.p. 60–70°). yield 90%, m.p. 87–94°.

α-Bromocrotonyl chloride. A one-molar equivalent of α-bromocrotonic acid was mixed with 1½ equivalents of pure thionyl chloride and heated under reflux for two hours. The product was obtained by vacuum-distillation, b.p. 108–109° (112 mm.), yield 82%, n_D^{29} 1.5201.

Anal. Calc'd for C_4H_4BrClO: C, 26.23; H, 2.19.

Found: C, 26.22; H, 2.03.

α-Bromocrotonamides. A cold benzene solution containing two molar-equivalents of the amine was slowly added to a cold dry benzene solution of one molar-equivalent of α-bromocrotonyl chloride. The reaction mixture was allowed to warm to room temperature and to remain at that temperature for one or two hours. The side product, an amine hydrochloride, was removed by filtration. The benzene was evaporated and the residue extracted with dry ether. The ether was evaporated and the crude products purified by vacuum-distillation or recrystallization from alcohol-water mixtures. The products prepared in this way are described in Table I.

α-Bromocrotonates. A dry benzene solution containing one molar-equivalent each of the corresponding alcohol and of pyridine was treated slowly with an equivalent of α-bromocrotonyl chloride in dry benzene at 0–5°. The reaction mixture was allowed to warm to

[2] Microanalyses for carbon, hydrogen, and nitrogen are by the Cark Microanalyticall Laboratory, Urbana, Illinois.

room temperature and stand at this temperature for a few hours. The pyridine hydrochloride was removed by filtration. The benzene was evaporated and the product extracted from the residue with dry ether. In the case of the reaction with benzyl alcohol the product was obtained by vacuum-distillation. The benzohydryl ester was purified by recrystallization from absolute alcohol. In preparing the α-bromocrotonates of the amino alcohols the pyridine was omitted from the reaction mixtures and an extra equivalent of the amino alcohol used instead. These products formed oily hydrochlorides and polymerized on attempted distillation. They were used in the crude form to prepare the α,β-diaminocrotonates. See Table II for a description of the α-bromocrotonates.

α,β-Dipiperidino- and α,β-Bis-(dimethylamino)-butyric acids. Method A. One equivalent of α-bromocrotonic acid was mixed with four molar-equivalents of piperidine and dimethylamine, respectively, and the reaction mixtures heated at 60° for 6–8 hours. The dimethylamine reaction mixture was heated in a sealed tube. The reaction mixtures were diluted with a combination of ether-ethanol (9:1). These mixtures were cooled and the by-product amine hydrobromides removed by filtration. The solvent was removed by distillation and the residues recrystallized from ether-alcohol (9:1) solution.

The α,β-dipiperidinobutyric acid was resolved into two racemic mixtures by fractional recrystallization.

Anal. Calc'd for $C_{14}H_{26}N_2O_2$: C, 66.11; H, 10.21; N, 11.01.

Found: C, 66.39; H, 10.18; N, 11.03; m.p. 124–126°, 20% yield.

Found: C, 66.29; H, 9.95; N, 11.29; m.p. 210–212°, 40% yield.

The α,β-bis-(dimethylamino)butyric acid resulted in 85% yield, m.p. 160–161°.

Anal. Calc'd for $C_8H_{18}N_2O_2$: C, 55.14; H, 10.41; N, 16.08.

Found: C, 55.19; H, 10.44; N, 15.97.

Method B. The high-melting isomer of α,β-dipiperidinobutyric acid was also obtained by hydrolysis of the known ethyl α,β-dipiperidinobutyrate (1, 2).

(a) One equivalent of ethyl-α,β-dipiperidinobutyrate and ten molar-equivalents of sodium hydroxide were dissolved in 80% ethyl alcohol and heated under reflux for three hours. The reaction mixture was then neutralized with a calculated amount of conc'd hydrochloric acid and the solvent removed by vacuum-distillation. The residue was extracted with an ether-alcohol (8:2) solution. The ether-alcohol solution was evaporated and the product recrystallized from petroleum ether (b.p. 60–70°), m.p. 211–212°, yield, 23%.

(b) An acid hydrolysis using 2% hydrochloric acid gave a 20% yield of the high-melting isomer. A maple syrup-like odor was observed in each of these hydrolysis reaction mixtures.

α,β-Diaminobutyrates. A cold benzene or ether solution containing three molar-equivalents of the amine was slowly added to one equivalent of the α-bromocrotonate dissolved in cold benzene or ether. The reaction mixture was allowed to warm up to room temperature and to stand at this temperature for 5–8 hours. The amine hydrobromide was removed by filtration and the solvent removed by distillation. The diaminobutyrates were purified by recrystallization from alcohol-water solutions or by distillation under reduced pressure. See Table III for the list of products prepared by this method.

α,β-Diaminobutyramides. Three molar-equivalents of the amine were refluxed for 8–12 hours with one equivalent of the α-bromocrotonamide in absolute alcohol. The solvent was removed by distillation and the product extracted from the residue with dry ether. The ether solution was saturated with dry hydrogen chloride to precipitate a hydrochloride of the diaminobutyramide. In general the α-bromocrotonamides did not form hydrochlorides under these conditions. The hydrochloride of the product was dissolved in water and the solution made strongly alkaline with sodium hydroxide. The resulting amides were purified by recrystallization from ethyl alcohol and water mixtures. The diaminobutyramides prepared in this way are described in Table IV.

α-Diethylamino-N -(p-phenetyl)crotonamide. An alcohol solution containing 5.0 g. (0.0194 mole) of α-bromo-N-(*p*-phenetyl)crotonamide (α-bromocroton-*p*-ethoxyanilide) and 4.5 g. (0.058 mole) of diethylamine was refluxed for 50 hours. The alcohol was removed by distillation and the residue extracted with dry ether. The dry ether solution was saturated

with dry hydrogen chloride and the oily precipitate recrystallized from alcohol and ether mixtures. This hydrochloride product was dissolved in water and the solution made alkaline with sodium hydroxide. The free amine separated as a colorless solid which was recrystallized from an 80% alcohol solution to give colorless plates, 1.0 g., (20% yield), m.p. 128–130°.

Anal. Calc'd for $C_{16}H_{24}N_2O_2$: C, 69.53; H, 8.75; N, 10.14.

Found: C, 69.83; H, 8.95; N, 10.30.

SUMMARY

1. A new and versatile reagent, α-bromocrotonyl chloride, has been prepared which may be used to synthesize α,β-diaminobutyramides and esters *via* the corresponding α-bromocrotonamides and esters.

2. Two α,β-diaminobutyric acids have been prepared.

3. The mechanisms of the reactions of these α-bromo-α,β-unsaturated carbonyl compounds with amines seem to be similar to those of the reactions of the previously studied α-bromo-α,β-unsaturated ketones (3, 8). The reactivity of the α-bromo-α,β-unsaturated carbonyl system in the amides is less than that in the ketones, esters or acids.

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[EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

AMINO- AND GUANIDINO-PHENYLGLUCOSIDES

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The amino- and guanidino-phenylglucosides described in this paper were synthesized for chemotherapeutic studies in experimental tuberculosis. The commercially accessible *o*-, *m*-, and *p*-nitrophenols and 2,4-dinitrophenol served as starting materials.

Pigman (1) prepared 2,4-dinitrophenyltetraacetyl-β-D-glucoside (I) by utilizing the Michael synthesis as modified by Mannich (2) (aqueous sodium hydroxide, acetone, acetobromoglucose). On repeating this procedure we were able to obtain I in only 9% yield in agreement with Pigman. By carrying out the reaction in dry acetone with potassium carbonate, the yield of I could be increased to 55%. This variation has also been applied successfully to the gluco-

TABLE I

EFFECT OF ACIDITY OF THE PHENOL

PHENOL	K_a at 25°C. (3)	YIELD OF GLUCOSIDE, %	
		K_2CO_3-Me_2CO (A)	$NaOH$-H_2O-Me_2CO (B)
2,4-Dinitro-	1.0×10^{-4}	55	9
o-Nitro-	6.8×10^{-8}	46	40
p-Nitro-	6.5×10^{-8}	35	24
m-Nitro-	1.0×10^{-8}	14	36

sidation of *o*- and *p*-nitrophenols. On the other hand, with *m*-nitrophenol the procedure developed by Mannich (2) was found preferable.

The data in Table I show that within this limited series the yield of glucoside varies directly with the acidity of the phenol in procedure A and inversely in procedure B with the exception of *o*-nitrophenol.

Hydrogenation of the nitrophenyltetraacetylglucosides with Raney nickel led readily to the amino compounds whose hydrochlorides condensed with cyanamide in ethyl acetate[1] to give good yields of the corresponding guanidino derivatives. In ethanol, the solvent usually employed, the cyanamide reaction failed to give the desired results. Further, no tractable products could be isolated when the deacetylated aminophenylglucoside hydrochlorides and cyanamide were brought to reaction in ethanol.

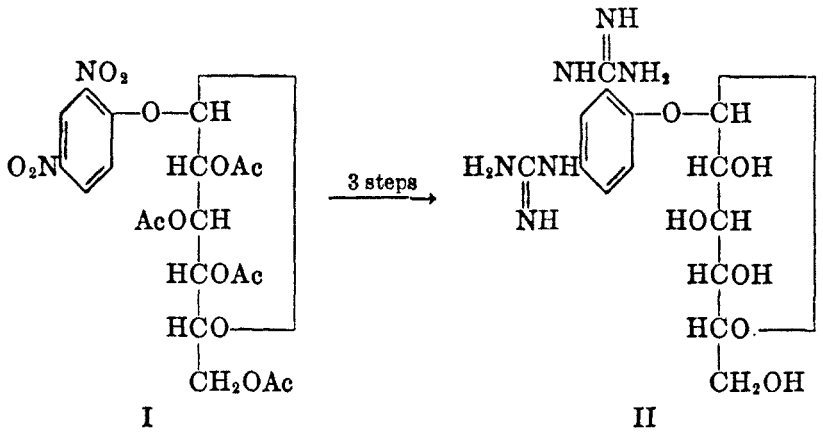
The amino- and guanidino-phenylglucosides were catalytically deacetylated with sodium methoxide in methanol.

Many of the basic glucosides or their salts were found to contain solvate water or ethanol. The water or ethanol content was determined by drying the com-

[1] Ethyl acetate as solvent was previously used to advantage in preparing 9-phenanthrylguanidine derivatives (4).

pounds to constant weight *in vacuo* at a temperature which would leave the molecule intact otherwise. However, in removing ethanol from *m*-aminophenyltetraacetyl-β-D-glucoside hydrochloride at 77°, hydrogen chloride was eliminated simultaneously, and pure *m*-aminophenyltetraacetyl-β-D-glucoside (base) resulted.

All compounds designated in the experimental part with NIH numbers were tested *in vitro*. None of these compounds showed significant inhibition of tubercle bacilli (H37Rv, Dubos-Davis medium).[2]



I II

Acknowledgment: We express thanks to Dr. Nelson K. Richtmyer of this Institute for helpful suggestions. The microanalyses are from the Institute service analytical laboratory under the direction of Mr. William C. Alford.

EXPERIMENTAL[3]

Acetobromoglucose.[4] β-Pentaacetylglucose, (30 g.), 40 ml. of 30–32% hydrogen bromide in acetic acid, and 10 ml. of acetic anhydride were allowed to stand overnight. Addition of 180 ml. of toluene and 10 ml. of acetic anhydride, evaporation of the solution to a sirup *in vacuo* (bath temperature 50–60°), and treatment of the sirup with 50 ml. of dry ether and and 50 ml. of ligroin (30–60°) gave, after two hours at room temperature and ice-cooling, 26 g. (82%) of product, m.p. 89–91°; lit. (6), m.p. 88–89°.

2,4-Dinitrophenyltetraacetyl-β-D-glucoside (I).[5] Five grams of 2,4-dinitrophenol, 5 g. of anhydrous potassium carbonate, 10 g. of acetobromoglucose, and 100 ml. of acetone (dried over potassium carbonate) were refluxed for 20 hours, diluted gradually (shaking) with an equal volume of water and ice-cooled. The precipitate was recrystallized from ethanol to give 6.8 g. (55%) of I, m.p. 176–177°, $[\alpha]_D^{20}$ + 34.9° (*c*, 1.09 in $CHCl_3$); lit. (1), m.p. 173–177° (cor.), $[\alpha]_D^{20}$ + 34.5° (*c*, 4 in $CHCl_3$).

[2] The compounds have been tested in the Tuberculosis Research Laboratory, U. S. Public Health Service, Cornell University Medical College, New York, N. Y., under the direction of Dr. Bernard D. Davis. An outline of the over-all plan of the cooperative project and methodological aspects will be given elsewhere; *cf.* "Cyclitol Derivatives. I." (5).

[3] All melting points were observed in a capillary and are uncorrected.

[4] We are indebted to Dr. H. G. Fletcher, Jr., of this Institute for the procedure used in this preparation.

[5] The β-configuration has been assigned to these glucosides on the basis of their rotation and mode of synthesis.

Anal. Calc'd for $C_{23}H_{22}N_2O_{14}$: C, 46.7; H, 4.3.
Found: C, 46.8; H, 4.4.

o-Nitrophenyltetraacetyl-β-D-glucoside was prepared as described for I (reflux time 2–6 hours, yield 46%); m.p. 160.5–161.5°, $[\alpha]_D^{20}$ + 43.0° (*c*, 1.20 in $CHCl_3$); lit. (7), m.p. 160–162°, $[\alpha]_D^{2'}$ + 45° ($CHCl_3$) and (8), m.p. 158–159°, $[\alpha]_D^{20}$ + 53.2° ($CHCl_3$).

The *p-isomer* (reflux time 15 hours, yield 35%) melted at 174–175° (7a, 8).

The *m-isomer* was more satisfactorily prepared by the Mannich procedure and had m.p. 136–137°, $[\alpha]_D^{20}$ − 34.8° (*c*, 0.5 in $CHCl_3$); lit. (1), $[\alpha]_D^{20}$ — 37° and (8), $[\alpha]_D^{20}$ − 26.8°.

2,4-Diaminophenyltetraacetyl-β-D-glucoside. Three grams of I, 3.0 g. of Raney nickel, and 75 ml. of methanol absorbed six moles of hydrogen during three hours. The mixture was filtered quickly through Filter-Cel and evaporated to dryness at reduced pressure (hydrogen atmosphere). Recrystallization of the residue from ethanol (under hydrogen) gave 2.3 g. (87%) of the diamine, m.p. 149–150°, $[\alpha]_D^{20}$ − 22.6° (*c*, 0.93 in methanol); glittering plates.

Anal. Calc'd for $C_{20}H_{26}N_2O_{10}$: C, 52.9; H, 5.8.
Found: C, 53.1; H, 6.1.

The *dihydrochloride* (NIH 3631) crystallized from methanol-ether in needles, m.p. 176–177.5° (dec.), $(\alpha)_D^{20}$ − 26.6° (*c*, 1.02 in methanol).

Anal. Calc'd for $C_{20}H_{26}Cl_2N_2O_{10}\cdot H_2O$: C, 44.0; H, 5.6; H_2O, 3.3.
Found: C, 43.8; H, 5.5; Loss (77°, 1 mm.), 3.8.

o-Aminophenyltetraacetyl-β-D-glucoside. The procedure used in this and in subsequent reductions was identical to the one above except that it was unnecessary to isolate and purify the products under hydrogen; yield 90%, m.p. 132–133°, $[\alpha]_D^{20}$ − 33.9° (*c*, 1.06 in methanol).

Anal. Calc'd for $C_{20}H_{25}NO_{10}$: C, 54.7; H, 5.7.
Found: C, 54.8; H, 5.7.

p-Aminophenyltetraacetyl-β-D-glucoside was obtained in a yield of 72%, m.p. 132–133.5°, $[\alpha]_D^{20}$ − 14.7° (*c*, 1.21 in $CHCl_3$). Helferich and Peters (9) used palladium-barium sulfate in this hydrogenation and reported a yield of 60%, m.p. 127–130°, $[\alpha]_D^{20}$ − 15.5°.

m-Aminophenyltetraacetyl-β-D-glucoside crystallized in glittering blades, m.p. 150–150.5°, $[\alpha]_D^{20}$ − 22.9° (*c*, 0.20 in methanol); yield 90%.

Anal. Calc'd for $C_{20}H_{25}NO_{10}$: C, 54.7; H, 5.7.
Found: C, 54.6; H, 5.9.

The *hydrochloride*, prepared with ethanolic hydrogen chloride, crystallized from methanol-ether in broad needles, m.p. below 125° (froth), $[\alpha]_D^{20}$ − 30.6° (*c*, 0.24 in methanol).

Anal. Calc'd for $C_{20}H_{26}ClNO_{10}\cdot C_2H_5OH$: C, 50.6; H, 6.2; Cl, 6.8; HCl + C_2H_5OH, 15.8.
Found: C, 51.0; H, 6.1; Cl, 7.1; Loss (77°, 1 mm.), 15.7.

The residue from the loss-in-weight determination proved to be the original, pure base.

2,4-Diaminophenyl-β-D-glucoside (NIH 3640). One gram of 2,4-diaminophenyltetraacetyl-β-D-glucoside, 10 ml. of methanol, and 0.5 ml. of methanolic sodium methoxide[6] gave, after one hour at 25° and one hour at 3°, 0.6 g. (95%) of glucoside; needles from water-ethanol, m.p. 189–191° (dec.), $(\alpha)_D^{20}$ − 47.8° (*c*, 0.90 in water).

Anal. Calc'd for $C_{12}H_{18}N_2O_6\cdot C_2H_5OH$: C, 50.6; H, 7.3; C_2H_5OH, 13.8.
Found: C, 50.7; H, 7.3; Loss (130°, 1 mm.), 12.6.

The *monohydrochloride* was obtained from the unstable dihydrochloride, either on allowing the latter to stand in air or by boiling it in methanol; needles from water-methanol which char at 190–200°, but do not melt below 300°.

Anal. Calc'd for $C_{12}H_{19}ClN_2O_6$: Cl, 11.0. Found: Cl, 11.3

o-Aminophenyl-β-D-glucoside (NIH 3634). This deacetylation was effected similarly to the one above. After 15 hours at 3° the yield was 75%, m.p. 183.5–184.5°, $[\alpha]_D^{20}$ − 71.2°. (*c*, 0.55 in water).

Anal. Calc'd for $C_{12}H_{17}NO_6\cdot\frac{1}{2}H_2O$: C, 50.6; H, 6.5; H_2O, 4.7.
Found: C, 50.4; H, 6.4; Loss (140°, 1 mm.), 4.8.

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[6] Three grams of sodium in 100 ml. of methanol.

A sample dried at 130° gave the following analysis:

Anal. Calc'd for $C_{12}H_{17}NO_6$: C, 53.1; H, 6.3.

Found: C, 52.8; H, 6.4.

p-Aminophenyl-β-D-glucoside (NIH 3646) was obtained in a yield of 65%, m.p. 156–158°, $[\alpha]_D^{20}$ − 55.5° (water); lit. (9), m.p. 157–160°, $[\alpha]_D^{20}$ − 65°.

m-Aminophenyl-β-D-glucoside (NIH 3773) crystallized from methanol in needles of m.p. 138–140°[7], $[\alpha]_D^{20}$ − 66.0° (*c*, 0.25 in water).

Anal. Calc'd for $C_{12}H_{17}NO_6 \cdot \frac{3}{4} H_2O$: C, 50.6; H, 6.6; H_2O, 4.7.

Found: C, 50.5; H, 6.9; Loss (77°, 1 mm.), 4.5.

On recrystallization from ethanol and drying for one hour at 77° the compound gave the following analysis:

Anal. Calc'd for $C_{12}H_{17}NO_6 \cdot C_2H_5OH$: C, 53.0; H, 7.3; C_2H_5OH, 14.5.

Found: C, 53.2; H, 6.8; Loss (135°, 1 mm.); 12.2.[8]

2,4-Diguanidinophenyltetraacetyl-β-D-glucoside dihydrochloride. One gram of 2,4-diaminophenyltetraacetyl-β-D-glucoside dihydrochloride, 0.5 g. of cyanamide,[9] and 50 ml. of ethyl acetate, was refluxed for one-half hour, cooled, decanted and the residue dried. The 1.1 g. of tan solid was dissolved in ethanol and the solution shaken with Norit. Addition of ether and cooling gave a solid which was filtered and ground in a mortar under ether. By repeating this purification process 0.8 g. (67%) of an amorphous, hygroscopic solid was obtained which was suitable for analysis after drying at 75°; m.p. 180–225° (dec.), $[\alpha]_D^{20}$ − 8.3° (*c*, 0.54 in ethanol).

Anal. Calc'd for $C_{22}H_{32}Cl_2N_6O_{10}$: Cl, 11.6; N, 13.7.

Found: Cl, 11.9; N, 13.5.

The *sulfate* (NIH 3752) was prepared by addition of 0.9 g. of the dihydrochloride in water to 0.4 g. of silver sulfate in 50–60 ml. of water, ice-cooling, filtering, evaporating the filtrate to dryness *in vacuo*, and triturating the residue with ethanol; 0.8 g. of plates from water-methanol, m.p. 296° (dec., evac. tube)[10], $[\alpha]_D^{20}$ − 17.9° (*c*, 0.43 in water).

Anal. Calc'd for $C_{22}H_{32}N_6O_{14}S$: C, 41.5; H, 5.1; N, 13.2.

Found: C, 41.5; H, 5.2; N, 13.1.

o-Guanidinophenyltetraacetyl-β-D-glucoside hydrochloride (NIH 3789). A mixture of 4.0 g. of *o*-aminophenyltetraacetyl-β-D-glucoside, 1.0 g. of cyanamide, 55 ml. of ethyl acetate, 5 ml. of ethanol, and 1.4 ml. of 20% ethanolic hydrogen chloride, refluxed 40 minutes and cooled gave 2.2 g. (50%) of hydrochloride, m.p. 182–187°; needles from 97% ethanol, m.p. 192–194°, $[\alpha]_D^{20}$ − 8.6° (*c*, 0.48 in water).

Anal. Calc'd for $C_{21}H_{28}ClN_3O_{10} \cdot \frac{1}{2}H_2O$: C, 47.9; H, 5.6; H_2O, 1.7.

Found: C, 47.7; H, 5.7; Loss (140°, 1 mm.), 1.7.[11]

p-Guanidinophenyltetraacetyl-β-D-glucoside hydrochloride (NIH 3786). Two grams of *p*-aminophenyltetraacetyl-β-D-glucoside, 0.5 g. of cyanamide, 25 ml. of ethyl acetate, and 0.8 ml. of 20% ethanolic hydrogen chloride, refluxed two hours and ice-cooled, gave 1.4 g. (60%) of product, m.p. 218–221.5°. It crystallized from water in large prisms which effloresce[12] immediately after filtration to a crystalline powder, m.p. 220–223°, $[\alpha]_D^{20}$ − 27.4° (*c*, 0.36 in water).

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[7] In a preheated bath this compound would melt as low as 115° with bubbling.

[8] The low loss-in-weight and hydrogen values are probably due to some ethanol loss when the sample was dried at 77° prior to analysis.

[9] The cyanamide used was a gift from the American Cyanamid Company. It was freed of about 20% of dicyandiamide by digestion with ether, filtration, and addition of ligroin (30–60°) to the filtrate.

[10] The substance did not melt in an open capillary.

[11] The dried sample was very hygroscopic and quickly attained its original weight.

[12] A recrystallization from methanol-ether gave a mixture of prisms and blades which, after filtration, yielded the same powder of m.p. 220–223°.

Anal. Calc'd for $C_{21}H_{28}ClN_3O_{10}$: C, 48.7; H, 5.5.
Found: C, 48.4; H, 5.5.

m-Guanidinophenyltetraacetyl-β-D-glucoside hydrochloride (NIH 3776). Two grams of *m*-aminophenyltetraacetyl-β-D-glucoside hydrochloride, 0.4 g. of cyanamide, and 25 ml. of ethyl acetate, refluxed 0.5 hour, gave 1.8 g. (80%) of product, m.p. 236–237°, $[\alpha]_D^{20}$ − 22.4° (*c*, 0.39 in water); large needles from methanol-ether.

Anal. Calc'd for $C_{21}H_{28}ClN_3O_{10}$: C, 48.7; H, 5.5.
Found: C, 48.5; H, 5.4.

2,4-Diguanidinophenyl-β-D-glucoside sulfate (NIH 3769) (II). A mixture of 0.7 g. of 2,4-diguanidinophenyltetraacetyl-β-D-glucoside sulfate, 5 ml. of methanol, and 3 ml. (over two moles) of methanolic sodium methoxide[6] was shaken for one hour and let stand for four hours at 25–30° and overnight at 3°. The mixture was filtered (Filter-Cel) and the filtrate diluted with ethanol-ether. Cooling gave 0.35 g. of an amorphous solid which, in a little ice-cold water, was treated with 0.4 ml. of 5 *N* H_2SO_4. Dilution with methanol and cooling gave 0.35 g. (70%) of amorphous sulfate.[13] It was dissolved in a little water and precipitated with methanol (cooling), then ground in a mortar with methanol and filtered. Finally, for analysis it was digested 0.5 hr. in boiling methanol and dried at 77° *in vacuo*; m.p. 220–225° (brown froth), $[\alpha]_D^{20}$ − 37.2° (*c*, 0.41 in water).

Anal. Calc'd for $C_{14}H_{24}N_6O_{10}S$: C, 35.9; H, 5.2; N, 17.9.
Found: C, 35.7; H, 5.3; N, 17.8.

o-Guanidinophenyl-β-D-glucoside (NIH 3842). One gram of *o*-guanidinophenyltetraacetyl-β-D-glucoside hydrochloride, 4 ml. of methanol, and 2 ml. of methanolic sodium methoxide,[6] were let stand seven hours, cooled at 2° and filtered. Dilution with dry ether gave an amorphous solid which crystallized on trituration with hot absolute ethanol; yield 0.5 g. (80%), m.p. 206–207° (dec.), $[\alpha]_D^{20}$ − 88.3° (*c*, 0.41 in water), needles from aqueous methanol-ether or 70% ethanol.

Anal. Calc'd for $C_{13}H_{19}N_3O_6$: C, 49.8; H, 6.1.
Found: C, 49.6; H, 6.1.

The *picrate* crystallized from methanol-ligroin (30–60°) or water in yellow needles, m.p. 208–210°.

Anal. Calc'd for $C_{19}H_{22}N_6O_{13}$: C, 42.1; H, 4.1.
Found: C, 41.9; H, 4.2.

p-Guanidinophenyl-β-D-glucoside picrate. This deacetylation was effected similarly to the previous one. The amorphous base in a little water was added to a hot solution of 0.5 g. of picric acid in 15 ml. of water to give 0.9 g. (80%) of picrate, m.p. 185–190°; yellow needles from water, m.p. 195–196.5°.

Anal. Calc'd for $C_{19}H_{22}N_6O_{13}\cdot 2H_2O$: C, 39.5; H, 4.5; H_2O, 6.2.
Found: C, 39.5; H, 4.7; Loss (117°, 1 mm.), 6.6.

The *hydrochloride* (NIH 3787), prepared by addition of a slight excess of 20% ethanolic hydrogen chloride to an ice-cold dioxane solution of the picrate and dilution with an equal volume of ether, crystallized from methanol-ether (Norit) in prisms of m.p. 223° (dec.), $[\alpha]_D^{20}$ − 53.0° (*c*, 0.33 in water).

Anal. Calc'd for $C_{13}H_{20}ClN_3O_6$: C, 44.6; H, 5.8.
Found: C, 44.6; H, 5.9.

m-Guanidinophenyl-β-D-glucoside (NIH 3783). This deacetylation was effected as described in the two previous experiments. From the methanol filtrate, diluted with 0.5 ml. of dry ether, 0.5 g. (80%) of small prisms separated. Recrystallized from water-ethanol, then methanol-ether, they melted at 200–202° (dec.), $[\alpha]_D^{20}$ −57.0° (*c*, 0.37 in water). A sample was dried at 97° for analysis.

Anal. Calc'd for $C_{13}H_{19}N_3O_6$: C, 49.8; H, 6.1.
Found: C, 49.5; H, 6.6.

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[13] Repeated efforts to crystallize this and several other salts failed.

SUMMARY

1. The β-D-glucosides of *o*-, *m*-, and *p*-aminophenol, 2,4-diaminophenol, and their guanidino analogs are described.

2. A variation of the Michael synthesis has given improved yields of certain nitrophenylglucoside tetraacetates.

3. Hydrogenation of the nitrophenylglucoside tetraacetates with Raney nickel yielded the corresponding amino compounds.

4. The latter, as their hydrochlorides, were converted to the guanidino derivatives in good yield with cyanamide in ethyl acetate.

5. Deacetylation of the tetraacetates of the basic glucosides has been effected with sodium methoxide in methanol.

BETHESDA 14, MD.

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[EXPERIMENTAL BIOLOGY AND MEDICINE INSTITUTE, NATIONAL INSTITUTES OF HEALTH]

AMINO- AND GUANIDINO-PHENYLGLUCOSAMINIDES

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In the foregoing communication (1), several amino- and guanidino-phenyl-β-D-glucosides were described. The present paper deals with analogous glucosaminide derivatives which have been tested for their activity in experimental tuberculosis.

To our knowledge, the first synthesis of a phenylglucosaminide was reported by Irvine and Hynd (2) and consisted in the reaction of a phenol (*e.g.*, salicylaldehyde) with 1-bromo-1-desoxy-3,4,6-triacetyl-D-glucosamine hydrobromide (I),[1] pyridine being used as a hydrogen bromide acceptor. Twenty years later, Helferich and Iloff (3) prepared phenyl N-acetyl-β-D-glucosaminide by heating phenol and pentaacetylglucosamine with *p*-toluenesulfonic acid and deacetylating the product with dilute sodium hydroxide. The following year Helferich, *et al* (4) obtained the completely deacetylated glucosaminide[2] by the interaction of sodium phenoxide and I (phenol as solvent) and subsequent alkaline hydrolysis. Finally, the N-*p*-tosyl derivative of this glycoside was prepared (5) from 1-bromo-1-desoxy-N-*p*-tosyl-3,4,6-triacetyl-D-glucosamine and sodium phenoxide followed by deacetylation with barium methoxide.

In preparing glucosaminides of type VIII from nitrophenols, it appeared necessary to mask the amino group of the sugar moiety with an acyl group capable of facile and selective removal at a desired step in the synthesis. The known N-carbobenzyloxy-1,3,4,6-tetraacetyl-D-glucosamine (6, 7) (II) appeared to be a suitable starting material. However, in the bromination of II with hydrogen bromide in acetic acid,[3] scission of the carbobenzyloxy group resulted giving I, identical with that prepared according to Irvine, *et al* (8) from D-glucosamine hydrochloride and acetyl bromide.

We then found that if potassium *p*-nitro- or 2,4-dinitro-phenoxide, the corresponding free phenol, and I were brought to reaction in dry acetone, 30–45% yields of the nitrophenyl-β-D-glucosaminides (III) were obtained and readily converted to the N-carbobenzyloxy derivatives (IV). Hydrogenation of IV in ethyl acetate with Raney nickel afforded the amino compounds (V) which, as hydrochlorides, were condensed with cyanamide to give the guanidines (VI). Removal of the carbobenzyloxy group of VI was effected with palladized charcoal and hydrogen and the acetyl groups were subsequently cleaved with methanolic sodium methoxide, giving the desired products (VIII).

2,4-Diaminophenyl-3,4,6-triacetyl-β-D-glucosaminide (IX) could be prepared

[1] In view of its high positive rotation, this compound is presumed to have the α-configuration.

[2] As Neuberger and Pitt Rivers (5) observed, designation of the glucosaminides of Helferich and co-workers (3, 4) as β is tentative and based only on their mode of formation and rotation. Similarly, the β-configuration assigned to our compounds is provisional.

[3] N-bromosuccinimide was without effect in a single attempt to brominate II.

either by the hydrogenation (Raney nickel) of III-b or by the hydrogenolysis (palladium-charcoal) of V-b. Sodium methoxide deacetylation of IX yielded 2,4-diaminophenyl-β-D-glucosaminide.

Compounds bearing an NIH number in the experimental part were tested *in vitro*. None of them showed significant inhibition of tubercle bacilli (H37Rv, Dubos-Davis medium).[4]

Acknowledgment: We are indebted to Mr. H. George Latham, Jr., of this Laboratory for the preparation of large amounts of 1-bromo-1-desoxy-3,4,6-triacetyl-D-glucosamine hydrobromide. The microanalyses are from the Institute service analytical laboratory under the direction of Mr. William C. Alford.

EXPERIMENTAL[5]

1-Bromo-1-desoxy-3,4,6-triacetyl-D-glucosamine hydrobromide (I).[1] (a) *From D-glucosamine hydrochloride.* The procedure of Irvine, *et al.* (8) was adapted to larger runs. A well-stirred mixture of 16.8 g. of D-glucosamine hydrochloride and 32 ml. of acetyl bromide was kept at 60–65° until the brown broth had changed to a viscous mass (40–60 minutes). Most of the excess reagent was distilled *in vacuo*. The residue was dried overnight *in vacuo* over potassium hydroxide and calcium chloride and digested with 50 ml. of boiling chloroform. Filtration gave 7.5–10.5 g. of starting material.[6] The filtrate was treated with Norit, then diluted with dry ether (stirring) until crystallization began. After cooling at 3° the precipitate was washed with acetone-ether (1:2) to give 7.5–13.5 g. of I, m.p. 153–155° (dec.), $[\alpha]_D^{20}$ +149° (*c*, 0.34 in acetone) in substantial agreement with the reported values (8).

(b) *From II.*[7] Five grams of II (6, 7), 7 ml. of 30% hydrogen bromide in acetic acid, and 2 ml. of acetic anhydride were shaken for 15 minutes and left at 25° overnight. Addition of 30 ml. of dry toluene and 2 ml. of acetic anhydride, evaporation to dryness *in vacuo*, trituration of the residue with dry ether, and ice-cooling gave 4.3 g. (85%) of I; m.p. 154–155° (dec.), $[\alpha]_D^{20}$ +150° (*c*, 0.49 in acetone) after a recrystallization from acetone ether.

2,4-Dinitrophenyl-3,4,6-triacetyl-β-D-glucosaminide[2] (III-b) *hydrochloride* (NIH 3347). To 10 g. of potassium *2,4*-dinitrophenoxide, 10 g. of *2,4*-dinitrophenol, and 150 ml. of acetone (dried over potassium carbonate) was added during 20–30 minutes (shaking), 9.6 g. of I. The mixture was left at 25° for *ca.* 15 hours. Ether and excess dilute potassium carbonate were added. The aqueous layer[8] was again extracted with ether and the combined extracts were washed once with water, dried, and acidified to Congo Red with alcoholic hydrogen chloride. The oily hydrochloride soon crystallized; yield 3.5 g. (32%), m.p. 198–199° (dec.), needles from methanol-ether, $[\alpha]_D^{20}$ −33.1° (*c*, 0.51 in methanol).

Anal. Calc'd for $C_{18}H_{22}ClN_3O_{12}$: Cl, 7.0. Found: Cl, 7.1.

The *base*, obtained from the hydrochloride with dilute aqueous ammonia, crystallized from ethanol in needles, m.p. 147–148°, $[\alpha]_D^{20}$ +63.1° (*c*, 0.21 in $CHCl_3$), after drying at 77°.

Anal. Calc'd for $C_{18}H_{21}N_3O_{12}$: C, 45.9; H, 4.5.

Found: C, 45.4; H, 4.6.

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[4] The compounds have been tested in the Tuberculosis Research Laboratory, U. S. Public Health Service, Cornell University Medical College, New York, N. Y., under the direction of Dr. Bernard D. Davis. An outline of the over-all plan and methodological aspects will be given elsewhere.

[5] All melting points were observed in a capillary and are uncorrected. Rotations were made in a 4-dm. tube.

[6] The recovered D-glucosamine salt could be reused in this experiment without purification.

[7] This reaction was carried out by Mr. H. George Latham, Jr., of this laboratory.

[8] Acidification of this aqueous layer gave 15 g. of 2,4-dinitrophenol.

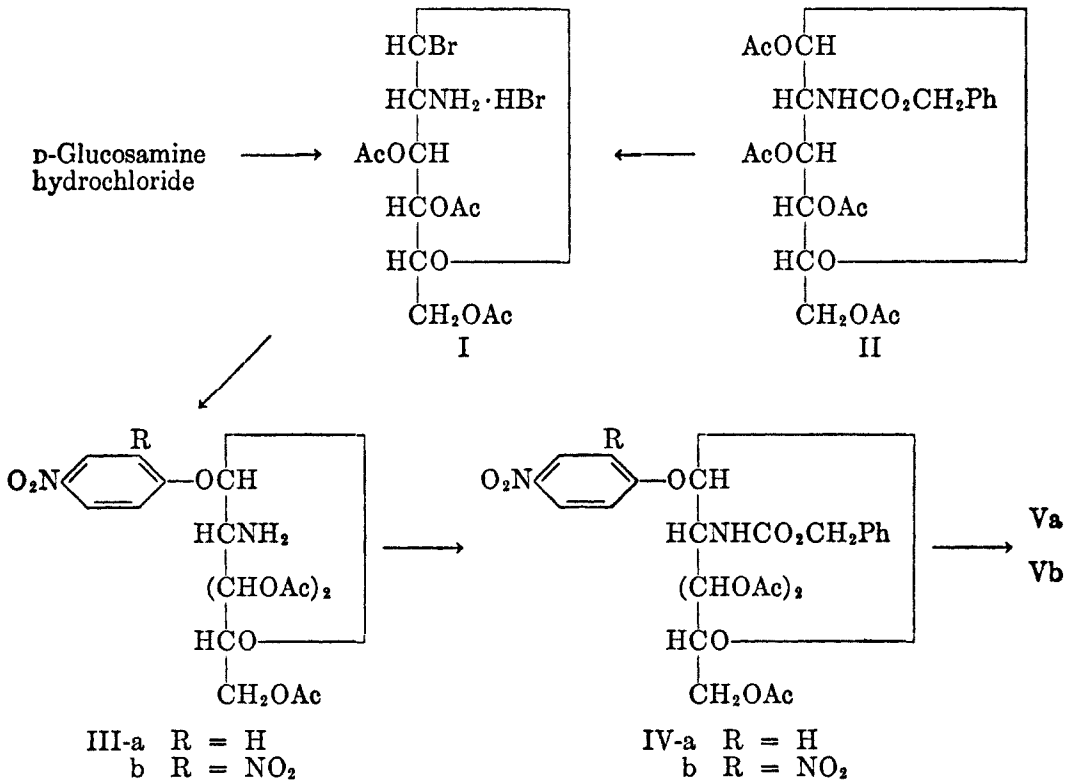
p-Nitrophenyl-3,4,6-triacetyl-β-D-glucosaminide (III-a) *hydrochloride* (NIH 3898). This compound was prepared as described for III-b; yield 44%, fine matted needles from methanol-ether, m.p. 218–220° (dec.), $[\alpha]_D^{20}$ −42.0° (*c*, 0.37 in methanol).

Anal. Calc'd for $C_{18}H_{23}ClN_2O_{10}$: Cl, 7.7. Found: Cl, 7.6.

2,4-Diaminophenyl-3,4,6-triacetyl-β-D-glucosaminide (IX) (NIH 3924). A mixture of 1.6 g. of III-b, 23 ml. of ethyl acetate,[9] and 2 g. of Raney nickel absorbed three moles of hydrogen during 3–5 hours. Rapid filtration at 0° through Filter-Cel into an equal volume of ligroin (30–60°) and ice-cooling gave 1.3 g. (90%) of IX. A quick recrystallization from ethyl acetate gave silvery plates of m.p. 104–107° to a froth; $[\alpha]_D^{20}$ −33.3° (*c*, 0.42 in ethyl acetate).

Anal. Calc'd for $C_{18}H_{27}N_3O_8 \cdot H_2O$: C, 50.3; H, 6.3; N, 9.8; H_2O, 4.2.

Found: C, 50.3; H, 6.4; N, 9.5; Loss (77°, 1 mm.), 4.0.



IX was also prepared in 50–70% yield by the hydrogenation of V-b in ethyl acetate-methanol with 5% palladium-charcoal; reaction time, three hours.

2,4-Diaminophenyl-β-D-glucosaminide (NIH 3913). A mixture of 0.8 g. of IX, 2 ml. of methanol, and 0.2 ml. of methanolic sodium methoxide[10] was shaken to solution and left for one hour at 25° and overnight at 3°; yield of dark brown prisms, m.p. 182–185°, 0.4 g. (75%). They could be obtained white by dissolving them in 10 ml. of boiling methanol, treating the solution with Norit, concentrating the filtrate *in vacuo* under hydrogen to 3 ml., and seeding; m.p. 184–186°, $[\alpha]_D^{20}$ −48.4° (*c*, 0.19 in water).

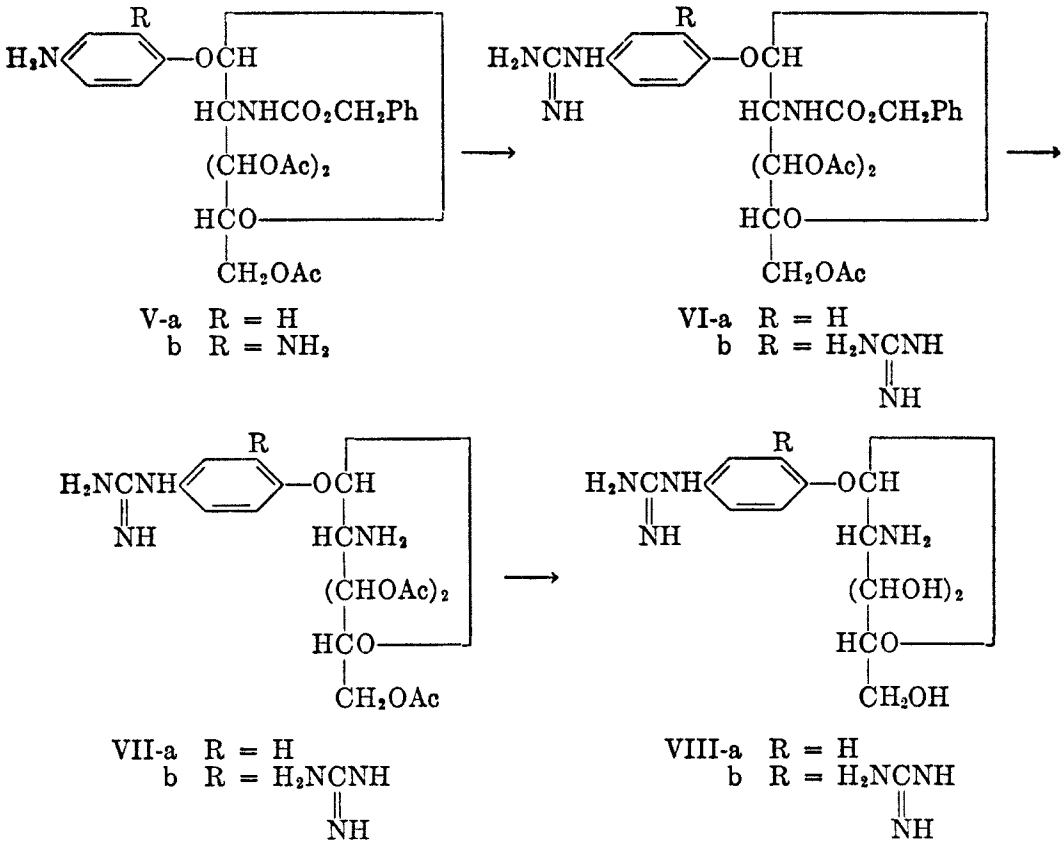
[9] With methanol as the solvent absorption proceeded smoothly, but the resultant filtrate became discolored so rapidly that isolation of IX in a reasonably pure state was practically impossible.

[10] Three grams of sodium in 100 ml. of methanol.

Anal. Calc'd for $C_{12}H_{19}N_3O_8$: C, 50.5; H, 6.7.
Found: C, 50.5; H, 7.0.

2,4,-Dinitrophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-D-glucosaminide (IV-b). To a stirred mixture of 2.0 g. of III-b hydrochloride, 0.8 g. of sodium bicarbonate, and 150 ml. of water was added during 15–20 minutes, 1.2 cc. of benzyl chlorocarbonate. After stirring for 2–3 hours the solid was washed with water and recrystallized from methanol; yield of needles 2.1 g. (88%), m.p. 172–173°, $[\alpha]_D^{20}$ +33.1° (*c*, 0.27 in $CHCl_3$).

Anal. Calc'd for $C_{26}H_{27}N_3O_{14}$: C, 51.6; H, 4.5.
Found: C, 51.6; H, 4.6.



III-b → 2,4-Diaminophenyl-3,4,6-tricetyl-β-D-glucosaminide (IX) ← V-b

p-Nitrophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-D-glucosaminide (IV-a). As described for IV-b, this product was obtained from aqueous methanol[11] in 90% yield. It crystallized from ethanol[11] as needles, m.p. 176–177°, $[\alpha]_D^{20}$ −8.2° (*c*, 0.46 in $CHCl_3$).

Anal. Calc'd for $C_{26}H_{28}N_2O_{12}$: C, 55.7; H, 5.0.
Found: C, 55.8; H, 5.1.

2,4-Diaminophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-D-glucosaminide (V-b). Two grams of IV-b and 25 cc. of ethyl acetate absorbed six moles of hydrogen (Raney nickel) during

[11] If the compound was not allowed to crystallize slowly from a warm solution, it precipitated as a gelatinous mass.

4–7 hours. Rapid filtration into two volumes of ligroin (30–60°) gave an oil which soon crystallized; yield 1.7 g. (94%), m.p. 149–150°, needles from propanol-ligroin, $[\alpha]_D^{20}$ ±0.0° (*c*, 0.45 in $CHCl_3$).

Anal. Calc'd for $C_{26}H_{31}N_3O_{10}$: C, 57.2; H, 5.7.

Found: C, 57.2; H, 5.7.

*p-Aminophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-*D*-glucosaminide* (V-a). Hydrogenation of IV-a as described for IV-b gave a 91% yield of V-a; needles from ethanol, m.p. 167.5–168°, $[\alpha]_D^{20}$ +14.7° (*c*, 0.46 in $CHCl_3$).

Anal. Calc'd for $C_{26}H_{30}N_2O_{10}$: C, 58.9; H, 5.7.

Found: C, 59.0; H, 5.6.

*2,4-Diguanidinophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-*D*-glucosaminide* (VI-b) *dihydrochloride.* To 1.5 g. of V-b, 0.5 g. of cyanamide, and 75 ml. of ethyl acetate was added 0.45 ml. of conc'd hydrochloric acid and the gelatinous mass was refluxed briskly for 20–24 hrs. During the first eight hours 0.4 g. of cyanamide was added at equal intervals in 0.2-g. portions. After ice-cooling the liquid was decanted from a brown, viscous residue which, in ethanol, was cleared with Norit. Addition of dry ether to the filtrate gave an amorphous hygroscopic solid which was again subjected to this precipitation process. After washing with ether and drying at 77°[12], the sample (1.0 g., 53%) was satisfactory for analysis; $[\alpha]_D^{20}$ +1.2° (*c*, 2.18 in water).

Anal. Calc'd for $C_{28}H_{37}Cl_2N_7O_{10}$: Cl, 10.1; N, 14.0.

Found: Cl, 9.9; N, 13.8.

The *sulfate* was prepared by adding 0.24 g. of silver sulfate in water to 0.54 g. of the dihydrochloride in water, cooling, filtering, and evaporating the filtrate *in vacuo*; oblong plates from water-methanol, m.p. 282–284° (dec.) in a bath preheated to 280°, $[\alpha]_D^{20}$ ±0.0° (*c*, 1.59 in water).

Anal. Calc'd for $C_{28}H_{37}N_7O_{14}S \cdot H_2O$: C, 45.1; H, 5.3; H_2O, 2.4.

Found: C, 44.9; H, 5.4; Loss (160°, 1 mm.), 2.4.[13]

*2,4-Diguanidinophenyl-3,4,6-triacetyl-β-*D*-glucosaminide* (VII-b) *sulfate*[14] Hydrogen was passed through a mixture of 0.5 g. of VI-b sulfate, 0.2 g. of 5% palladium-charcoal, and 10 ml. of water for six hours. The filtered solution was concentrated *in vacuo* to *ca.* 3 ml., ice-cooled, and treated with 0.15 ml. of 5 *N* H_2SO_4. Dilution with a few drops of dioxane gave 0.3 g. (60%) of cubic prisms, m.p. 205° (dec.); $[\alpha]_D^{20}$ −31.8° (*c*, 0.45 in water) after a recrystallization from water. Upon drying at 78° the sample was very hygroscopic but soon became stable as the crystalline pentahydrate.

Anal. Calc'd for $C_{20}H_{32}N_7O_{14}S_{3/2} \cdot 5H_2O$: C, 32.8; H, 5.8; H_2O, 12.3.

Found: C, 32.3; H, 5.9; Loss (97°, 1 mm.), 12.1.[13]

A dried sample was also analyzed.[12]

Anal. Calc'd for $C_{20}H_{32}N_7O_{14}S_{3/2}$: C, 37.4; H, 5.0.

Found: C, 36.8; H, 5.2.

*p-Guanidinophenyl-3,4,6-triacetyl-β-*D*-glucosaminide dihydrochloride* (VII-a). A methanol-ether solution of V-a was acidified to Congo Red with alcoholic hydrogen chloride to give a gelatinous hydrochloride which was filtered, washed with ether, and dried in the desiccator. This hydrochloride (1.5 g.), 0.5 g. of cyanamide, and 20 ml. of 97% ethanol were refluxed for 2–3 hours. Dilution with an equal volume of ether and frequent warming gave 0.9 g. of hygroscopic needles of VI-a hydrochloride. The latter (1.1 g), 0.4 g. of 5% palladium-charcoal, and 25 ml. of methanol were treated with a stream of hydrogen for 6–8 hours. The filtered solution was ice-cooled, acidified to Congo Red with alcoholic hydrogen chloride, diluted with 70 ml. of ether, and cooled in ice to give 0.9 g. of crude VII-a dihydrochloride. For analysis it was recrystallized from methanol-ether, than methanol-ethyl acetate;[11] needles, m.p. 226–227° (dec.), $[\alpha]_D^{20}$ −28.1° (*c*, 0.32 in water).

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[12] The dried compound was very hygroscopic and had to be weighed in a "pig."

[13] On exposure to air the dried sample quickly attained its original weight.

[14] The amorphous trihydrochloride (NIH 3899) was tested.

Anal. Calc'd for $C_{18}H_{28}Cl_2N_4O_8$: C, 44.6; H, 5.5; Cl, 13.9.
Found: C, 44.4; H, 5.6; Cl, 13.8.

The found values are corrected for 1.1% of water, determined by a weight loss at 77°.[13]

2,4-Diguanidinophenyl-β-D-glucosaminide (VIII-b) *sulfate* (NIH 4086). A mixture of 0.6 g. of VII-b sulfate, 6 ml. of methanol, and 3 ml. of methanolic sodium methoxide[10] was shaken for 1–2 hours, cooled to 3°, and filtered. The filtrate, diluted with one volume of ether, gave an amorphous base which, in methanol, was treated with 0.6 ml. of 5 *N* H_2SO_4. The resultant solid was recrystallized from water-dioxane to give 0.4 g. (83%) of sulfate, m.p. 240° (dec.) in a bath preheated to 230°; needles $[\alpha]_D^{20}$ −48.7° (*c*, 0.37 in water). For analysis it was dried at 97° for three hours.[12]

Anal. Calc'd for $C_{14}H_{26}N_7O_{11}S_3/_2$: C, 32.6; H, 5.1; S, 9.3.
Found: C, 32.4; H, 5.2; S, 9.6.

A sample dried to constant weight at 97° gained 11.7% on exposure to air; calc'd gain to $C_{14}H_{26}N_7O_{11}S_3/_2 \cdot 3H_2O$, 10.5%. Thus the air-stable sample appears to be a trihydrate.

p-Guanidinophenyl-β-D-glucosaminide (VIII-a) (NIH 4092). A mixture of 0.6 g. of crude VII-a dihydrochloride, 4 ml. of ethanol, and 4 ml. of sodium methoxide solution[10] gave 0.4 g. of VIII-a, m.p. 224–225° (dec.), containing a little sodium chloride, after two hours at 25° and 1.5 hours at 3°. Recrystallization from water (1 ml.)-methanol (6 ml.) gave heavy prisms or needles, m.p. 225–226° (dec.), $[\alpha]_D^{20}$ −66.7° (*c*, 0.24 in water). The analytical sample was dried at 97°.

Anal. Calc'd for $C_{13}H_{20}N_4O_5$: C, 59.0; H, 6.5.
Found: C, 49.6; H, 6.5.

SUMMARY

Starting from *p*-nitrophenol and 2,4-dinitrophenol, the β-D-glucosaminide derivatives (VIII) of *p*-guanidinophenol and 2,4-diguanidinophenol have been synthesized and found ineffective *in vitro* against tubercule bacilli (H37Rv, Dubos-Davis medium).

2,4-Diaminophenyl-3,4,6-triacetyl-β-D-glucosaminide (IX) was prepared either from 2,4-dinitrophenyl-3,4,6-triacetyl-β-D-glucosaminide (III-b) or from 2,4-diaminophenyl-N-carbobenzyloxy-3,4,6-triacetyl-β-D-glucosaminide (V-b) and deacetylated with methanolic sodium methoxide.

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STEROIDS. IX. THE DIENONE-PHENOL REARRANGEMENT IN THE CHOLESTEROL SERIES

J. ROMO, CARL DJERASSI, AND G. ROSENKRANZ

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Woodward and Singh (1) on the basis of model experiments in the naphthalene series have clearly demonstrated that the acid-catalyzed rearrangement of steroidal 1,4-dien-3-ones (I), first studied by Inhoffen and collaborators (2), does *not* result in the formation of 1-methyl phenols (II) as believed originally (2), but in products of unknown constitution.

In the preceding paper of this series (3), it was demonstrated that the *authentic* 1-methyl-3-hydroxy steroids (II) can be obtained by dienone-phenol rearrangement of a 1,4,6-trien-3-one (IV) followed by hydrogenation of the resulting 6-dehydro-1-methylphenol (V). Our initial study was limited to the androstane series (IV, R = O, OH) and resulted in the first synthesis of authentic, estrogenically potent, 1-methylestrone and 1-methylestradiol (II, R = O, OH; R'_4 = H).

Since Inhoffen (2) had described the synthesis of a "sterinphenol" by dienone-phenol rearrangement of 1,4-cholestadien-3-one (I, R = C_8H_{17}) and had assigned to it structure II (R = C_8H_{17}), now known to be incorrect (1, 3), it was deemed necessary to prepare the authentic aromatic cholesterol derivative by the procedure which had proved successful in our hands in the androstane series (3).

1,4,6-Cholestatrien-3-one (IV, R = C_8H_{17}), the required starting material, was previously obtained (4) as crystals with m.p. 82–83°, u.v. maxima at 224, 256, and 300 mμ, by dibromination of Δ^4-cholesten-3-one and dehydrobromination. Martens (5) has attempted to prepare this substance by Wohl-Ziegler bromination of 1,4-cholestadien-3-one (I, R = C_8H_{17}) and subsequent collidine treatment of the 6-bromo derivative III; however the trienone IV was obtained only as an oil, characterized by an impure semicarbazone. Repetition of this sequence of reactions in our laboratory gave the 6-bromo compound III, identical with that described by Martens (5), and dehydrobromination smoothly afforded the crystalline 1,4,6-cholestatrien-3-one (IV, R = C_8H_{17}) identical in all respects with the specimen prepared by the alternate procedure (4). Dienone-phenol rearrangement of this trienone in the customary manner afforded a phenolic acetate (Vb), m.p. 114°, $[\alpha]_D^{20}$ −99.6°, which on saponification led to the free 6-dehydro-1-methyl phenol (Va), m.p. 146°, $[\alpha]_D^{20}$ −131°, u.v. maxima (Fig. 1) at 228, 266, and 304 mμ, and on methylation to the methyl ether Vc. The phenol V thus exhibited the typical negative rotation of 6-dehydrophenols (6) and the characteristic ultraviolet absorption spectrum of a phenol with an additional double bond in the *meta* position (3, 4, 7). Catalytic hydrogenation of the acetate Vb and saponification produced 1-methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (IIa) with m.p. 128°, $[\alpha]_D^{20}$ +135° and a characteristic phenolic spectrum shown in Fig. 1. As observed already in several instances (3, 4), hydro-

genation of the 6,7 double bond results in a large increase in the rotation and in a bathochromic shift of the main ultraviolet maximum (at 268 mμ) with concomitant lowering of the extinction coefficient. This 1-methyl phenol (II, R = C_8H_{17}) differed completely in its properties from those of the so-called "sterinphenol," to which has previously been assigned (2) the constitution II, and which possesses m.p. 145–146° (2, 8), $[\alpha]_D^{20}$ +161° (8). Inhoffen's "sterinphenol" should therefore also be classed among the "x-methyl*hetero*phenols" (*cf.* 3).

Dehydrogenation of the 6-dehydro acetate Vb with selenium dioxide in acetic acid solution yielded the naphthalenic analog, 1-methyl-3-hydroxy-19-nor-1,3,5,6,8-cholestapentaene (VIa), which rapidly decomposed on exposure to light and air. Aside from tetradehydroneoergosterol (9), VIa appears to be the

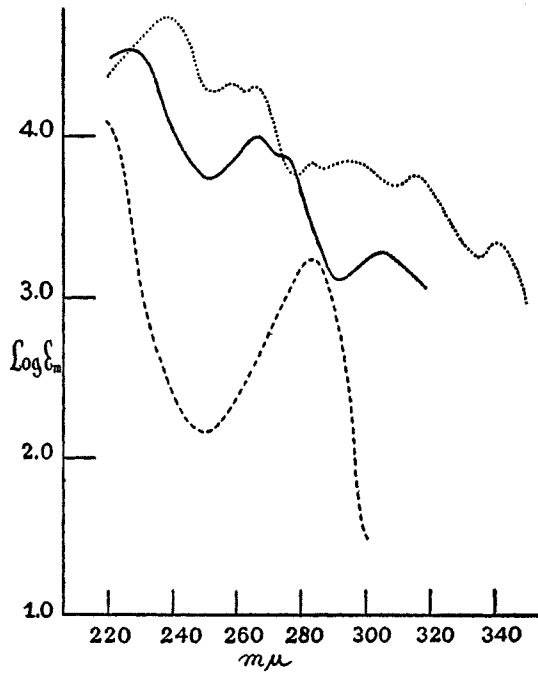


FIG. 1. ULTRAVIOLET ABSORPTION SPECTRA (in 95% ethanol solution): Va, ——; IIa, - - -; VIa, ...

only naphthalenic sterol (hydrocarbon side chain) known. In contrast to the corresponding androstane derivatives (II, V, VI, R = O, OH), the presently described phenols of the cholesterol series are only very slightly soluble in aqueous alkali; they give no color with alcoholic ferric chloride solution.

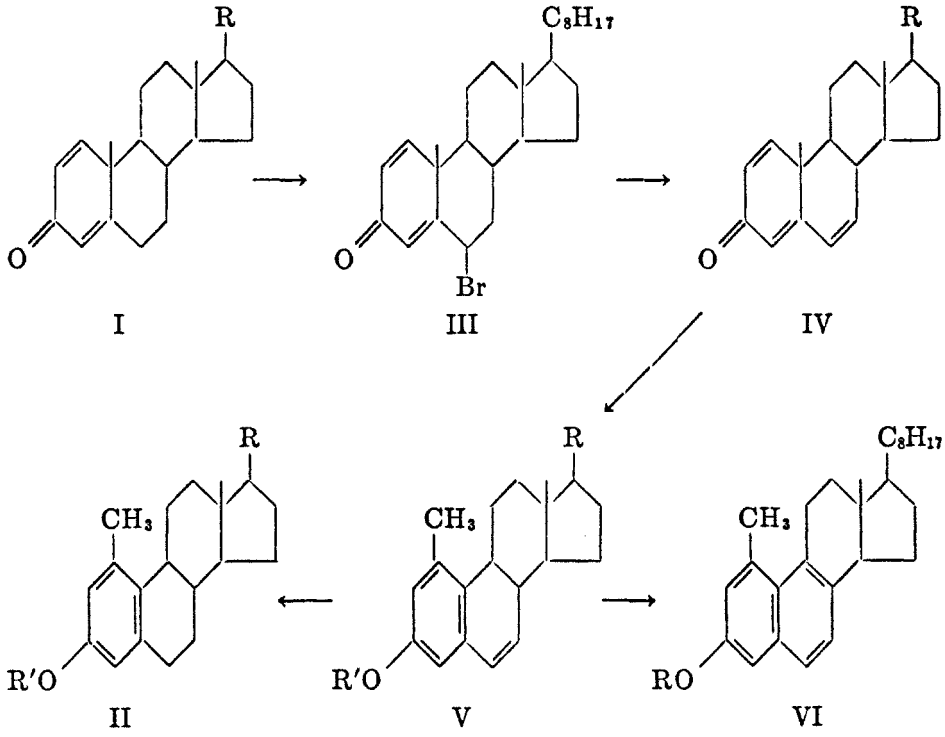
EXPERIMENTAL[1]

6-Bromo-1,4-cholestadien-3-one (III). A mixture of 3.0 g. of 1,4-cholestadien-3-one (I, R = C_8H_{17}), 1.41 g. of N-bromosuccinimide, 0.1 g. of benzoyl peroxide and 80 cc. of car-

[1] All melting points are corrected and were determined on the Kofler block. Rotations were carried out on 60–100 mg. of substance in 10 cc. of chloroform in a 2 dm. tube,

bon tetrachloride was refluxed in the presence of strong light (photoflood lamp) until all the succinimide had risen to the surface of the solution (*ca.* forty minutes). After filtration and evaporation *in vacuo*, the residue was crystallized from ether-methanol yielding 2.2 g. (61%) of the 6-bromo derivative III. The analytical sample was obtained as colorless needles from ether-methanol, m.p. 142–144°, $[\alpha]_D^{20}$ +30.6°, u.v. maximum at 250 mμ (log E 4.24); lit. (5): 47% yield, m.p. 144–145°, u.v. max. at 248 mμ.

Anal. Calc'd for $C_{27}H_{39}BrO$: C, 70.55; H, 8.55.
Found: C, 70.62; H, 8.79.



a. R = C_8H_{17}; R′ = H
b. R = C_8H_{17}; R′ = C_6H_5CO
c. R = C_8H_{17}; R′ = 3,5-$(NO_2)_2C_6H_3CO$

a. R = C_8H_{17}; R′ = H
b. R = C_8H_{17}; R′ = CH_3CO
c. R = C_8H_{17}; R′ = CH_3

a. R = H
b. R = *p*-$NO_2C_6H_4CO$

1,4,6-Cholestatrien-3-one (*IV*, *R* = C_8H_{17}). The dehydrobromination was accomplished by refluxing 0.7 g. of the 6-bromo derivative III with 3 cc. of collidine for fifteen minutes,

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while all spectra were taken in 95% ethanol solution. We are indebted to the Srtas. Ann Rochmann and Paquita Revaque for these determinations and to Srta. Amparo Barba of our Microanalytical Department and Mr. Joseph F. Alicino, Metuchen, New Jersey for the microanalyses. The alumina used in all chromatograms was obtained from the Aluminum Company of America, grade F-20, minus 80-mesh.

which resulted in the formation of 95% of the theoretical amount of collidine hydrobromide. The usual work-up afforded 300 mg. (52%) of cholestatrienone with m.p. 75–78°, which was raised on further recrystallization to m.p. 80–81°, undepressed on admixture with another specimen (4), u.v. maxima at 224 (log E 4.09), 256 (log E 4.03) and 300 mμ (log E 4.09). The present procedure affords unequivocal proof for the structure of the trienone IV, but the alternate method (4) is preferable for large scale work.

Dienone-phenol rearrangement of 1,4,6-cholestatrien-3-one. A solution of 5 g. of the above trienone IV (crude material of m.p. 70–80° could be used) and 1.5 g. of *p*-toluenesulfonic acid in 200 cc. of acetic anhydride was heated on the steam-bath for four hours and then poured into water. After twenty minutes, the product was extracted with ether, washed free of acid, and the solvent evaporated. The residue was purified by filtering a hexane solution through a column of alumina (50 g.) and recrystallizing from ether-hexane; yield, 4.5 g. (81%), m.p. 105–107°. The analytical sample of *1-methyl-3-aceloxy-19-nor-1,3,5,6-cholestatetraene* (*Vb*) had m.p. 112–114° $[\alpha]_D^{20}$ −99.6°, u.v. maxima at 224 (log E 4.42) and 266 mμ (log E 3.94).

Anal. Calc'd for $C_{29}H_{42}O_2$: C, 82.41; H, 10.01.
Found: C, 82.68; H, 9.91.

Saponification with boiling 1% methanolic alkali followed by several recrystallizations from hexane afforded the *free phenol Va* with m.p. 144–146°, $[\alpha]_D^{20}$ −131°, u.v. spectrum Fig. 1.

Anal. Calc'd for $C_{24}H_{40}O$: C, 85.20; H, 10.59.
Found: C, 85.33; H, 10.22.

The *methyl ether Vc* was prepared in the usual manner (8) with dimethyl sulfate and crystallized as colorless prims from ether-methanol, m.p. 64–65°, $[\alpha]_D^{20}$ −115.3°.

Anal. Calc'd for $C_{28}H_{42}O$: C, 85.21; H, 10.72.
Found: C, 85.01; H, 10.92.

1-Methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (*IIa*). One and one-half grams of the 6-dehydro acetate Vb was hydrogenated in 100 cc. of ethyl acetate with 150 mg. of palladium-on-barium sulfate catalyst (American Platinum Works, Newark, N. J.) at room temperature and atmospheric pressure. The oily product was saponified with 2% methanolic potassium hydroxide and the *phenol* IIa was purified by passage through a short column of alumina and crystallization from pentane; yield, 900 mg., m.p. 126.5–128°, $[\alpha]_D^{20}$ +135.6°, u.v. spectrum Fig. 1. The so-called "sterinphenol," previously believed (2) to have this structure melts at 145–146° (2, 8), $[\alpha]_D^{20}$ +161° (8).

Anal. Calc'd for $C_{27}H_{42}O$: C, 84.75; H, 11.06.
Found: C, 84.70; H, 11.27.

The *3,5-dinitrobenzoate* IIc showed m.p. 105–107°, $[\alpha]_D^{20}$ +98.9°, after recrystallization from methanol-ethyl acetate, while the corresponding derivative of Inhoffen's "sterinphenol" melted at 179–180° (2).

Anal. Calc'd for $C_{34}H_{44}N_2O_6$: C, 70.80; H, 7.69.
Found: C, 71.08; H, 7.94.

The *benzoate IIb*, prepared with benzoyl chloride and pyridine, crystallized as needles from acetone-methanol, m.p. 136–138°, $[\alpha]_D^{20}$ +117°.

Anal. Calc'd for $C_{34}H_{46}O_2$: C, 83.89; H, 9.52.
Found: C, 83.90; H, 9.66.

1-Methyl-3-hydroxy-19-nor-1,3,5,6,8-cholestapentaene (*VIa*). After refluxing a solution of 1.5 g. of the acetate Vb in 50 cc. of glacial acetic acid with 0.25 g. of freshly sublimed selenium dioxide for thirty minutes, water was added, the product was extracted with ether, washed with sodium carbonate solution and evaporated. The residue (1.3 g.) was saponified by boiling for thirty minutes with 1% methanolic potassium hydroxide solution, yielding 0.9 g. of an oil, which on chromatographing over 20 g. of alumina afforded 0.7 g. of yellowish oil. Treatment with a saturated ethanol solution of picric acid led to 0.6 g. of a red picrate, m.p. 148–149°. Five hundred milligrams of the picrate was decomposed by partitioning between ether and dilute ammonium hydroxide solution and the phenol, thus regenerated, was crystallized from pentane leading to pale yellow crystals of the phenol

VIa (0.3 g.) with m.p. 154–155°, $[\alpha]_D^{20}$ +47.7°. The substance rapidly turned brownish on exposure to light and air. Its ultraviolet absorption spectrum is depicted in Fig. 1 and though clearly demonstrating the presence of the naphthol moiety, differs somewhat from that of 1-methylequilenin (3), possibly due to the lability of the substance.

Anal. Calc'd for $C_{27}H_{38}O$: C, 85.65; H, 10.11.
Found: C, 85.34; H, 9.96.

The *p-nitrobenzoate VIb* was prepared by heating 100 mg. of the above phenol (VIa) for fifteen minutes with 2 cc. of pyridine and 500 mg. of freshly prepared *p*-nitrobenzoyl chloride, and after recrystallization from chloroform-methanol was obtained as yellowish needles with m.p. 146–148°, $[\alpha]_D^{20}$ +38.7°.

Anal. Calc'd for $C_{34}H_{41}NO_4$: C, 77.38; H, 7.83.
Found: C, 77.49; H, 8.03.

SUMMARY

1,4,6-Cholestatrien-3-one (IV), prepared by two independent methods, was subjected to the dienone-phenol rearrangement yielding a 1-methyl-6-dehydro phenol (V), which on hydrogenation produced the authentic 1-methyl-3-hydroxy-1,3,5-triene II of the cholesterol series. This product proved to be different from Inhoffen's "sterinphenol" obtained by dienone-phenol rearrangement of 1,4-cholestadien-3-one (I) and thus affords further proof that the dienone-phenol rearrangement in the steroid series proceeds in a different manner in the presence of an additional conjugated double bond. Dehydrogenation of the 6-dehydro derivative Vb with selenium dioxide led to the first naphthalenic analog in the cholesterol series.

MEXICO CITY, D. F.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF TEXAS]

SYNTHESIS OF 5-BENZOHYDRYL-5-SUBSTITUTED HYDANTOINS[1]

HENRY R. HENZE AND WILLIAM B. LESLIE[2]

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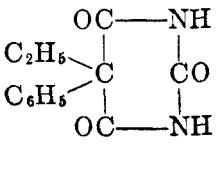
At present, there is no cure for epilepsy based upon the administration of medicinals. However, a satisfactory though temporary relief is noted in many epileptic individuals during the period of their continued use of phenobarbital[3] (I), Dilantin[4] (II), or Mesantoin[5] (III), or a combination of the former with one of



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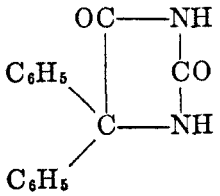

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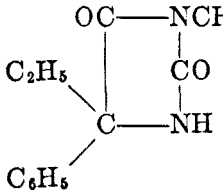


III

the hydantoin derivatives. Phenobarbital, perhaps, is superior to Dilantin in the alleviation of the *petit mal* type of epilepsy (1), but is likely to produce central depression and hypnosis in the dosages required to control the *grand mal* type. Dilantin is most widely employed in treatment of the *grand mal* and psychomotor seizures and does not usually exhibit hypnotic effect. Although Dilantin appears to possess the greater margin of safety with regard to fatal dose, it frequently produces toxic reactions to a mild degree when administered to epileptics. The formula of Mesantoin (III) reveals that it is a 3-methyl derivative of nirvanol, 5-ethyl-5-phenylhydantoin (2), use of which was discontinued because of its production of a characteristic and very disagreeable skin eruption.[6]

It was at one time concluded that the anti-epileptic activity of certain barbiturates, hydantoins, and aryl ketones may be due to the presence of phenyl groups in their structures (3). While it is true that essentially all of the hydantoin derivatives of pronounced anticonvulsant activity do possess at least one phenyl

[1] From the Ph.D. dissertation of William B. Leslie, June, 1944.

[2] Present address: Clovis, New Mexico.

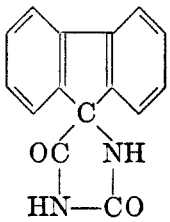
[3] Phenobarbital, U.S.P., 5-ethyl-5-phenylbarbituric acid, used also in the form of its sodium salt.

[4] Dilantin, trade mark of Parke, Davis and Company for the sodium salt of 5,5-diphenylhydantoin, Diphenylhydantoin, U.S.P.

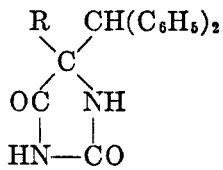
[5] Mesantoin, trade mark of Sandoz Chemical Company for 5-ethyl-3-methyl-5-phenylhydantoin.

[6] It is of considerable interest that Sabotka, Holzman, and Kahn, *J. Am. Chem. Soc.*, **54**, 4697 (1932); *Am. J. Diseases Children*, **45**, 1216 (1933) have been able to accomplish the resolution of this racemic hydantoin; apparently, the *dextro*-isomer is essentially free from this undesirable effect upon the skin.

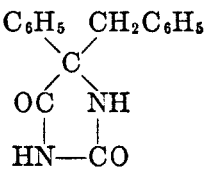
group attached directly to the 5-C position of the heterocyclic nucleus (4, 5), the requirement of this partial structure for such activity has not been demonstrated. A few hydantoins, such as the 5,5-dithienyl derivative, and some other compounds, such as Tridione,[7] which are not hydantoins, are powerful anticonvulsants, while a large number of 5-phenyl-5-substituted hydantoins are without any measurable degree of this activity (5). In short, no absolute relationship between structure and anticonvulsant activity has, as yet, been established. For the time being, while awaiting the development of a more rational approach, search for better anticonvulsants is likely to continue to involve synthesis of heterocyclic compounds having one or more phenyl substituents.



IV



V



VI

A *spiro*-hydantoin (IV), 5,5-biphenylenehydantoin, first synthesized in this laboratory (6), has been found to possess considerable anticonvulsant activity; enough, indeed, to warrant some clinical testing. The close structural similarity of IV to II is obvious. As far as is known, there have been no substituted hydantoins which possess two phenyl groups attached indirectly to the 5-C position of hydantoin, that is, as the benzohydryl grouping, subjected to pharmacological investigation. It should be noted that 5-benzohydrylhydantoin (V, R = H) is isomeric with 5-benzyl-5-phenylhydantoin (VI) which is known to be strongly anticonvulsant. Therefore, synthesis of a few examples of this type (V) was the purpose of this investigation.

The sequence selection for preparation of such 5-benzohydrylhydantoins (V) was as follows:

$$RCHO \rightarrow RCHOHCN \rightarrow RCHOHCOOC_2H_5 \rightarrow RCH(OMgBr)C(OMgBr)(C_6H_5)_2 \rightarrow RCHOHC(OH)(C_6H_5)_2 \rightarrow RCOCH(C_6H_5)_2 \rightarrow V$$

There are available several patents describing processes whereby esters of α-hydroxy acids may be prepared from cyanohydrins. One of these processes (7) was selected because it allows the preparation of the ester directly from the aldehyde, without isolation of the intermediate cyanohydrin.

The hydroxy esters were used for the preparation of 1,1-diphenyl-1,2-glycols. The ketones necessary for production of the hydantoins were obtained through dehydration of the glycols by means of 25% sulfuric acid. The synthesis of the hydantoins was accomplished by the method of Henze and Long (8). Through the courtesy of Parke, Davis and Company, these five hydantoin derivatives

[7] Tridione (Trimethadione, N.N.R.) is the trade mark of Abbott Laboratories for 3,5,5-trimethyloxazolidine-2,4-dione which is particularly valuable in control of *petit mal*.

have received pharmacological testing. The three 5-alkyl-5-benzohydrylhydantoins possess considerable anticonvulsant activity but are quite toxic, the methyl derivative tending to produce convulsions. 5-Benzohydrylhydantoin and 5-benzohydryl-5-phenylhydantoin are without anticonvulsant activity in the dosages employed. Thus, again, it is demonstrated that the mere presence of the 5-phenyl substituent does not insure anticonvulsant activity of the hydantoin,

TABLE I

ETHYL ESTERS OF CERTAIN α-HYDROXY ACIDS, $RCHOHCOOC_2H_5$

R—	B.P., °C.	MM.	YIELD, %	d_4^{20}	n_D^{20}	MOLECULAR REFRACTION	
						Σ	Calc'd
H[a]	69 157.7–157.9	25 754	55.0	1.1005	1.4180	23.85	23.84
CH_3[b]	65.5 153.0–153.2	25 754	45.0	1.0341	1.4131	28.47	28.49
C_2H_5[c]	74.5 167.0	25 747	57.0	1.0069	1.4179	33.09	33.08
C_3H_7[d]	88.5 184.3–184.6	25 745	57.5	0.9839	1.4220	37.75	37.71
C_6H_5[e]	127 264.5–265.5	9 756	52.5	1.1258[f]	1.5136[f]	47.96	48.16

[a] Schreiner, *Ann.*, **197**, 1 (1897), reported b.p. 160° (cor.) (760 mm.); d^{23} 1.0826; Palomaa, *Ann. Acad. Sci. Fennicae*, **A4**, 1 (1913); through *Chem. Zentr.*, **84**, II, 1959 (1913), reported b.p. 158°; d_4^{15} 1.0869. [b] Schreiner, *Ann.*, **197**, 1 (1897), reported b.p. 154.5° (cor.) (760 mm.); d_{25}^{19} 1.0308; Smith and Claborn, *Ind. Eng. Chem.*, **32**, 692 (1940), reported $n^{25}D$ 1.4121; Walden and Swinne, *Z. physik. Chem.*, **79**, 723 (1912), recorded d_4^{25} 1.0299. [c] Schreiner; *Ann.*, **197**, 1 (1897), reported b.p. 167° (cor.) (760 mm.); d^{10} 0.9952. [d] Menozzi, *Gazz. chim. ital.*, **14**, 19 (1884), reported b.p. 190°; d^{15} 0.9883. Nicolle, *Bull. soc. chim.*, **2** 150, (1938), reported b.p. 170–180° (760 mm.). [e] Beyer, *J. prakt. Chem.*, [2] **31**, 389 (1885), reported b.p. 253–255°; Darapsky, *J. prakt. chem.*, (2) **96**, 297 (1917), reported b.p. 141° (15 mm.); McKenzie, *J. Chem. Soc.*, **75**, 755 (1899), reported m.p. 37°; Michael and Jeanpretre, *Ber.*, **25** 1784 (1892), claimed m.p. 34°; Findlay and Turner, *J. Chem. Soc.*, **87**, 753 (1905), reported "the ester obtained in this work melted at 29° after fractionation and at 30° after recrystallization . . . but could not be raised by further recrystallizations." [f] These data were obtained on supercooled liquid material; the product solidified, m.p. 30°.

nor does the absence of the 5-phenyl substituent preclude anticonvulsant activity in this series.

EXPERIMENTAL

Preparation of the ethyl esters of α-hydroxy acids. In general, 200 ml. of dioxane, 2.74 moles of a carefully-fractionated aldehyde, and 0.4–0.5 g. of sodium hydroxide dissolved in 39.3 g. (2.18 moles) of water were placed in a flask provided with a thermometer, mechanical stirrer, and dropping-funnel the stem of which extended well into the lower portion of the flask. Meanwhile, 77 g. (2.74 moles) of commercial grade (96%) liquid hydrogen cyanide was

drawn into a 250-ml. flask and diluted with 50 ml. of cold dioxane.[8] The reaction flask was immersed in an ice-bath and the hydrogen cyanide-dioxane mixture was added slowly through the dropping-funnel into the well-stirred, alkaline solution of the aldehyde.[9] The reaction was exothermic but was maintained below 25°. If evolution of heat ceased, addition of a few drops of concentrated sodium hydroxide solution hastened the reaction. The stirred reaction mixture was allowed to come to room temperature and then was heated to about 75°.

After the mixture had cooled to room temperature, the flask was placed in an ice-salt mixture, and 199 g. (4.11 moles) of 95% ethyl alcohol (containing 0.55 mole of water) was added, and the dropping-funnel was replaced by a glass inlet tube, through which a fairly

TABLE II

1,1-DIPHENYL-1,2-DIOLS, $(C_6H_5)_2C(OH)CH(OH)R$

R	YIELD, %	M.P., °C. (cor.)
H[a]	58.5	122.5–123.0
CH_3[b, c, d]	78.5	95.2–95.4
C_2H_5[e, f, g]	92.0	92
C_3H_7[h]	89.0	89
C_6H_5[i]	72.5	166.5

[a] Tiffeneau, *Ann. chim.*, [8] **10**, 344 (1907) reported m.p. 122°; Pall and Weidenkaff, *Ber.*, **39**, 2063 (1906), prepared this glycol (m.p. 121°) from ethyl glycolate in 44% yield. [b] When this preparation was repeated employing 183 g. (1.16 moles) of bromobenzene, 30.5 g. (1.26 gram-atoms) of magnesium and 600 ml. of absolute ether to prepare the Grignard reagent [by this method a 94.7% yield of the Grignard reagent has been obtained, see *J. Am. Chem. Soc.*, **51**, 1576 (1929)] an 82.3% yield of the glycol was obtained starting from 39.4 g. (0.33 mole) of ethyl lactate. [c] Stoermer and Riebel, *Ber.*, **39**, 2302 (1906), prepared this glycol by the interaction of 30 g. (0.125 mole) of ethyl lactate with phenylmagnesium bromide prepared from 79.8 g. (0.51 mole) of bromobenzene and 12.3 g. (0.51 gram-atom) of magnesium. Since each mole of ester requires three moles of Grignard reagent, it is evident that this reaction was carried out with a deficiency of phenylmagnesium bromide. The melting point of the recrystallized product was reported as 96.5°. [d] Smith and Hoehn, *J. Am. Chem. Soc.*, **63**, 1177 (1941), prepared this glycol in but 38% yield (calculated on the basis of the ester used) because they repeated the error made by Stoermer and Riebel; m.p. 95°. [e] Roger, *Helv. Chim. Acta*, **12**, 1061 (1929), prepared this glycol from ethyl α-hydroxybutyrate and phenylmagnesium bromide, in 55% yield; m.p. 115–116°. [f] McKenzie and Roger, *J. Chem. Soc.*, 571, (1927) prepared this glycol by a molecular arrangement of 2,3-diphenyl-2-hydroxybutylamine. [g] *Anal.* Calc'd for $C_{16}H_{16}O_2$: C, 79.31; H, 7.49. Found: C, 79.45; H, 7.64. [h] *Anal.* Calc'd for $C_{17}H_{20}O_2$: C, 79.65; H, 7.87. Found: C, 79.56; H, 8.04. [i] Acree, *Ber.*, **37**, 2863 (1904), reported m.p. 167°.

rapid stream of dry hydrogen chloride was passed. The temperature of the reaction mixture was kept below 20° until saturation was complete (about two hours), then the flask was fitted with a condenser and heated for a period of 5½ hours at the reflux temperature; considerable ammonium chloride separated. After cooling, the salt was removed by filtration,

[8] Since hydrogen cyanide boils at 26°, its vapor pressure at room temperature is decreased appreciably by dilution with dioxane.

[9] The reaction proceeded equally well if the aldehyde was added through the dropping-funnel to the hydrogen cyanide dissolved in the dioxane and sodium hydroxide solution. This sequence of addition might be advantageous in case the aldehyde readily undergoes the aldol type of condensation.

the filter cake was washed with 50 ml. of dioxane, and the washings were added to the filtrate which was replaced in the flask and saturated with ammonia at ice-bath temperature. Again, precipitated ammonium chloride was filtered off and washed with dioxane. The filtrate was distilled at 150 mm. using a warm-water bath as source of heat. The ester was distilled at 25 mm. or less; considerable still residue resulted. The ester was redistilled

TABLE III

BENZOHYDRYL KETONES, $(C_6H_5)_2CHCOR$

R	M.P., °C. (cor.)	B.P., °C.	MM.	YIELD, %	n_D^{20}	d_4^{20}	MOLECULAR REFRACTION	
							Σ	Calc'd
H[a]		116–117	1.5	49	1.5893	1.0980	59.66	60.26
CH_3[b]	60.0–60.5			92				
C_2H_5[c, d]	29	130–131	1.5	93				
C_3H_7[e, f]				95	1.5621	1.0436	73.52	74.06
C_6H_5[g, h]	138.0–138.5			43				

[a] Behal and Sommelet, *Bull. soc. chim.*, [3] **31**, 307 (1904), prepared a small quantity of diphenylacetaldehyde by dehydration of the glycol with oxalic acid and reported b.p. 168–170° (10 mm.); n_D^{19} 1.5899; d^{19} 1.1048; ΣMR 60.15; MR calc'd, 59.90. Klages and Kessler, *Ber.*, **39**, 1755 (1906), prepared this aldehyde by dehydration of the glycol by sulfuric acid and reported b.p. 166° (9 mm.); n_D^{21} 1.5920; d_4^{21} 1.1061; ΣMR 60.15; MR calc'd, 59.96. [b] Stoermer and Riebel, *Ber.*, **39**, 2302 (1906), prepared this ketone by heating the glycol with very dilute hydrochloric acid at 180°. The ketone was said to be dimorphic, for two forms were isolated; m.p. 46° and 61°. [c] Maxim, *Ann. chim.*, [10] **9**, 81 (1928), prepared this ketone in 31% yield by the interaction of diphenylacetamide and ethylmagnesium bromide; b.p. 186° (14 mm.); Roger, *Helv. Chim. Acta*, **12**, 1061 (1929), obtained a small amount of this ketone from dehydration of the glycol and reported b.p. 178° (17 mm.). [d] *Anal.* Calc'd for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.41; H, 7.33. [e] Billard, *Bull. soc. chim.*, [4] **29**, 429 (1921), reported the preparation of an impure sample of this ketone, of b.p. 185–192° (13 mm.), by the dehydration and rearrangement of 1,2-diphenyl-1-propyl-1,2-ethanediol. [f] *Anal.* Calc'd for $C_{17}H_{18}O$: C, 85.68; H, 7.61. Found: C, 85.41; H, 7.59. [g] This ketone was prepared from 40 g. (0.14 mole) of 1,1,2-triphenylethane-1,2-diol and 150 ml. of 25% sulfuric acid. Because of the high melting point (166.5°) of the glycol, it was necessary to reflux the mixture vigorously for more than an hour. After filtration, the crude ketone stood overnight in contact with ether; after being dried, wt. 19.8 g.; m.p. 134–135°. Recrystallization from 500 ml. of Skellysolve C yielded 16.3 g. (43%) of white needles melting at 138.0–138.5°. The ether extract yielded 14.9 g. of product (m.p. 91–95°) which could not be brought to sharper m.p. than 90–100° after recrystallizations from several different solvents. In another preparation, 80 g. of trichloroacetyl chloride was allowed to react with 800 ml. of dry benzene in the presence of anhydrous aluminum chloride. Purification followed directions of Biltz, *Ber.*, **32**, 654 (1899), (who failed to report a m.p. for his product). After repeated recrystallizations from Skellysolve C, alcohol, glacial acetic acid, etc., a yellow crystalline powder (m.p. 135°) resulted. [h] Boyle, McKenzie, and Mitchel, *Ber.*, **70**, 2153 (1937), prepared this ketone from phenylmagnesium bromide and α-chlorophenylacetyl chloride, m.p. 135.5–136.5°.

through an efficient 25-cm., glass helices-packed column yielding products of about one or two degree boiling range. Table I lists the esters resynthesized.

Preparation of 1,1-diphenyl-1,2-glycols. A Grignard reagent was prepared from 27 g. (1.11 gram-atoms) of magnesium and 181 g. (1.15 moles) of bromobenzene in 450 ml. of anhydrous ether. The ethyl ester of the appropriate α-hydroxy acid (0.33 mole) was added to the reagent causing vigorous reaction. The mixture was heated for 2–3 hours while approxi-

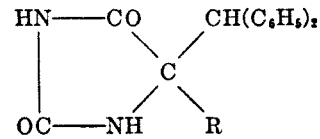
mately one-half of the solvent was distilled off. The resultant mixture was poured into 80 ml. of glacial acetic acid and 400 g. of cracked ice, and was stirred to dissolve any glycol present. After separation of the two layers, the ether layer was washed with dilute alkali and then with water before being warmed until the temperature reached 65°. After cooling to room temperature, the glycol was precipitated by the addition of two 50-ml. portions of Skellysolve F. One recrystallization was sufficient to yield the glycols listed in Table II.

Preparation of diphenylacetaldehyde and benzohydryl ketones. Approximately 0.2 mole of purified glycol and 100–150 ml. of 25% (by volume) sulfuric acid were heated to reflux temperature for about 3½ hours. The organic material was separated, and if solid was purified by crystallization from Skellysolve C or ethyl alcohol. The liquid ketones were purified by distillation at 1.5 mm. Data for these ketones are collected in Table III.

Preparation of 5-benzohydryl-5-substituted hydantoins. One-tenth mole of purified ketone was dissolved in 225 g. of molten, commercial grade acetamide, and 7.16 g. (0.11 mole) of potassium cyanide was added with stirring; the mixture was allowed to cool before 34 g. of ammonium carbonate was added. The reaction mixture was placed in a glass liner, sealed in a Monel pressure vessel and heated at 110° for 16 hours. After cooling, the mixture was dissolved in about 450 ml. of hot water, and was cooled and filtered. Acidification of the filtrate caused precipitation of solid material which was separated and combined with that obtained

TABLE IV

5-BENZOHYDRYL-5-SUBSTITUTED HYDANTOINS



R	YIELD, %	M.P., °C. (cor.)	N	
			Calc'd	Found
H	44	223.0–223.5	10.52	10.66
CH_3	76	265.0–265.5	10.00	9.95
C_2H_5	77	219.2–219.5	9.52	9.63
C_3H_7	68	236.7–236.9	9.06	8.84
C_6H_5	76	264.0–264.5	8.18	8.06

prior to acidification. The crude hydantoin was purified, either by solution in 10% sodium hydroxide solution, followed by filtration and reacidification, or by recrystallization from glacial acetic acid. In general, the benzohydrylhydantoins were quite soluble in hot glacial acetic acid, only moderately soluble in hot alcohol, and insoluble in water. For comparison with this procedure, which is that developed by Henze and Long (8), the procedure of Bucherer and Lieb (9) was tried for preparation of the methyl and propyl analogs. This method gave a slightly larger yield of crude methyl derivative, but a much poorer yield of the propyl product. Data for these benzohydrylhydantoins are collected in Table IV.

In the case of benzohydryl phenyl ketone, owing to its low solubility, it was necessary to employ 440 g. of molten acetamide for the 0.1 mole of ketone. The crude hydantoin, after trituration with hot benzene melted at 264.0–264.5°; recrystallization from glacial acetic acid or diluted alcohol failed to alter the melting point.

Anal. Calc'd for $C_{22}H_{18}N_2O_2$: N, 8.18. Found: N, 7.16.

A 0.4347-g. sample of this material was heated for two hours at 150° and 10 mm. pressure and was found to have lost 0.0434 g.; the melting point remained 264.0-264.5°.

Anal. Calc'd for $C_{22}H_{18}N_2O_2$: N, 8.18. Found: N, 8.08.

From the mother liquor in this preparation there was recovered 10.5 g. of unreacted ketone.

SUMMARY

Five 1,1-diphenyl-1,2-glycols, one of which was new, have been prepared from ethyl esters of α-hydroxy acids by means of the Grignard reaction.

The glycols were dehydrated to yield diphenylacetaldehyde and four benzohydryl alkyl or phenyl ketones.

These benzohydryl ketones have been converted into five, new 5-benzohydryl-5-substituted hydantoins.

AUSTIN, TEXAS.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF NEW MEXICO]

SYNTHESIS OF IMIDAZOLINES, DIAZEPINES, TRIAZEPINES, AND IMIDAZOLIDONES FROM A 1,2-DIAMINE AND 1,1-DICARBOXYLIC ESTERS[1]

IRWIN J. PACHTER AND J. L. RIEBSOMER

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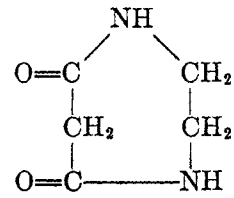
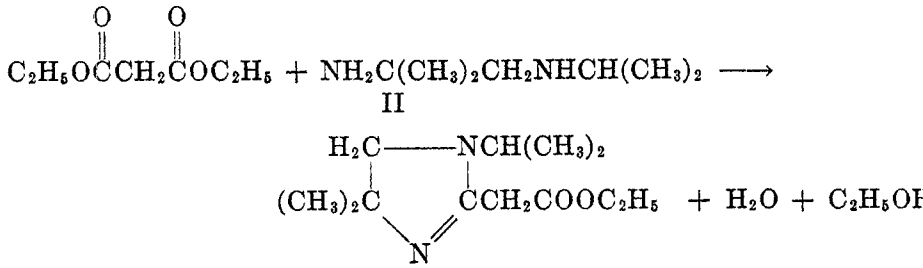
A. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE WITH MALONIC ESTER

Freund (1) heated a mixture of malonic ester and ethylenediamine and obtained a high-melting condensation product with the empirical formula $C_5H_8N_2O_2$. Largely upon the basis of a nitrogen analysis he suggested a formula (I) for this substance and named it ethylenemalonamide. This work was later confirmed by Dox (2).



I

In the present investigation, the main product obtained when malonic ester was heated with N-(2-aminoisobutyl)isopropylamine (II) was a solid crystalline material, which was soluble in alcohol and dilute hydrochloric acid but insoluble in water. The compound formed a picrate and analysis gave results which are in agreement with the structure III.



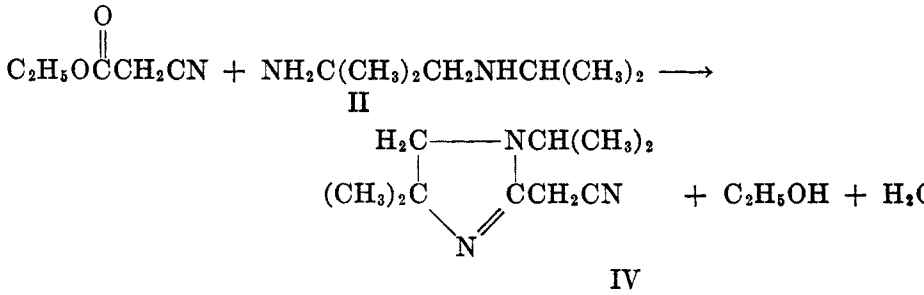
II

III

The proof of structure of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III) was accomplished by an independent synthesis following the method of Copeland and Day (3) who found that *o*-phenylenediamine condenses

[1] This publication was abstracted from the thesis presented by Mr. Pachter to the graduate faculty of the University of New Mexico in partial fulfillment of the requirements for the M.S. degree. Mr. Pachter's present address is Department of Chemistry, University of Southern California.

with ethyl cyanoacetate to yield 2-cyanomethylbenzimidazole. By a similar reaction between II and ethyl cyanoacetate an analogous product (IV) was obtained.

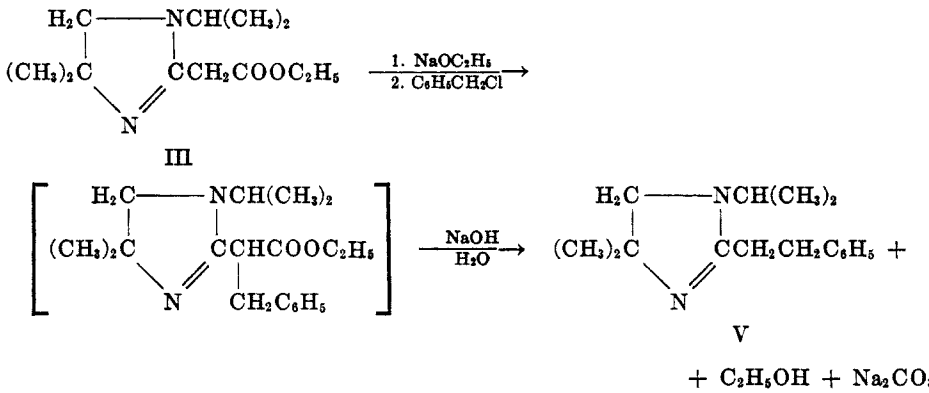


IV

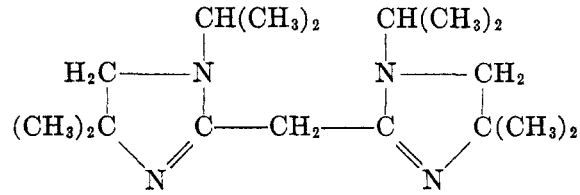
The 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV) was a monoacid base, formed a picrate, and had a neutral equivalent and nitrogen content which conformed to the structural formula presented. When refluxed with alcoholic hydrogen chloride, IV was converted to a compound which was identical in all respects with III.

Neither III nor IV yielded the corresponding acid upon hydrolysis. Only the decarboxylated product 1-isopropyl-2,4,4-trimethyl-2-imidazoline was obtained. This suggested that III might be used in a malonic ester-type synthesis and hence give a useful method for the preparation of the imidazolines.

The sodio derivative of III was found to react with benzyl chloride and upon hydrolysis produced 4,4-dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline (V).

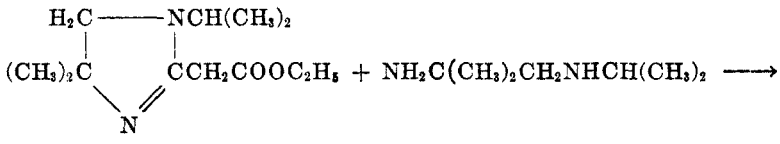


V

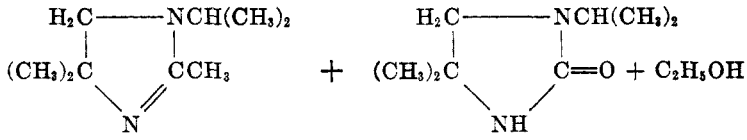


VI

was not formed. Instead, the following reaction occurred.



III II



VII VIII

The properties of the 1-isopropyl-2,4,4-trimethyl-2-imidazoline (VII) were in agreement with those previously found for this compound (5).

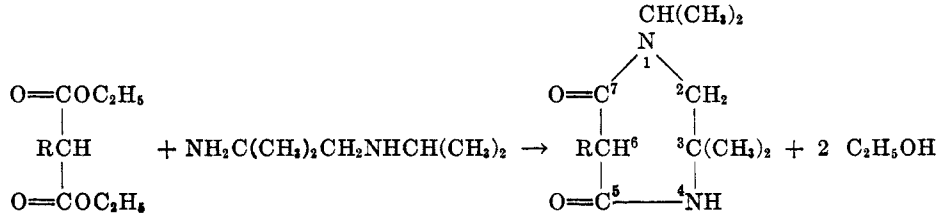
4,4-Dimethyl-1-isopropyl-2-imidazolidone (VIII) was formed in this reaction by a mechanism which at present is unexplained. It was synthesized by heating a mixture of II, chlorocarbonic ester, and anhydrous potassium carbonate. It is believed that a urethan was first produced in this reaction which then formed VIII by losing a molecule of ethanol.

B. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE WITH MONOSUBSTITUTED MALONIC ESTERS

Dox (2) investigated the reactions of monosubstituted alkylmalonic esters with ethylenediamine. He reported that the products were amorphous and colloidal and probably polymeric, that their melting points were high but not sharp, and that decomposition occurred upon melting with darkening in color and evolution of gas.

The reaction of monosubstituted malonic esters with N-(2-aminoisobutyl)-isopropylamine (II) gave compounds which were strikingly different in nature from those mentioned above. They were relatively low-melting solids, formed large crystals, were stable at their melting points and, indeed, were even distilled under reduced pressure at temperatures above 200° without decomposition. Our preparations and those of Dox, in fact, were similar only in analysis. Analysis of the compounds indicated formulas which corresponded to seven-membered rings.

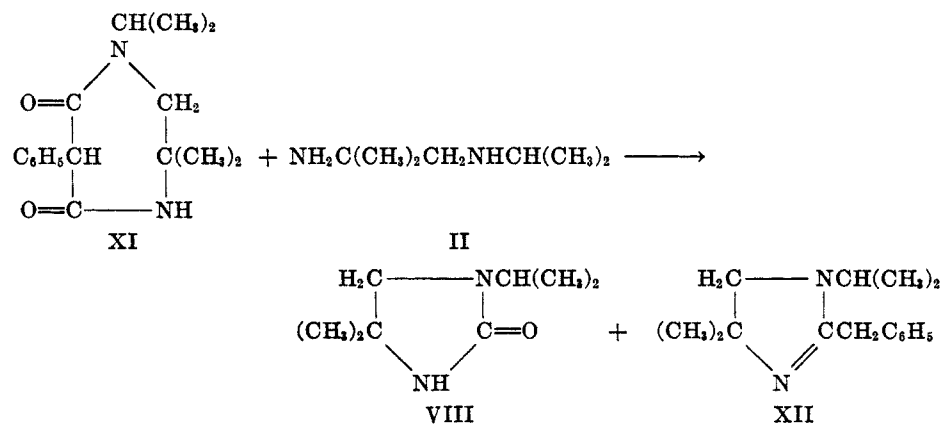
Diethyl-*n*-butyl malonate, diethylbenzyl malonate, and diethylphenyl malonate reacted with one equivalent of II, as indicated by the general equation below, to form 6-*n*-butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (IX), 6-benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (X) and 6 - phenyl - 5,7 - diketo -3,3 - dimethyl - 1 - isopropylhexahydro - 1,4 - diazepine (XI), respectively. These compounds were neutral in character in contrast to the basic products obtained from malonic ester.



II

In the past there has been some contention as to whether seven-membered rings similar to these are actually formed (6) or whether, instead of cyclizing, the molecules polymerize. The fact that definite melting points and boiling points were obtained for compounds (IX) and (X) is rather good evidence against polymerization in these compounds. More conclusive proof for the seven-membered ring structures was obtained from molecular weight determinations by the boiling-point elevation method. For compound (X), molecular weight 288, in benzene solution at a concentration of 0.0508 *M* the molecular weight 350 was obtained. At a concentration of 0.110 *M*, the value found was 405. When concentration was plotted against apparent molecular weight, an extrapolation to zero concentration gave a molecular weight close to the expected value of 288. These data suggest that as the concentration increases, hydrogen bonding between diazepine rings results in a rapid increase in the apparent molecular weight.

When XI was heated with an excess of II, the seven-membered ring opened and reclosed forming the imidazolidone (VIII) and 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline (XII), the latter compound being identical with the imidazoline prepared directly from II and phenylacetic acid.

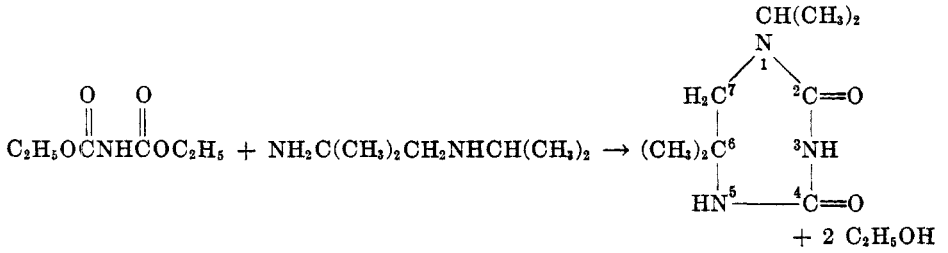


XI II VIII XII

Compounds (VIII) and (XII) were both formed as by-products in the synthesis of XI.

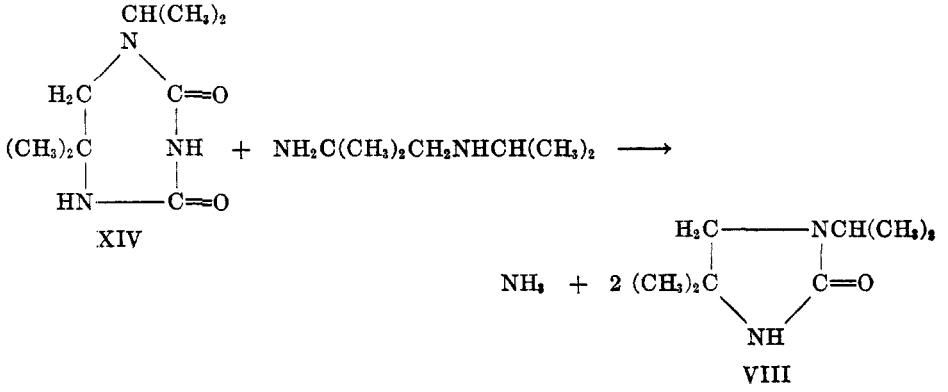
C. THE REACTIONS OF N-(2-AMINOISOBUTYL)ISOPROPYLAMINE AND IMIDODICARBOXYLIC ESTER

The condensation of N-(2-aminoisobutyl)isopropylamine (II) and diethyl imidodicarboxylate followed a somewhat different course and the crystalline cyclic diamide 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV) was obtained.



II XIV

With a second equivalent of II, compound (XIV) opened and reclosed to form ammonia and two equivalents of 4,4-dimethyl-1-isopropyl-2-imidazolidone (VIII) in almost quantitative yield.



XIV VIII

EXPERIMENTAL

PART A

All of the following reactions involving N-(2-aminoisobutyl)isopropylamine (II) were carried out under a 4′ × $\frac{5}{8}$″ helix-packed column which was equipped with a decanter still-head. In those reactions in which water was a product, benzene was added to the reaction mixture and, as it distilled, the water formed in the reaction was carried out as an azeotropic mixture. At the still-head the water separated and the benzene returned to the column. In those reactions in which alcohol was the only volatile product, benzene was not usually added and the still-head merely served as a receptable for the alcohol which distilled during the reaction. The absence of benzene in these latter instances did not affect the courses of the reactions since the same results were obtained when the reactions were carried out with benzene added.

Ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III). To 160 g. (1 mole) of malonic ester was added 65 g. (0.5 mole) of II and the mixture was heated for 8 hours between 125° and 145° until no more water-alcohol mixture came over at the top of the column. Benzene was added and the temperature was raised to 165° for one hour.

The reaction mixture was cooled and a half gram of solid material, melting point over 310° was removed. The filtrate was extracted with 45 ml. of concentrated hydrochloric acid in 50 ml. of water. The aqueous layer was made basic and an oil separated which solidified. This product was recrystallized from ethanol and 57 g. (51%) of the ester, m.p. 59–59.3°, was obtained.

Anal. Calc'd for III, $C_{12}H_{22}N_2O_2$: N, 12.4; Neutral equivalent, 226.

Found: N, 12.7; Neutral equivalent, 222.

A *picrate* of III was prepared by adding 1 g. of picric acid dissolved in 5 ml. of ethanol to 1 g. of III in 3 ml. of ethanol and refluxing the solution for a few minutes. Upon cooling, a crystalline solid separated which gave, upon recrystallization from ethanol, the picrate, m.p. 103–104°.

Anal. Calc'd for $C_{17}H_{25}N_5O_9$: N, 15.8. Found: N, 15.4.

2-Cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV). To 65 g. (0.5 mole) of II was added 113 g. (1 mole) of cyanoacetic ester and the mixture was heated to 110° for seven hours. Benzene was then added and the temperature was raised to 160° for two hours. The reaction mixture was cooled and the crystals were filtered and recrystallized from ethanol to give 54 g. (61%) of the nitrile (IV), m.p. 197°.

Anal. Calc'd for IV, $C_{10}H_{17}N_3$: N, 23.4; Neutral equivalent, 179.

Found: N, 23.3; Neutral equivalent, 178.

A *picrate* of IV was prepared by dissolving 1 g. of IV in the least amount of ethanol and adding the solution to a saturated alcoholic solution of 1 g. of picric acid. Yellow crystals formed immediately which were recrystallized from ethanol to give the picrate, m.p. 177–179°.

Anal. Calc'd for $C_{16}H_{20}N_6O_7$: N, 20.6. Found: N, 20.6.

Conversion of 2-cyanomethyl-4,4-dimethyl-1-isopropyl-2-imidazoline (IV) *to ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate* (III). A 10-g. sample of IV was refluxed with 150 ml. of a 10% alcoholic hydrogen chloride solution for 4.5 hours. Ammonium chloride was removed to lessen bumping after the first hour and again after 2.5 hours. The excess alcohol was removed by distillation until 50–75 ml. remained. Again the ammonium chloride was removed and the distillation continued over a water-bath until no more alcohol came over. The residue was neutralized with a saturated solution of sodium bicarbonate. Warming was necessary to decompose the hydrochloride of the ester. The material which separated and solidified was filtered, dried, and recrystallized from ethanol giving 9.7 g. (78%) of III, m.p. 59–59.3°. A mixed m.p. with III prepared previously showed no depression.

A *picrate* of this material was prepared by the usual method. The crystals which formed were recrystallized from ethanol giving the picrate, m.p. 103–104°. A mixed m.p. with the picrate of III, m.p. 103–104° gave no depression.

4,4-Dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline (V). To 2.5 g. of sodium dissolved in 100 ml. of absolute alcohol was added 22.6 g. (0.1 mole) of the ester (III). After the solid dissolved, 12.5 g. (0.15 mole) of benzyl chloride was added slowly with stirring. The mixture was then refluxed with stirring for four hours. The sodium chloride was removed and the filtrate was distilled over a water-bath until no more alcohol came over. The residue was refluxed with 1.5 times the theoretical amount of 10% aqueous sodium hydroxide for two hours. The oily layer was separated and acidified with hydrochloric acid, any insoluble material being discarded. The acid solution was treated with 10% sodium hydroxide and an oil separated. This layer was dried over magnesium sulfate and distilled to give 10.0 g. (41%) of the imidazoline (V), b.p. 168–170° at 15 mm. It was later found that hot alkali results in some disruption of the imidazoline ring. It is possible that the yield would be increased if the hydrolysis were carried out in acid solution.

Anal. Calc'd for V, $C_{16}H_{24}N_2$: N, 11.5; Neutral equivalent, 244.

Found: N, 11.4; Neutral equivalent, 245.

A *picrate* of V was prepared by the usual procedure and when recrystallized from ethanol, it melted at 120–121°. Since the melting point of the picrate was close to that of picric acid (122°), a mixed melting point was taken and found to be 85–115°.

Anal. Calc'd for $C_{22}H_{27}N_5O_7$: N, 14.8. Found: N, 14.7.

4,4-Dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline. Direct synthesis. To 5 g. of β-phenylpropionic acid was added 8 g. of the diamine (II) and the mixture was heated at 140° for 4 hours. Benzene was added and the temperature was gradually raised to 200° over a second 4-hour period. The benzene and unreacted diamine were then removed by distillation and as much as possible of the remaining liquid was dissolved in a 5% solution of hydrochloric acid. The acid solution was extracted with ether and the ether layer was discarded. An excess of concentrated ammonium hydroxide was added and an oil separated. Extracted with ether, dried over calcium chloride, and distilled it gave the imidazoline, b.p. 175° at 20 mm.

Anal. Calc'd for $C_{16}H_{24}N_2$: N, 11.5; Neutral equivalent, 244.

Found: N, 11.2; Neutral equivalent 244.5.

The *picrate* of this imidazoline was prepared, m.p. 120–121°.

Anal. Calc'd for $C_{22}H_{27}N_5O_7$: N, 14.8. Found: N, 14.6.

A mixed melting point of this picrate with the picrate of V showed no depression.

Reaction of ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III) *with* II *to yield 1-isopropyl-2,4,4-trimethyl-2-imidazoline* (VII) *and 4,4-dimethyl-1-isopropyl-2-imidazolidone* (VIII). To 22.6 g. (0.1 mole) of III was added 16.2 g. (0.125 mole) of II. The mixture was heated to 140–150° for 5 hours and after that the temperature was raised slowly to 200° over a second 5-hour period. The reaction mixture was cooled in ice overnight. The crystals (VIII) that formed were washed with petroleum ether. The filtrate and the washings were fractionally distilled. After the petroleum ether and unreacted diamine were removed, the product was distilled to give 8 g. of the imidazoline (VII), b.p. 89–90° at 28 mm. From the residue in the distilling flask, an additional small amount of crystals was obtained.

(*a*) *The liquid fraction* (VII).

Anal. Calc'd for VII, $C_9H_{18}N_2$: N, 18.2; Neutral equivalent 154.

Found: N, 17.9; Neutral equivalent, 152.

A *picrate* of VII was prepared by the usual method which melted at 183° and gave no depression in m.p. when mixed with a specimen of the picrate of 1-isopropyl-2,4,4-trimethyl-2-imidazoline, m.p. 183°.

Anal. Calc'd for $C_{15}H_{21}N_5O_7$: N, 18.3. Found: N, 18.2.

(*b*) *The solid fraction* (VIII). The two crops of crystals were combined and purified by recrystallization from ethanol; yield, 13.9 g. (89%); m.p. 164°.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: N, 17.9. Found: N, 17.9.

Independent synthesis of 4,4-dimethyl-1-isopropyl-2-imidazolidone. To 26 g. (0.2 mole) of II was added 21.6 g. (0.2 mole) of chlorocarbonic ester. The reaction was very vigorous and some cooling was necessary. The resulting warm viscous liquid was mixed with 21 g. of anhydrous potassium carbonate (50% excess) and the mixture was heated under reflux on a metal-bath at 200°. After a few minutes there was a copious evolution of carbon dioxide which continued for a short time. The mixture was then heated at 200° for 5 hours using an air-cooled condenser which permitted water and alcohol to escape at the top. When the reaction was complete, the solid was pulverized and extracted with two 25-ml. portions of ethanol. The ethanol extracts were combined and evaporated to 25 ml. Upon cooling, 13.4 g. (47%) of the 2-imidazolidone crystallized. The product was washed with petroleum ether, and recrystallized from ethanol, m.p. 164°.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9.

Found: C, 61.6; H, 10.7; N, 17.7.

A mixed m.p. with compound (VIII) was 164°, thus establishing the identity of VIII.

PART B

6-n-Butyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (IX). A solution of 32.4 g. (0.15 mole) of diethyl *n*-butyl malonate and 26 g. (0.2 mole) of II was heated 8 hours

between 140 and 160°. The reaction mixture was distilled. A forerun consisting of a liquid and a solid distilled up to a temperature of 217° at 4 mm. The main portion distilled at 217 to 226° at 4 mm. and was purified by crystallization from ethanol to give 14 g. (55%) of IX, m.p. 108°.

Anal. Calc'd for IX, $C_{14}H_{26}N_2O_2$: N, 11.0. Found: N, 10.8.

A solid was isolated from the forerun, which upon recrystallization from ethanol, melted at 164° and gave no depression in melting point when mixed with VIII.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: N, 17.9. Found: N, 17.7.

At the time this reaction was run, it was not known that diazepines undergo further reaction with an additional quantity of II (see below), and it is probable that the yields of diazepines may be raised somewhat by using only a small excess of II.

6-Benzyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (X). A mixture of 50 g. (0.20 mole) of diethylbenzyl malonate and 34 g. (0.25 mole) of II was heated at 140–150° for 5 hours after which the temperature was slowly increased to 200° during a second 5-hour period. After cooling to room temperature, 25 ml. of petroleum ether was added and the mixture was kept at 0° for one hour. The solid was recrystallized from ethanol to give 34.5 g. (60%) of X, m.p. 152°.

Anal. Calc'd for X, $C_{17}H_{24}N_2O_2$: C, 71.2; H, 8.4; N, 9.7.
Found: C, 70.9; H, 8.2; N, 9.8.

The mother liquor from the original crystallization was distilled at reduced pressure and the fraction b.p. 150–185° at 30 mm. was collected. A small additional amount of X remained in the distilling flask. Upon cooling the distilled fraction, 10 g. of a solid crystallized which upon recrystallization from ethanol, melted at 164°. When mixed with an authentic specimen of VIII, it showed no depression in m.p. The remainder of the 150–185° fraction was distilled and 9 g. of a fraction, b.p. 166–170° at 16 mm., was collected which was basic in character and formed a picrate, m.p. 120–121°. The picrate showed no depression in m.p. when admixed with the picrate of 4,4-dimethyl-1-isopropyl-2-β-phenylethyl-2-imidazoline.

6-Phenyl-5,7-diketo-3,3-dimethyl-1-isopropylhexahydro-1,4-diazepine (XI). Forty-six g. (0.20 mole) of diethylphenyl malonate was heated with 30 g. (0.23 mole) of II for 6 hours at 150 to 170°. Upon cooling, crystals of XI formed. These crystals were recrystallized from ethanol to give 34 g. (62%) of XI, m.p. 222°.

Anal. Calc'd for XI, $C_{16}H_{22}N_2O_2$: N, 10.0. Found: N, 10.0.

The mother liquor from the main product was distilled and after a small low-boiling forerun, a fraction of 11 g., b.p. 140–170° at 18 mm., was collected. When this fraction was cooled, 2.5 g. of a solid, m.p. 161°, was isolated. It presumably was VIII but this was not established. The remainder of the 140–170° fraction was redistilled and a 7-g. fraction was collected at 156–159° at 18 mm. It formed a picrate, m.p. 146°. The picrate prepared from 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline was prepared and found to melt at 147°.

Anal. Calc'd for $C_{21}H_{25}N_5O_7$: N, 15.3. Found: N, 15.2.

A mixed melting point of this picrate with the picrate prepared from the above 7-g. fraction (b.p. 156–159° at 18 mm.) was 146–147°. Hence the identity of this fraction was established.

Reaction of 6-phenyl-5,7-diketo-4,4-dimethyl-1-isopropylhexahydro-1,4-diazepine (XI) *with* II. To 13.7 g. (0.05 mole) of XI was added 9.0 g. (0.075 mole) of II and the mixture was heated at 150° for 6 hours after which the temperature was raised gradually to 210° during a second 6-hour period. The reaction mixture was cooled and filtered (the mother liquor was saved) and the solid obtained was recrystallized from ethanol to give 7.5 g. (96%) of VIII, m.p. 164°. A mixed melting point with an authentic specimen of VIII gave no depression.

The mother liquor from above was distilled at 17 mm. and the main fraction of 4 g. was collected at 156–159°. This compound (XII) was basic in character and its boiling point suggested that it might be 2-benzyl-4,4-dimethyl-1-isopropyl-2-imidazoline. A *picrate* was prepared of the latter compound as well as from a sample of XII by the usual method. Each picrate had m.p. 147°. A mixed melting point showed no depression.

Anal. Calc'd for $C_{21}H_{25}N_5O_7$: N, 15.3. Found: N, 15.2.

PART C

2,4-Diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV). To 24.2 g. (0.15 mole) of imidodicarboxylic ester was added 26 g. (0.20 mole) of N-(2-aminoisobutyl)isopropylamine (II) and the mixture was heated for four hours at 120–140°. Upon cooling, the mass solidified and upon recrystallization from alcohol gave 25 g. (84%) of XIV, m.p. 206°.

Anal. Calc'd for $C_9H_{17}N_3O_2$: C, 54.3; H, 8.6; N, 21.1.

Found: C, 54.0; H, 8.4; N, 21.0.

Reaction of 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine (XIV) *with* II *to yield 4,4-dimethyl-1-isopropyl-2-imidazolidone* (VIII). To 17 g. (0.075 mole) of XIV was added 20 g. (0.15 mole) of II and the mixture was heated for five hours with the temperature gradually being raised from 140° to 200°. When cooled, the product solidified and upon recrystallization from ethanol gave 21.2 g. (91.5%) of VIII, m.p. 164°. A mixed melting point of this compound with an authentic specimen of VIII showed no depression.

Anal. Calc'd for VIII, $C_8H_{16}N_2O$: C, 61.5; H, 10.3; N, 17.9.

Found: C, 61.5; H, 10.2; N, 17.9.

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SUMMARY

1. N-(2-aminoisobutyl)isopropylamine (II) reacts with ethyl malonate to produce ethyl 4,4-dimethyl-1-isopropyl-2-imidazolinyl-2-acetate (III), which upon reaction with an excess of (II) produces 1-isopropyl-2,4,4-trimethyl-2-imidazoline and 4,4-dimethyl-1-isopropyl-2-imidazolidone.

2. Monosubstituted malonic esters react with (II) to produce diazepines which upon reaction with excess of (II) form imidazolines and imidazolidones.

3. Imidodicarboxylic ester reacts with (II) to form 2,4-diketo-6,6-dimethyl-1-isopropylhexahydro-1,3,5-triazepine which reacts with an excess of (II) to produce ammonia and 4,4-dimethyl-1-isopropyl-2-imidazolidone.

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[FROM THE WEIZMANN INSTITUTE OF SCIENCE AND THE GROSVENOR LABORATORY]

THE USE, FOR CONDENSATION REACTIONS, OF POTASSIUM HYDROXIDE IN SOLVENTS OF THE ACETAL TYPE

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In a previous paper (1), it has been reported that the combination of potassium hydroxide with acetal gives a reagent which permits the condensation of aldehydes and ketones with chloroform in good yields. A further study of this system has revealed certain properties which make its application to other syntheses attractive. Even when used in its technical form (87% KOH), potassium hydroxide in these solvents does attack ester groups only slowly, so that it is possible to alkylate acetoacetic and malonic ester and similar esters containing reactive methylene and methine groups, without having to use alkali alkoxides in anhydrous alcohols (2). Upon addition of the esters to the potassium hydroxide-acetal system, the enolates are formed as thick, creamy precipitates. Obviously, hydrolysis of the esters will be more extensive when the less reactive halides are used. The best yields, are, therefore, obtained with benzyl and allyl chlorides or ethyl bromoacetate. Less reactive halides, *e.g.*, isobutyl bromide, give inferior yields, a phenomenon which has also been observed in comparative experiments with other condensing agents (3); however, these halides are not hydrolyzed or dehydrohalogenated by the potassium hydroxide-acetal system.

Potassium hydroxide and carbonate have been recommended occasionally, especially in the old literature (4, 5) as condensing agents in such alkylation reactions, but a repetition of some of the experiments described has shown that the method is limited to very few substances containing reactive methylene groups, and to low-molecular alkyl *iodides* only. On the other hand, the observation(6) is significant that ethyl acetoacetate can be alkylated by β-diethylaminoethyl chloride, using aqueous-alcoholic potassium hydroxide as condensing agent. The activity of the halide is so great[1] that the rate of alkylation is far greater than that of hydrolysis.

Table I, which summarizes our alkylation experiments, shows that the scope of the new reagent is somewhat wider than that of alkali alkoxides. Not only such hydrogen atoms as are activated by two neighboring C=O or C≡N groups are replaced by alkyl groups but also ethyl phenylacetate[2] and ethyl isobutyrate[3]

[1] No physical data bearing on this point appear to be available. The analogous β-acetoxyethyl chloride is half as reactive towards iodide ion as butyl chloride (7).

[2] Ethyl phenylacetate has been alkylated before in the form of its potassio-derivative (8). Of course, the corresponding nitrile (benzyl cyanide) has been known for a long time to have replaceable hydrogen atoms. Mostly, sodium amide has been used as a condensing agent (9), but also solid sodium hydroxide (10, 11, 12, 13) and sodium in liquid ammonia (14) have been employed.

[3] Hudson and Hauser (15, compare 16, 17) have alkylated ethyl isobutyrate after converting it into its sodium enolate with triphenylmethyl sodium (yields with methyl iodide, ethyl iodide, and benzyl chloride were 58%, 42%, and 55%, respectively). Isobutyronitrile has been alkylated with sodium amide by Ziegler and Ohlinger (18), who have also observed reduced yields with isobutyl bromide (and cyclohexyl bromide).

TABLE I

ALKYLATION REACTIONS WITH KOH[a] IN ACETAL-TYPE SOLVENTS

SOLVENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
A	300	Ethyl acetoacetate, 0.5	Benzyl chloride, 0.5	80[c]	Ethyl benzylacetoacetate[b]	61.4	156–160	(13)	
					Ethyl dibenzylacetoacetate	6.8	204–210	(16)[d]	
A	150	Ethyl acetoacetate, 0.25	Benzyl chloride, 0.5	80[e]	Ethylbenzylacetoacetate	15.0			
					Ethyl dibenzylacetoacetate	75.2			
C	150	Ethyl acetoacetate, 0.25	Benzyl chloride, 0.5	80[e]	Ethyl benzylacetoacetate	14.5			
					Ethyl dibenzylacetoacetate	74.8			
A	360	Ethyl benzylacetoacetate, 0.5	Benzyl chloride, 0.5	80[e]	Ethyl dibenzylacetoacetate	77.4			Ethyl benzylacetoacetate, 14
B	300	Ethyl acetoacetate, 0.5	Butyl bromide, 0.5	75[f]	Ethyl butylacetoacetate	37.6	112–115	(15)	Butyl bromide, 58.4
A	360	Ethyl butylacetoacetate, 0.5	Benzyl chloride, 0.5	80[h]	Ethyl benzylbutylacetoacetate	55.1[i]	178–185	(16)	Ethyl butylacetoacetate, 30.1 Benzyl chloride, 39.6
B	600	Ethyl acetoacetate, 0.5	Isobutyl bromide, 0.5	75[e]	Ethyl isobutylacetoacetate[j]	43.0	104–107	(15)	Isobutyl bromide, 43.8
					Ethyl diisobutylacetoacetate[k]	4.1	135–140	(15)	

TABLE I—*Continued*

SOLVENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
B	400	Ethyl acetoacetate, 0.4	Methallyl chloride, 0.4	25	Ethyl methallylacetoacetate	100	114–116	(20)	
B	400	Ethyl acetoacetate, 0.2	Methallyl chloride, 0.4	25[l]	Ethyl dimethallylacetoacetate	90	151–152	(20)	
A	300	Diethyl malonate, 0.5	Benzyl chloride, 0.5	75[j]	Diethyl benzylmalonate	23.8	170–175	(15)	Diethyl malonate, 35.0 Benzyl chloride, 74.0
A	340	Ethyl ethoxalylacetate,[m, n] 0.5	Benzyl chloride, 0.5	75[o]	Diethyl benzylmalonate[p]	44.0	170–175	(15)	Benzyl chloride, 50.6
B	300	Ethyl cyclopentanone-2-carboxylate, 0.5	Benzyl chloride, 0.5	75[j,s]	Ethyl 2-benzylcyclopentanone-2-carboxylate[q, r]	65.0[t]	186–190	(14)	Keto-ester, 28.2 Benzyl chloride, 30.1
B	360	Ethyl cyclopentanone-2-carboxylate, 0.5	Isobutyl bromide, 0.5	75[t]	Ethyl 2-isobutylcyclopentanone-2-carboxylate[q, u]	34.0	138–142	(15)	Keto-ester, 46.2 Isobutyl bromide, 61.2
B	360	Ethyl cyclopentanone-2-carboxylate, 0.5	Ethyl bromoacetate, 0.5	70[j]	Diethyl cyclopentanone-2-carboxylate-2-acetate[v]	62.0	163–167	(15)	
B	300	Ethyl phenylacetate, 0.5	Benzyl chloride, 0.5	70[j]	Ethyl benzylphenylacetate[w]	30.3	212–214	(18)	Ethyl phenylacetate, 25.0 Phenylacetic acid, 41.2 Benzyl chloride, 63.2

TABLE I—*Continued*

SOLVENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
C	300	Ethyl phenylacetate, 0.5	Benzyl chloride, 0.5	50[f]	Ethyl benzylphenylacetate	37.8			Ethyl phenylacetate, 19.5 Phenylacetic acid, 36.7 Benzyl chloride, 50.6
A	300	Butyl isobutyrate, 0.5	Benzyl chloride, 0.5	80[f]	Butyl benzylisobutyrate[z,y]	23.0	156–160	(18)	Butyl isobutyrate, 29.2 Isobutyric acid, 45.4 Benzyl chloride, 63.2
C	240	Butyl isobutyrate, 0.5	Benzyl chloride, 0.5	50[f,g]	Butyl benzylisobutyrate	23.8			
B	300	Ethyl cyanoacetate, 0.5	Benzyl chloride, 0.5	45[f]	Ethyl benzylcyanoacetate	30.5[aa]	165–170	(17)	Ethyl cyanoacetate, 39.6
					Ethyl dibenzylcyanoacetate[z]	14.3	225–227	(15)[bb]	Benzyl chloride, 39.6
B	300	Ethyl cyanoacetate, 0.25	Benzyl chloride, 0.5	45[p]	Ethyl benzylcyanoacetate	14.8			Ethyl cyanoacetate, 35.4
					Ethyl dibenzylcyanoacetate	25.3			Benzyl chloride, 46.6
B	360	Ethyl cyclohexenylcyanoacetate,[dd] 0.5	Benzyl chloride, 0.5	35[cc]	Ethyl benzylcyclohexenylcyanoacetate[ee]	53.7	223–225	(15)	Ethyl cyclohexenylcyanoacetate, 23.7 Benzyl chloride, 44.3

TABLE I—*Continued*

SOLVENT	CC.	FIRST REACTANT, MOLE	HALIDE, MOLE	TEMP., °C.	PRODUCT	YIELD, %	B.P., °C.	(MM.)	RECOVERED, %
B	190	Ethyl phenylcyanoacetate, 0.6	Chloroacetonitrile, 0.5	12[ee]	α-Phenyl-α carbethoxysuccinonitrile[ff, gg]	87.7	190–195	(12)	Ethyl phenylcyanoacetate[hh] 18.2
B	190	Indene, 0.25	Benzyl chloride, 0.5	25[ii]	1-Benzylindene[ij]	59.7	180–182	(17)[ll]	
					1,3-Dibenzylindene[kk]	14.4	205–210	(12)	
A	400	Ethyl acetoacetate, 0.5	β-Diethylaminoethyl chloride, 0.5	25[f]	Ethyl β-diethylaminoethylacetoacetate[mm]	25.0	145–146	(24)	
A	400	Ethyl phenylacetate, 0.5	β-Diethylaminoethyl chloride, 0.5	25[f]	Ethyl β-diethylaminoethylphenylacetate[nn]	16.9	171–172	(15)	
A	400	Indene, 0.5	β-Diethylaminoethyl chloride, 0.5	25[f]	β-Diethylaminoethylindene[oo]	20.0	166	(21)	

[a] Procedure: To 0.5 mole of KOH (equals 33 g. of technical potassium hydroxide) in acetal solvent was added a mixture of the first reactant and the halide at the temperature indicated. Solvents are: acetaldehydediethylacetal (A); acetaldehydedipropylacetal (B); 1-butoxy-2-ethoxyethane (C) [*cf.* Weizmann, *et al.*, *J. Soc. Chem. Ind.* (*London*), **67,** 203 (1948)]. [b] The same result was obtained in butyraldehydedibutylacetal. [c] The temperature rose spontaneously to 90°; the reaction was completed at 70° (1 hour). [d] M.p. 56–57°. [e] The mixture was heated 2 hours at 80°. [f] The mixture was heated 3 hours at 90°. [g] The reaction started at 80°. [h] The mixture was heated 3 hours at 100°. [i] In acetaldehydedipropylacetal (3 hours at 100°), the yield was 65%. [j] Rohn, *Ann.*, **190,** 306 (1878) (alcohol-free enolate in benzene). Compare Freylon, *Ann. chim.* [8] **9,** 555 (1906); Rupe and Courvoisier, *Helv. Chim. Acta*, **6,** 1049 (1923). [k] Mixter, *Ber.*, **7,** 501 (1874). [l] 24 hours; then 2 hours at 50°. [m] Prepared according to Wislicenus, *Ann.*, **246,** 315 (1888); *Ber.*, **19,** 3225 (1886). Yield, 65%; b.p. 131–132°/24 mm. [n] Alkylations of esters of this type have been studied before. Wislicenus and Kiesewetter, *Ber.*, **31,** 194 (1898). Wislicenus and Silberstein, *Ber.*, **43,** 1825 (1910). Mebus, *Monatsh.* **26,** 485 (1905). Neuberg and Peterson, *Bio.Z.*, **67,** 39 (1914). [o] The mixture was heated 1 hour at 80°. [p] By thermal decomposition (evolution of carbon monoxide) of the ethyl benzylethoxalylacetate formed. Before distillation, the product showed the characteristic deep-red color reaction with ferric chloride. Wislicenus and Muenzesheimer, *Ber.*, **31,** 551 (1898). [q] The product did not show any color reaction with ferric chloride. [r] Calc'd for $C_{15}H_{18}O_3$: C, 73.2; H, 7.3. Found: C, 72.9; H, 7.5. [s] When the reaction

can be benzylated, or condensed with β-diethylaminoethyl chloride. The reaction applies to esters of other aryl- and dialkyl-acetic acids as well. Indene, too, can be benzylated and β-diethylaminoethylated with comparative ease.

The following additional observations result from an inspection of Table I. Diethyl malonate responds to the method less smoothly than ethyl acetoacetate or the alkyl-substitution products of the latter. In the time, *e.g.*, required for 24% benzylation, about half of the diethyl malonate and half of the benzyl chloride are destroyed. Similarly, while ethyl phenylacetate is benzylated to the extent of 30%, some 40% is hydrolyzed; in this case, no appreciable hydrolysis of the benzyl chloride takes place. Likewise, butyl isobutyrate is 45% hydrolyzed and 23% benzylated. It is interesting that ethyl cyanoacetate can be monoalkylated without difficulty, while the usual methods (19) give mainly the dialkylation products.

The question arose whether the Claisen condensation, too, would be catalyzed by the system potassium hydroxide-acetal. This is not the case. Ethyl acetate did not condense with acetone to acetylacetone, nor ethyl adipate to ethyl cyclopentanone-2-carboxylate, which is easily achieved by metallic sodium or sodium amide. In the latter case, practically all of the ethyl adipate was recovered unchanged, *i.e.*, unsaponified, even after prolonged heating.

On the other hand, it is possible to use the new reagent to effect the Michael

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FOOTNOTES TO TABLE I—*Continued*

mixture was heated at 100° for six hours, the yield of benzylation product rose to 80.1%; 14.2% of the benzyl chloride and 12.8% of unreacted ester were recovered. [t] The mixture was heated 6 hours at 90°. [u] Calc'd for $C_{12}H_{20}O_3$: C, 67.9; H, 9.5. Found: C, 67.5; H, 9.6. [v] Koetz, *Ann.*, **350**, 235 (1906). [w] Meyer, *Ber.*, **21**, 1306 (1888). [x] This acid and its derivatives have been prepared so far only by somewhat devious routes. Haller and Bauer, *Compt. rend.* **149**, 8 (1909); **150**, 1474 (1910); *Ann. chim.*, [9], **1**, 29 (1914); [9], **9**, 20 (1918). Haller, *Compt. rend.*, **154**, 557 (1912). Stenzl and Fichter, *Helv. Chim. Acta*, **17**, 669 (1934). [y] Calc'd for $C_{15}H_{22}O_2$: C, 76.9; H, 9.4. Found: C, 76.57; H, 9.3. [z] Hessler, Am., **22**, 176 (1899). [aa] When the addition of the reagents was carried out at 30° and the mixture heated at 50° for two hours, the yield in mono- and dibenzylated product, respectively, was 46.2 and 23.1%; 15.8% of the benzyl chloride and 14.2% of the ethyl cyanoacetate were recovered. [bb] Thick syrup, which crystallized upon standing, m.p. 33°. [cc] The mixture was heated 1 hour at 70°. [dd] The butylation of ethyl cyclohexenylcyanoacetate was described by Weizmann, Sulzbacher, and Bergmann, *J. Chem. Soc.*, 772 (1947). [ee] The temperature rose spontaneously to 70°; the reaction was completed at 90° (3 hours). [ff] The corresponding α-carbomethoxy compound has been described by Corson and Stoughton, *J. Am. Chem. Soc.*, **50**, 2825 (1928). [gg] Calc'd for $C_{12}H_{12}N_2O_2$: N, 12.3. Found: N, 12.0. [hh] Including the excess used. [ii] The mixture was heated two hours at 85°. [jj] Calc'd for $C_{16}H_{14}$: C, 93.2; H, 6.8; Mol. wt., 206. Found: C, 92.9; H, 7.0. Mol. wt., 218. Thiele and Buehner [*Ann.*, **347**, 263 (1906)] prepared this hydrocarbon from indene and benzyl chloride with powdered potassium hydroxide at 160° (6 hours), Weissgerber [*Ber.*, **44**, 1436, 2216 (1911)] from indene-sodium and benzyl chloride in toluene. In both cases, the yields appear inferior to those observed in the present investigation. [kk] Thiele and Buehner (ref. 25). [ll] From methyl alcohol, leaflets, m.p. 63°. [mm] Calc'd for $C_{12}H_{23}NO_3$: C, 62.9; H, 10.0; N, 6.1. Found: C, 62.8; H, 10.2; N, 5.9. [nn] Calc'd for $C_{16}H_{25}NO_2$: C, 73.0; H, 9.5; N, 5.3. Found: C, 72.7; H, 9.5; N, 5.1. [oo] Calc'd for $C_{15}H_{21}N$: C, 83.7; H, 10.0; N, 6.5. Found: C, 83.4; H, 10.0; N, 6.7.

condensation, *i.e.*, the addition of reactive methylene or methine groups to α,β-unsaturated aldehydes, ketones, and esters; the usual reagents in this case are sodium ethoxide and metallic sodium, or—occasionally—diethylamine (20). The results are listed in Table II. Again, the resistance of ester groups to hydrolysis under these experimental conditions is remarkable (21).

Equally, condensation of reactive methylene groups with aldehydes and ketones can be effected with the system potassium hydroxide-acetal. Examples studied are the preparation of triphenylacrylonitrile from benzophenone and benzyl cyanide (22, 23, 24) and of anisylidene-indene from indene and anisaldehyde (25); also, indene was condensed with acetone (26), benzophenone (26) and 2-ethylhexanal[4] and fluorene with anisaldehyde (28). No secondary reactions were observed in contrast with those cases in which alcoholic alkali is used as condensing agent, and in which the corresponding cinnamylidene derivatives are frequently formed (29, 30, 31)[5] together with the benzylidene compounds.

Not only acetals and ketals, both non-cyclic and cyclic, but also the dialkylethers of ethylene glycol can be used as solvents in the reactions enumerated, without significant change in the results. Also the reaction between ketones and chloroform can be carried out satisfactorily in ethylbutyl glycol ether; however, in the case of acetone, it was not possible to separate the condensation product from the solvent by fractional distillation. On the other hand the reaction is limited to potassium hydroxide, since neither sodium hydroxide nor lithium hydroxide behave analogously. Apparently, we have here another of the rare instances in which potassium and sodium hydroxide are not equivalent, not merely sources of hydroxyl ion; the cation, too, plays a—so far obscure—role. Indeed, we suspect that potassium hydroxide forms a molecular compound with the above-defined solvents, although attempts to isolate such a molecular compound have failed.

The system potassium hydroxide–acetal presents a very characteristic and rather unusual picture. Upon addition of potassium hydroxide in the form of pellets or sticks to the well agitated solvents, the solid disintegrates rapidly; when heated at 150°, it melts to a heavy bottom layer, which upon cooling with continued agitation, solidifies to a mechanically stable, chemically reactive suspension of a finely divided microcrystalline powder. One can thus dispense with the cumbersome preparation of powdered potassium hydroxide, in any event as long as one uses a solvent with a boiling point not lower than 150°. Otherwise, the choice of the solvent will be determined by the boiling point of the starting materials and especially of the desired end product, so that the recovery of the solvent will not be complicated unduly by the reagents employed or the substances formed.

[4] Practically no benzofulvene has been prepared so far by alkaline condensation of aliphatic aldehydes and indene; the customary method utilizes indenylmagnesium bromide. The only exception is the condensation of 1-methylindene with paraformaldehyde, effected with methanolic potassium hydroxide (Wuest, 27).

[5] Also the substance of m.p. 176°, obtained by Sieglitz (32) from fluorene and *o*-chlorobenzaldehyde, is *o*-chlorocinnamylidene-, not *o*-chlorobenzylidene-fluorene.

TABLE II

MICHAEL REACTIONS WITH KOH[a] IN ACETALDEHYDEDIPROPYLACETAL

ACETAL, CC.	FIRST REACTANT	SECOND REACTANT	PRODUCT	YIELD		B.P., °C.	(MM.)	RECOVERED,[b] %	
				GRAMS	%			First Reactant	Second Reactant
180	Diethyl maleate	Diethyl malonate[c]	Ethyl propane-1,1,2,3-tetracarboxylate[d]	72.0	72.3	194–197	(16)	19.4	34.4
200	Benzalacetophenone	Diethyl malonate[c]	Ethyl α-carbethoxy-β-phenyl-γ-benzoylbutyrate[e]	78.0	70.6	218–220	(2)	20.0	40.6
300	Benzalacetone	Diethyl malonate[c]	Ethyl α-carbethoxy-β-phenyl-γ-acetylbutyrate[f]	77.0	83.9	205–210	(17)	13.7	30.5
180	Diethyl maleate	Ethyl acetoacetate[g]	Triethyl α-acetyltricarballylate[h]	65.0	71.7	195–196 189	(16) (12)	21.3	31.7
180	Diethyl maleate[i]	Benzyl cyanide	Diethyl 3-phenyl-3-cyanopropane-1,2-dicarboxylate[k]	65.4	74.3	220–222	(14)	21.3	30.0
180	Benzalacetone	Acetonitrile[l]	β-Phenyl-γ-acetylbutyronitrile[m,n]	35.0	82.3	235–236	(13)	13.7	Not recovered
180	2-Butylidene butanal	Ethyl acetoacetate	2-Ethyl-3-propyl-4-acetyl-4-carbethoxy-1-butanal[o]	47.0	61.2	155–165[p]	(12)		

[a] Procedure: To 0.3 mole of KOH (1 mole equals 66 g. of technical potassium hydroxide) in the acetal was added 0.3 mole of the first reactant (unsaturated) and 0.4 mole of the second reactant at 20°; this was followed by heating for 1 hour at 90°. [b] The figure for the second component includes the 25% excess employed. [c] Exothermic reaction; the temperature rises to 40°. [d] Michael and Schulthess, *J. prakt. Chem.*, [2] **45**, 56 (1892). [e] Compare

EXPERIMENTAL PART

Tables I and II are self-explanatory; the reaction products in each case were treated with ice-water (if necessary, neutralised) and the solvent layers separated, washed, dried, and subjected to fractional distillation.

Triphenylacrylonitrile. To the system potassium hydroxide (13 g.) and acetaldehydedibutylacetal (250 cc.), a mixture of 25 g. of benzyl cyanide and 30 g. of benzophenone was added at 10°. The fairly exothermic reaction was completed at 50° (one hour) and the product isolated by removal of the acetal *in vacuo*. The nitrile crystallized upon trituration with alcohol and showed the expected melting point (165°) and the characteristic red-violet color reaction with concentrated sulfuric acid. Yield, 80%.

The condensation reactions of *indene* and *fluorene* with aldehydes and ketones are summarized in Table III.

Preparation of acetals (33). In the condensation of aldehydes with primary alcohols, a small amount of gaseous hydrochloric acid, dissolved in the appropriate alcohol was used as a catalyst; the components were mixed at 0° and the exothermic reaction was completed by keeping the mixture at room temperature for 24 hours.

Acetaldehydedibutylacetal, from 1 mole of acetaldehyde and 4 moles of butyl alcohol; conversion (calc'd on aldehyde) 77%, yield (calc'd on aldehyde) 84%; b.p. 184°.

Acetaldehydedipropylacetal, from 1 mole of acetaldehyde and 3 moles of propyl alcohol; conversion 88%, yield 100%; b.p. 143°.

Butyraldehydediethylacetal, from 1 mole of butyraldehyde and 4 moles of ethyl alcohol; conversion 87%, yield 80%; b.p. 143°.

Butyraldehydedipropylacetal, from 1 mole of butyraldehyde and 4 moles propyl alcohol; conversion 81%, yield 70%; b.p. 182°.

Butyraldehydedibutylacetal, from 1 mole of butyraldehyde and 4 moles of butyl alcohol; conversion 85%, yield 60%; b.p. 218°.

FOOTNOTES TO TABLE II—*Continued*

Beilstein, **10** (Suppl), 424. The product was a viscous oil, which solidified upon trituration with dilute methanol; from alcohol, m.p. 66–67°. Found: C, 71.5; H, 6.2. Calc'd for $C_{22}H_{24}O_5$: C, 71.7; H, 6.5. Hydrolysis with conc'd aqueous potassium hydroxide solution, acidification, and extraction with ether gave the acid which lost carbon dioxide at 150°. β-Phenyl-γ-benzoylbutyric acid formed needles (from alcohol), m.p. 152°. (Vorlaender and Knoetzsch, *Ann.*, **294,** 332 (1897). [f] Found: C, 66.4; H, 7.2. Calc'd for $C_{17}H_{22}O_5$: C, 66.6; H, 7.2. The *dimethyl* ester has been described by Kohler and Allen, *J. Am. Chem. Soc.*, **45,** 1987 (1923), and by Qudrat-I-Khuda, *J. Indian Chem. Soc.*, **8,** 215 (1931) [*Chem. Zentral.*, I, 222 (1932)]. Treatment as in [e] gave β-phenyl-γ-acetylbutyric acid; from dilute alcohol, m.p. 84–85° [Vorlaender and Knoetzsch, *Ann.*, **294,** 321 (1897)]. [g] The temperature rises to 27°. [h] Ferric chloride gives a purple-red color reaction. [Fichter and Probst, *Ann.*, **372,** 73 (1910)]. Preparation from diethyl fumarate and ethyl acetoacetate with sodium metal or sodium ethoxide: Ruhemann and Browning, *J. Chem. Soc.*, **73,** 727 (1898); Mitter and Roy, *J. Indian Chem. Soc.*, **5,** 3 (1928) [*Chem. Zentral.*, I, 2394 (1928)]. [i] The temperature rises to 50°. [k] Found: C, 66.8; H, 6.9; N, 4.9. Calc'd for $C_{16}H_{19}NO_4$: C, 66.4; H, 6.6; N, 4.9. Saponification, first with 60% sulfuric acid, then with concentrated aqueous potassium hydroxide gave the corresponding 1-phenylpropane-1,2,3-tricarboxylic acid, prisms, m.p. 196–199°. [Stobbe and Fischer, *Ann.*, **315,** 231, 245 (1901); Hecht, *Monatsh.*, **24,** 371 (1903); Wegscheider, *Ber.*, **44,** 908 (1911)]. For the reaction of benzyl cyanide and diethyl fumarate, see Henze, *Ber.*, **33,** 966 (1900). [l] The temperature rises to 40°; the reaction was completed at 75° (1 hour). [m] Saponification gave β-phenyl-γ-acetylbutyric acid. [n] A hard resin was also formed in this reaction. [o] The compound reduced ammoniacal silver nitrate solution and gave a purple-blue color with ferric chloride. *Anal.* Calc'd for $C_{14}H_{24}O_4$: C, 65.6; H, 9.4. Found: C, 65.9; H, 9.9. [p] The two components cannot be separated by fractional distillation.

2-Ethylhexanaldimethylacetal, from 1 mole of 2-ethylhexanal and 6 moles of methanol; conversion 67%, yield 100%; b.p. 182–184°.

The preparation of *cyclic acetals* by azeotropic condensation has been described in a previous communication (34); the method is not applicable to the lowest-boiling representatives of the aliphatic ketones. It was, however, observed that the preparation of 2-methyl-2-ethyldioxolane from methyl ethyl ketone and ethylene glycol was much easier than literature data (35, 36, 37) would have led one to suspect. A mixture of 124 g. of glycol, 1152 g. of methyl ethyl ketone, 11.5 g. of gaseous hydrochloric acid, and 25 g. of anhydrous mag-

TABLE III

CONDENSATION REACTIONS OF INDENE AND FLUORENE WITH KOH[a] IN ACETALDEHYDEDIPROPYLACETAL

ACETAL, CC.	HYDROCARBON, MOLE	CARBONYL COMPOUND, MOLE	PRODUCT	YIELD, %	M.P., °C.	RECOVERED, %
150	Indene, 0.2	Anisaldehyde,[b] 0.2	Anisylidene-indene	79.1	119[c]	Indene, 10.8
150	Indene, 0.1	Benzophenone,[b] 0.1	Benzhydryl-ideneindene	62.6	111[d]	Indene, 25.8 Benzo-phenone, 25.8
100	Indene, 0.2	Acetone,[b] 0.2	Isopropyl-ideneindene	78.5	B.p. 142/16 mm.	Indene, 15.1
165	Indene, 0.17	2-Ethylhexanal,[b] 0.17	2-Ethylhexyl-idenein-dene[e]	66.4	B.p. 140–145/12 mm.	
150	Fluorene, 0.2	Anisaldehyde,[g] 0.2	Anisylidene-fluorene[h, i]	85.4	132–133[f]	Fluorene, 10.5

[a] Procedure: To 0.25 mole of KOH (16.5 g. of technical potassium hydroxide) in the acetal was added a mixture of the hydrocarbon and the carbonyl compound at 20°. [b] The mixture was heated for one hour at 80°. [c] Recrystallization from alcohol or ethyl acetate. [d] Recrystallization from alcohol or isopropyl alcohol. [e] Golden-yellow oil. Calc'd for $C_{17}H_{22}$: C, 90.7; H, 9.3; Mol. wt., 226. Found: C, 90.0; H, 9.8; Mol. wt., 235. [f] Recrystallization from isopropyl alcohol. [g] The mixture was heated for two hours at 80°. [h] Calc'd for $C_{21}H_{16}O$: C, 88.7; H, 5.7. Found: C, 88.5; H, 5.9. [i] The condensation with sodium ethoxide gives, after 5 days, a yield of 64% [Thiele and Henle, *Ann.*, **347**, 301 (1906)].

nesium sulfate was kept at room temperature for one week; it was then neutralized with solid sodium carbonate, filtered, and subjected to fractionation; b.p. 115°. Conversion 95%, yield, 100%.

Alkylation with solid potassium hydroxide and alkyl iodide. Some of Michael's experiments (4) were repeated, for the sake of comparison with the method described in the present paper:

(a) *Ethylation of ethyl acetoacetate.* When 17 g. of finely powdered caustic potash (0.3 mole of KOH) was gradually added to the well agitated mixture of 39 g. (0.3 mole) of ethyl

acetoacetate and 47 g. (0.3 mole) of ethyl iodide, only a slight rise in temperature was observed. The mixture was warmed at 60° during one hour, cold water was added, and the organic layer separated, dried, and fractionated. The yield of ethyl monoethylacetoacetate, b.p. 198–200°, was 25 g. (52.7%). Michael obtained a 64.2% yield.

(b) *Methylation of diethyl malonate.* The addition of 17.0 g. of finely powdered potash (0.3 mole of KOH) to the mixture of 48 g. (0.3 mole) of diethyl malonate and 43 g. (0.3 mole) of methyl iodide caused an exothermic reaction. When it subsided, the product was worked up as above. There was isolated 32 g. (61.3%) of diethyl monoethylmalonate, b.p. 199–201° (Michael, 82.9%).

(c) Attempts to *ethylate ethyl monoethylacetoacetate* by means of powdered potassium hydroxide and ethyl iodide failed completely.

SUMMARY

The combination of potassium hydroxide with solvents of the acetal and ethylene glycol dialkylether type affords a system which can be used (a) for the alkylation of compounds containing a reactive methylene or methine group, (b) the Michael condensation, and (c) the condensation of reactive methylene groups with aldehydes and ketones, in addition to (d) the condensation of chloroform with aldehydes and ketones, reported previously. The system does not bring about the Claisen condensation. The influence of the reactivity of the components on the scope of these reactions has been studied. There are reported 26 examples of type (a), 7 of type (b), and 6 of type (c).

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCES]

ABSORPTION SPECTRA OF CAROTENOIDS; STRUCTURE OF VITAMIN A_2

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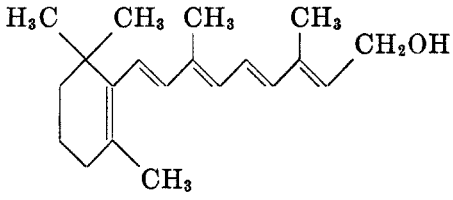
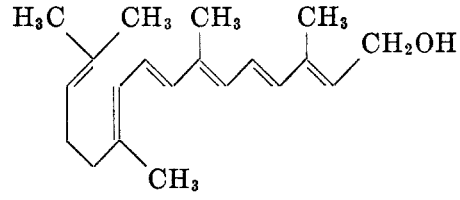
The ultraviolet absorption maxima of heteroannular dienes and trienes of the steroid series can be calculated with an accuracy of a few mμ from equation 1, in which m is the number of alkyl groups or ring residues attached to the polyene

$$1.\ \lambda_{max} = 214 + 5m + 30\ (n - 2) + 5e$$

system, n is the number of conjugated double bonds, and e is the number of exocyclic double bonds (1, 2). A solvent effect, if any, is minor. For the pentaene alcohol vitamin A_1 the maximum calculated from the same equation (334 mμ) is in the order of magnitude of that found (326 mμ) but somewhat higher.



I Vitamin A_1



II

For vitamin A_2, however, the value 329 mμ calculated for formula II, proposed by Karrer, Geiger, and Bretscher (3) and favored by Shantz (4), is so divergent from the observed maximum of 351 mμ as to suggest that the formula may be incorrect. This discrepancy between observed and calculated absorption maximum prompted the following analysis of spectrographic data for carotenoids, conducted in the hope that an accurate method of calculation specific to these multiply unsaturated compounds might afford a basis for deduction of the actual structure.

Polyene systems. A typical carotenoid containing a polyene system of ten or eleven double bonds has a three-banded absorption spectrum in which the band of greatest intensity occupies a position almost exactly half-way between the other two and which thus represents the peak of a broad band differing from the single bands of dienes and trienes only in having fine detail in the form of shoulders that are usually developed into well-defined companion bands of shorter and longer wave length. The present analysis will thus be based solely upon the position of the maxima of the median bands of highest extinction coefficient.

The position of the absorption maxima of typical carotenoids is influenced to a considerable degree by the nature of the solvent, and it appears that sensitivity to solvent effect increases with increasing number of conjugated double bonds.

[1] On leave of absence from Harvard University as delegate of the National Academy of Sciences to the dedication of the Weizmann Institute, November 2, 1949.

Whereas solvents exert little effect on the absorption characteristics of steroid dienes (1), maxima recorded (5) for dehydrolycopene, which has fifteen conjugated double bonds, are as follows (mμ): hexane, 504; chloroform, 528, benzene, 531; pyridine, 535; carbon disulfide, 557. Wald (6) has noted that the spectra of carotenoid polyenes are very nearly the same in pentane, hexane, and ethanol, which have comparable refractive indexes, but are considerably displaced when the solvent is chloroform. Even greater displacements are observed in other solvents, particularly carbon disulfide. Thus, measurements in an aliphatic hydrocarbon or ethanol would seem the most suitable basis for comparison, but only a few results are available for ethanol solution. Maxima determined for hexane solutions are usually available and are taken as the basis for the present analysis; where data for hexane solutions are lacking, determinations made in petroleum ether, ligroin, or pentane are taken as equivalent to those in hexane.

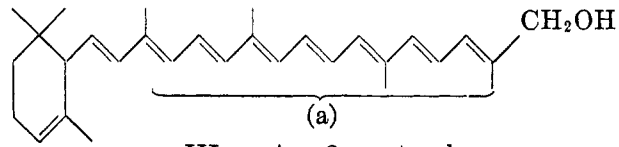
TABLE I

MAXIMA CALCULATED FROM EQUATION 1

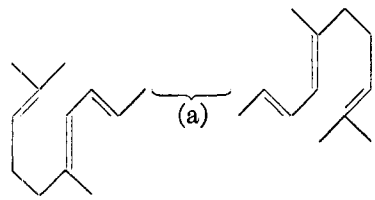
COMPOUND	n	m	$\lambda_{max.}^{Hexane}$ mμ	
			Calc'd	Found
α-Apo-2-carotenol	8	6	424	420
Lycopene type[a]	11	8	524	474 (av.)
Dehydrolycopene	15	10	654	504

[a] Lycopene, lycoxanthin, and lycophyll (see Table II).

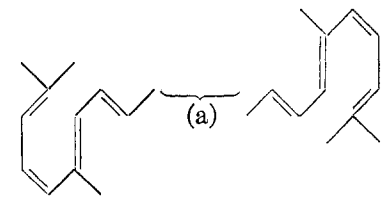
The inadequacy of equation 1 as applied to higher polyenes is demonstrated by the comparison given in Table I of maxima calculated and found (5) for the open-chain substances α-apo-2-carotenol (III), lycopene (IV), and dehydrolycopene (V), which contain, respectively, 8, 11, and 15 conjugated double bonds.



III α-Apo-2-carotenol



IV Lycopene



V Dehydrolycopene

The comparison suggests that the bathochromic effect of an additional double bond is not a constant quantity as assumed in Equation 1 but decreases with

lncreasing number of conjugated double bonds.[2] As an approximation, the reiationship can be described as a proportionality as expressed in equation 2, in which m is the number of alkyl substituents, n is the number of double bonds in conjugation, and A, x, and y are constants for the series. Substitution in 2 of the

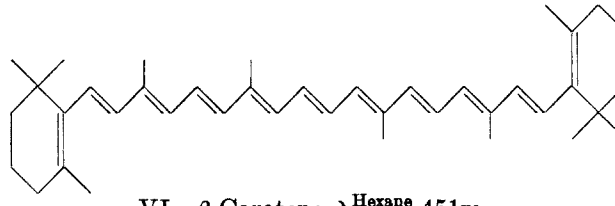
$$2.\ \lambda_{max} = A + 5m + n\ (x - ny)$$

maxima and values for m and n of the polyenes III, IV, and V and of the arbitrarily assumed quantity A = 114 gives three simultaneous equations that yield the values y = 1.80, 1.61, and 1.69. From the average, y = 1.7, values found for x are 48.10, 47.79, and 48.16; av. x = 48.01. Hence equation 3 expresses the data. The series constant A was so selected that solution of the equation for

$$3.\ \lambda_{max}^{Hexane} = 114 + 5\,m + n\ (48.0 + 1.7\,n)$$

n = 1 and for n = 2 gives the values 160 and 203 mμ, which are reasonably close to the maxima of ethylene and butadiene, respectively. The maxima calculated for III, IV, and V are 419, 476 and 501.5 mμ.

The bicyclic β-carotene (VI) contains the same number of conjugated double bonds as lycopene (eleven) but the chromophoric system has ten C-substituents as compared with eight for lycopene. If no other factor were involved, β-carotene



VI β-Carotene, λ_{max}^{Hexane} 451mμ

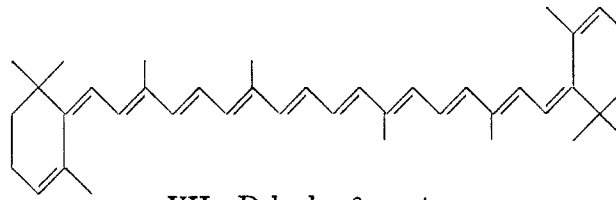
should absorb at a wave length 10 mμ longer than lycopene, but actually the median maximum is 23 mμ less than that of lycopene. The hypsochromic effect evidently involved most likely is steric; possibly ring closure results in hindrance between the ring methyl groups and the side chain that prevents coplanarity and hence maximum resonance. γ-Carotene (λ_{max}^{Hexane} 462 mμ) is intermediate in structure, for one end of the molecule resembles lycopene and the other end resembles β-carotene. Since γ-carotene contains one more alkyl substituent than lycopene, the steric effect of ring closure (S) can be evaluated as follows:

$$S = \lambda^{\gamma\text{-Carotene}} - \lambda^{Lycopene} - 5 = -17$$

Comparison of γ- and β-carotene indicates the value S = -16. In these hydrocarbons with eleven double bonds the average effect of the presence of a ring characterized as having an internal double bond (R_i) is -16.5 mμ. Thus equation 3 can be modified by addition of the term $-16.5\ R_i$, where R_i is the number of rings of the type defined. Thus for vitamin A_1 (m = 6, n = 5, R_i = 1) the maximum is calculated as 114 + 30 + 197.5 − 16.5 = 325 (found, 326).

[2] Described by Brooker, Keyes, and Williams (7) as a convergent series; see also Kuhn (8).

Dehydro-β-carotene (VII) contains a second type of ring structure characterized by the presence of an exocyclic double bond (designation: R_e).



VII Dehydro-β-carotene

The exocyclic double bond *per se* may produce a bathochromic shift, and ring closure may be attended with a steric effect operating in the opposite direction. The net effect per ring as estimated from the value of λ_{max}^{Hexane} found for dehydro-β-carotene (475 mμ) and that calculated from equation 3 (495 mμ) is 10 mμ.

All the above inferences are summarized in the following general equation for calculation of absorption maxima of carotenoid polyenes and of such oxygenated derivatives as carry no carbonyl groups in conjugation with the polyene system.

$$4.\ \lambda_{max}^{Hexane} = 114 + 5m + n\,(48.0 - 1.7\,n) - 16.5\,R_i - 10\,R_e$$

[m = no. of C-substituents; n = no. of conjugated double bonds; R_i = no. of rings with an internal double bond (type: VI); R_e = no. of rings with an external double bond (type: VII)].

A comparison of maxima for nineteen carotenoids calculated from equation 4 with those recorded in the compilation of Karrer and Jucker (5), is given in Table II. The agreement is good except in the case of β-apo-2-carotenol, and the reported maximum thus appears in doubt. The substances are probably of all-*trans* configuration except 5,6-dihydro-α-carotene, which is partly *cisoid*. The table includes computations pertaining to the solvent effect. Little or no displacement of the spectrum occurs in ethanol solution as compared with hexane solution, but displacements of increasing magnitude are noted in chloroform, benzene, pyridine, and carbon disulfide. For α-apo-2-carotenol, with eight double bonds, the displacement between carbon disulfide and hexane solution is 25 mμ; for dehydrolycopene, with fifteen double bonds, the displacement is 53 mμ. The suggestion that the bathochromic solvent effect is proportional to the number of conjugated double bonds was tested by computation of the quantity $c = (\lambda^{Solvent} - \lambda^{Hexane})/n$, and the results tabulated indicate that this quantity is indeed a constant for a given solvent. The average values found for c may be used with fair assurance for calculation of λ_{max} in one solvent from the value found for another solvent. The dependence of the solvent effect upon n explains why no effect has been apparent among steroid dienes.

Aldehydes, ketones, acids. The α,β-unsaturated carbonyl compounds of the carotenoid series seem to differ considerably in absorption characteristics from steroid enones and dienones; the relationships appear more comparable with those noted among corresponding polyenes. Thus compounds VIII and IX,

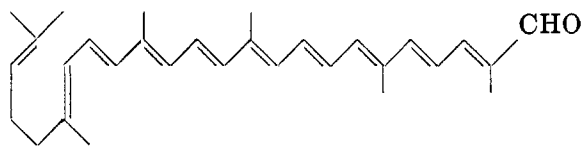
TABLE II

ABSORPTION MAXIMA FOR CAROTENOID POLYENES AND DERIVATIVES CALCULATED FROM EQUATION 4

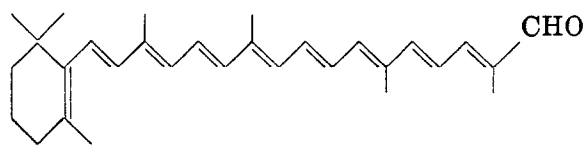
COMPOUND	n	m	RINGS		$c = \frac{\lambda \text{ Solvent} - \lambda \text{ Hexane}}{n}$					λ_{max}^{Hexane}	
			R_1	R_2	EtOH	Chf	C_6H_6	Py	CS_2	Calc'd	Found
α-Apo-2-carotenol	8	6	–	–	0.4				4.0	419	420
5,6-Dihydro-α-carotene	9	6	–	–	0.05	1.1	2.2		4.9	438	442.5
Lycopene	11	8	–	–	−0.3	0.4	1.1		2.7	476	475.5
Lycoxanthin	11	8	–	–	0.09		1.3		3.0	476	473
Lycophyll	11	8	–	–	0.09		1.3		3.0	476	473
Dehydrolycopene	15	10	–	–		1.6	1.7	2.1	3.6	501.5	504
Vitamin A_1	5	6	1	–	0					325	326
β-Apo-2-carotenol	9	8	1	–	0.3				3.7	432	423
α-Carotene	10	8	1	–		0.7			3.0	447.5	447.5
5,6-Dihydro-β-carotene	10	8	1	–	0.05	1.0	1.1		2.9	447.5	447.5
Xanthophyll	10	8	1	–	−0.1	0.9			2.8	447.5	447.5
Capsanthol	10	8	1	–		0.8	1.4	1.5	2.9	447.5	448[a]
γ-Carotene	11	9	1	–		1.2	1.4		3.1	465	462
Rubixanthin	11	9	1	–	0.1	1.1			2.9	465	462
β-Carotene	11	10	2	–		1.4			3.1	453	451
Cryptoxanthin	11	10	2	–		1.1			2.9	453	451
Zeaxanthin	11	10	2	–	−0.05	1.0			2.8	453	451.5
Dihydrorhodoxanthin	11	10	2	–	−0.2	0.7			2.5	453	452
Dehydro-β-carotene	12	10	–	2		0.8			2.4	475	475
Averages..... c =					0.03	1.0	1.4	1.8	3.1		

[a] Taken as equal to λ_{max}^{EtOH}.

with nine double bonds conjugated with a carbonyl group, have maxima (λ_{max}^{Hexane} 473, 454 mμ) not far from those calculated for structurally related polyenes with ten conjugated ethylenic linkages (454, 442.5 mμ). Computation from available



VIII Apo-3-lycopenal



IX β-Apo-2-carotenal

data by the methods developed above has led to the empirical equations 5, 6, and 7 given below, and calculated maxima are compared with those found in Table IV. Data are available for open-chain aldehydes having 8, 9, and 10 conjutaged ethylenic linkages (Table III: α-citraurin and α-apo-2-carotenal, apo-3-lycopinal, and apo-2-lycopenal), and solution of simultaneous equations as before affords the values of x and y given in equation 5. Unfortunately evidence regarding the effect of a ring with an internal double bond (R_i) is conflicting. In the case of retinene$_1$, or vitamin A_1 aldehyde, the effect of such a ring appears to be negligible; in the case of β-apo-2-carotenal (IX) and its hydroxy derivative β-citraurin, the effect is 20–24 mμ. No reason for this discrepancy is apparent; equation 5 includes a term ($-10\ R_i$) that averages the two divergent estimates.

The data in this and related series are very meagre as well as partly conflicting, but the following tentative conclusions seem indicated. Aldehydes have the same absorption characteristics as the corresponding acids, and esters are equivalent to acids. In a dialdehyde or diacid the second functional group is counted merely

Aldehydes, dialdehydes, acids, diacids

$$5.\ \lambda_{max}^{Hexane} = 114 + 5m + n\,(55.5 - 2.1\,n) - 10\ R_i$$

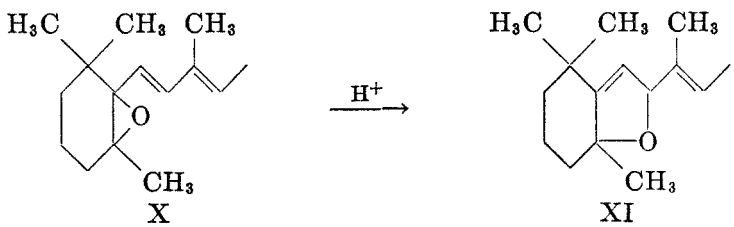
Ketones:

$$6.\ \lambda_{max}^{Hexane} = 100 + 5m + n\,(55.5 - 2.1n) - 10\ R_i$$

Diketones:

$$7.\ \lambda_{max}^{Hexane} = 120 + 5m + n\,(55.5 - 2.1n) - 10\ R_i - 18\ R_e$$

as a carbon-substituent, equivalent to an alkyl group, and the equation for the monofunctional compounds is then applicable. Ketones are slightly less powerful chromophores than aldehydes and acids. In diketones, unlike dialdehydes and diacids, the second carbonyl group has an appreciable bathochromic effect. The diketone system is treated as a unit and the second carbonyl group is not counted as an alkyl substituent; terminal groups attached to the system —CO(CH=CH)$_n$CO— are not counted as alkyl substituents. In some instances the agreement with reliable data is only very approximate (retinene$_1$); in other instances the data are incomplete or uncertain (parentheses). Where the only measurements available are in a solvent other than hexane or ligroin (last column), the solvent concerned is indicated. The effect of a ring with an external double bond (R_e), as estimated from a single instance (rhodoxanthin), appears to be twice as great as in the polyene series.



X XI

TABLE III

Aldehydes, Ketones, Acids

Compound	n	m	Rings		$c = \frac{\lambda \text{ Solvent} - \lambda \text{ Hexane}}{n}$				λ_{max}^{Hexane}	
			R_i	R_e	EtOH	Chf	C_6H_6	CS_2	Calc'd	Found
Aldehydes and Dialdehydes (Equation 5)										
Retinene$_1$[a]	5	5	1		3.0	4.4			354	365
Apo-1-azafrinal	6	4						5.0	391	(431[b])
α-Citraurin	8	5						5.0	449	450
α-Apo-2-carotenal	8	5						4.2	449	450
Apo-3-lycopenal	9	6					1.7	4.4	473	473
β-Apo-2-carotenal	9	7	1					4.0	468	454
β-Citraurin	9	7	1				1.0	3.6	468	458
Apo-2-lycopenal	10	6						3.8	489	490.5
Apo-3,12-lycopenedial	8	5						4.0	449	452
Apo-2,12-lycopenedial	9	5				2.5		3.8	468	468
Acids,[c] Diacids,[c] Aldehyde-acids (Equation 5)										
Vitamin A acid	5	5	1						354	EtOH 351.5[d]
Azafrin	7	4				1.1			420	422.5
3,8-Dimethyldecapentaene-1,10-dicarboxylic acid	5	3							CS_2 375[e]	CS_2 (419[b])
Crocetin	7	5				1.4		4.1	425	424.5
Bixin	9	5							Chf 481[e]	Chf 475
Apo-2-norbixinal	7	4						4.1	420	424
Apo-1-norbixinal	8	5				1.4		4.1	449	445
Ketones (Equation 6)										
Myxoxanthophyll (?)	10	6							475	EtOH 471
Capsanthin	10	7	1				1.1	2.8	470	475
Semi-β-carotenone	10	6	1				1.7	3.0	465	469
Myxoxanthin (?)	11	8	1		0.5	0.7		2.1	486	(465[b])
Anhydrosemi-β-carotene	11	9	1			0.8	0.9	2.6	491	480
Diketones, Ketoaldehydes (Equation 7)										
β-Carotenone	9	4				2.6	2.2	3.5	469	466
Physalienone	9	4				2.7		4.0	469	464
Capsanthinone	9	4					1.7	3.4	469	472
Capsorubin	9	4					1.3	3.2	469	474
Anhydrocapsanthinone	10	6	1				1.6	3.4	485	483
Astaxanthin	11	8	2						496	Py 493
Bisanhydro-β-carotenone	11	8	2						496	494
Rhodoxanthin	12	8		2	0.7	1.8	1.3	3.1	488	488
β-Carotenonaldehyde	7	3				2.7	2.1	3.9	421	431
4-Hydroxy-β-carotenonaldehyde	7	3					2.3	3.8	421	433

[a] Constants from Wald (6). [b] Only one band reported. [c] Esters and acids have identical absorption characteristics. [d] See Wendler, Slater, and Tishler (9). [e] Calculated from [c] for crocetin.

Oxides. Carotenoid epoxides (X) and the furanoid oxides (XI) into which they are converted by acids are listed in Table IV. It appears that an oxide linkage adjacent to the conjugated system has a slight bathochromic effect and that a ring with an internal double bond produces a slightly greater hypsochromic shift than in the polyenes. The empirical equation 8 used for calculation is a slight modification of the polyene equation 4.

$$8.\ \lambda_{max}^{Hexane} = 118 + 5m + n\,(48.0 - 1.7\,n) - 23\,R_i$$

TABLE IV

OXIDES (EQUATION 8)

COMPOUND	n	m	R_i	$c = \frac{\lambda \text{ Solvent} - \lambda \text{ Hexane}}{n}$					λ_{max}^{Hexane}	
				EtOH	Chf	C_6H_6	Py	CS_2	Calc'd	Found
EPOXIDES AND DIEPOXIDES										
α-Carotene monoepoxide	9	6			1.3	1.4		3.2	442	442
Xanthophyll epoxide	9	6		0.3		1.2		3.3	442	442
β-Carotene monoepoxide	10	8	1		1.2	1.3		3.2	445	447
Cryptoxanthin epoxide	10	8	1						445	EtOH 449
Antheroxanthin	10	8	1						445	Chf 460.5
β-Carotene diepoxide	9	6			1.4	1.4		3.2	442	443
Cryptoxanthin diepoxide	9	6							442	EtOH 442
Violaxanthin	9	6		−0.1	1.0			3.0	442	443
FURANOID OXIDES AND DIOXIDES										
Flavochrome	8	6			1.4	1.5		3.6	423	422
Flavoxanthin	8	6		0	1.1			3.5	423	421
Chryanthemoxanthin	8	6		0	1.1			3.5	423	421
Mutatochrome = Citroxanthin	9	8	1		1.2	1.4		3.5	429	427
Cryptoflavin	9	8	1						429	EtOH 430
Mutatoxanthin	9	8	1	0.1	1.1	1.4	1.9	3.7	429	426
Cryptochrome	7	6							401	CS_2 424
Aurochrome	7	6							401	CS_2 428

Solvent effect. The average coefficients (c) relating absorption maxima in various solvents to the maxima in hexane are summarized in Table V. Only in the series of polyene carotenoids is there a sufficient body of data for comparison of absorption characteristics in hexane, ethanol, chloroform, benzene, and carbon disulfide. The concordance of the maxima in ethanol and in hexane and the progressive bathochromic shifts that occur in the other three solvents appear to bear some relationship to the refractive indexes. Wald (6) suggested that the large displacements in the spectra of retinene$_1$ and rhodoxanthin between hexane and ethanol or chloroform represent a specific characteristic of carotenoids which contain a conjugated carbonyl group. According to the present analysis the displacements are abnormal only in the case of retinene$_1$; rhodoxanthin contains

twelve ethylenic linkages, and the displacement per double bond is about the same as in the polyene series. The available data suggest that ketones, diketones, and oxides are comparable with respect to solvent effect to polyenes and that the spectra of aldehydes and acids are subject to somewhat greater displacements.

Vitamin A_2. The observations concerning vitamins A_1 and A_2 requiring interpretation in terms of structural formulas are summarized in the following

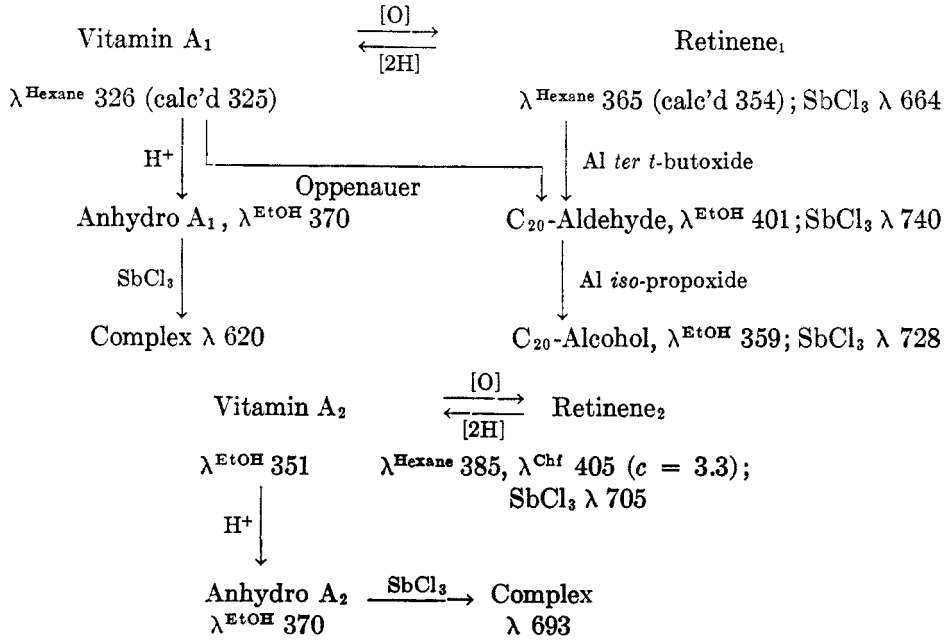
TABLE V

SOLVENT EFFECT

COMPOUND TYPE	COEFFICIENTS (c) FOR SOLVENTS (n_D^{20} IN PARENTHESES)					
	Hexane (1.357)	EtOH (1.361)	Chf (1.446)	C_6H_6 (1.502)	Py (1.501)	CS_2 (1.628)
Polyene systems	0	0.03 (12[a])	1.0 (14[a])	1.4 (8[a])	1.8 (2[a])	3.1 (18[a])
Aldehydes, dialdehydes	0	3.0 (1)	3.4 (2)	1.3 (2)		4.2 (9)
Acids, diacids, aldehyde-acids	0	1.4 (1)	1.2 (2)			4.1 (3)
Ketones	0	0.5 (1)	0.7 (2)	1.8 (3)		2.8 (3)
Diketones, ketoaldehydes	0	0.7 (1)	2.5 (4)	1.8 (7)		3.5 (8)
Oxides (1,2- and 1,4-)	0	0 (5)	1.2 (9)	1.4 (7)	1.9 (1)	3.4 (10)

[a] Number of comparisons.

chart of transformations, which gives the maxima (in mμ) of the sole or median absorption bands of the derivatives and of the antimony trichloride complexes.



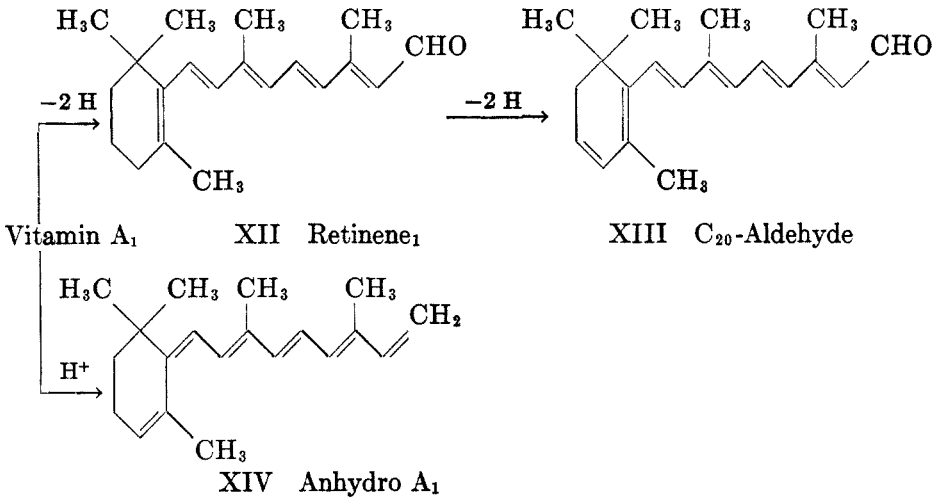
Vitamin A_1 is oxidized reversibly *in vivo* to the aldehyde retinene (10); oxidation can be accomplished by adsorption on manganese dioxide from petroleum ether

(11, 6), and reduction has been effected enzymatically *in vitro* (12). Vitamin A_1 is easily dehydrated to an anhydro compound; Oppenauer oxidation of the alcohol or aldehyde gives a C_{20}-aldehyde very similar in absorption characteristics to the aldehyde of vitamin A_2 and reducible to an alcohol similar to or identical with A_2 (13, 14). Vitamin A_2, isolated in pure form by Shantz (4), distills in a high vacuum at a temperature only about 3° higher than A_1 (15) and is so similar to A_1 in chromatographic characteristics and ease of dehydration that it must be an allylic alcohol of nearly the same molecular weight. From a comparison with the distillation characteristics (elimination maxima) of saturated and unsaturated fatty acids, Gray and Cawley (16) concluded that A_2 has the same number of carbon atoms as A_1 but contains one additional conjugated double bond. Although anhydro A_2 (4) contains seven double bonds whereas anhydro A_1 contains six, it has a three-banded spectrum with maxima corresponding exactly in position to those of anhydro A_2 and differing only in being somewhat less intense. The two anhydro compounds are differentiated, however, by the absorption maxima of the antimony trichloride complexes: 620 mμ for A_1 and 693 mμ for A_2 (17).

Chemical evidence of structure is incomplete and in part conflicting. Karrer found that ozonization of vitamin A_2 preparations containing very little A_1 gave some 8% of acetone (3) and 55–60% of formaldehyde (18). He pointed out that the result does not necessarily indicate a mixture of isomers having the groupings $(CH_3)_2C=$ and $CH_2=C(CH_3)-$ but may be the result of rearrangement induced by ozone; both lycopene and β-carotene were found to yield considerable formaldehyde on ozonization. Analytical evidence is not extensive. A single analysis reported by Shantz (4) for crystalline vitamin A_2 phenylazobenzoate is in good agreement with the open-chain formula $C_{20}H_{30}O$ for vitamin A_2 (II) proposed by Karrer, but also agrees satisfactorily with the formula $C_{20}H_{28}O$ for a cyclic structure. A single analysis of Shantz's anhydro A_2 agrees with the formula $C_{20}H_{28}$ but not with the formula $C_{20}H_{26}$, and a single analysis of the best preparation of A_2 in Karrer's laboratory is in fair agreement with the formula $C_{20}H_{30}O$ and does not check with the formula $C_{20}H_{28}O$. Two conflicting conclusions based upon mixed melting point determinations have been reported. Karrer and Bretscher (18) found that the allophanate of vitamin A_2 did not depress the melting point (73°) of the allophanate of dihydrophytol and concluded that A_2 has the open-chain structure II. Morton, Salah, and Stubbs (14) found that the 2,4-dinitrophenylhydrazones of retinene$_2$ and the C_{20}-aldehyde from vitamin A_1 melt at the same temperature and show no depression on admixture, and they concluded that A_2 has a cyclic structure. It thus appears that ozonization probably follows an anomalous course, that analytical evidence favors an open-chain structure but is not conclusive, and that in this series closely related compounds may or may not exhibit easily recognized melting point depressions.

Even in the A_1 series the structures cannot be deduced unambiguously from existing spectrographic data for the carotenoids because these data include certain inconsistencies, as noted above, and because there is no basis for estima-

tion of the chromophoric power of certain possible structural types. Retinene$_1$ (n = 5) can hardly have any structure other than XII and yet the maximum

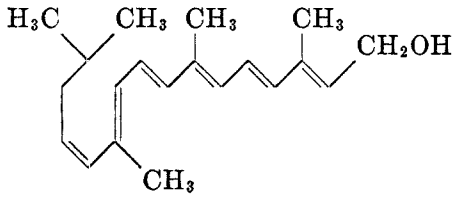


at 365 mμ is 24 mμ higher than expected in analogy with β-apo-2-carotenal (IX, n = 9). However the maximum found for retinene$_1$ is surely the better basis for comparison with the value 401 mμ reported for the C_{20}-aldehyde obtained by Oppenauer oxidation of either A_1 or retinene$_1$. The bathochromic shift suggests that the conjugated system has been lengthened. Oppenauer oxidation of pregnenolone under certain conditions has been shown to be attended with introduction of an additional double bond (19), and hence the C_{20}-aldehyde may be dehydroretinene$_1$, XIII, as suggested by Haworth, *et al.* (13). The maximum calculated for XIII from equation 5 on the assumption that the R_i effect is negligible, as in the case of retinene$_1$, is 396 mμ, in agreement with the observed maximum. There is no basis for judging whether or not the presence of two double bonds in the ring should produce a bathochromic displacement, and hence formula XIII tentatively satisfies the known requirements.

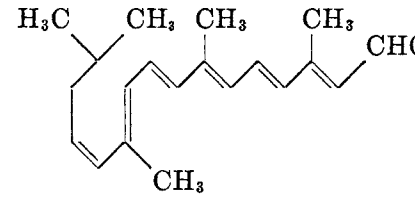
The expected product of dehydration of vitamin A_1 is the hexaene XIV, which has a ring with an external double bond. If the R_e effect is the same as in the dodecaene dehydro-β-carotene, the maximum calculated for XIV (356 mμ) is considerably less than that found (370 mμ). If the R_e effect is negligible in the hexaene, like the R_i effect in retinene$_1$, XIV should have a maximum of 366 mμ, close to that found.

Since in the retina of certain fresh water fish vitamin A_2 and retinene$_2$ are components of a reversible oxido-reduction system (10), it seems necessary to accept the proposition that no bond migration or other abnormality is involved in the oxidation of A_2 to the aldehyde or in the reverse process of chemical or enzymatic reduction. This proposition means for one thing that, if vitamin A_2 is an allylic alcohol, the carbonyl group of retinene$_2$ must be conjugated with the polyene system. Experimental evidence that this is the case is found in the large displacement of the spectrum between hexane and chloroform (c = 3.3).

Vitamin A_2 contains one double bond more than vitamin A_1, and in the Karrer formula II this additional double bond is not conjugated with the other five. The absorption maximum calculated for II from equation 4 is 336 mμ, which is considerably lower than the value found (351 mμ). The maximum calculated from equation 5 for the corresponding aldehyde (359 mμ) is also wholly out of line with the maximum observed for retinene$_2$ (385 mμ). The evidence of Gray and Cawley (16) cited above indicates conjugation of the sixth double bond with the other five. One possibility is that the substance is the open-chain polyene alcohol XV and that retinene$_2$ is the aldehyde XVI. Reliable calculation of the maxima for these structures can be made from equations 4 and 5; that for the

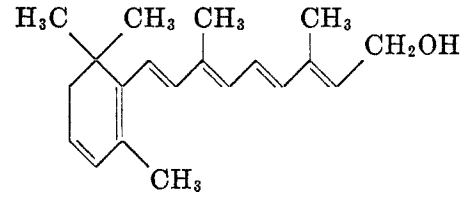


XV, $\lambda_{calc'd}^{Hexane}$ 366 mμ



XVI, $\lambda_{calc'd}^{Hexane}$ 391 mμ

aldehyde agrees with the value found for retinene$_2$ but the maximum calculated for the alcohol XV (366 mμ) is incompatible with that found for vitamin A_2 (351 mμ), and hence the formulation must be rejected. Another possibility is that vitamin A_2 has the structure XVII, considered by Gillam, Heilbron, Jones,

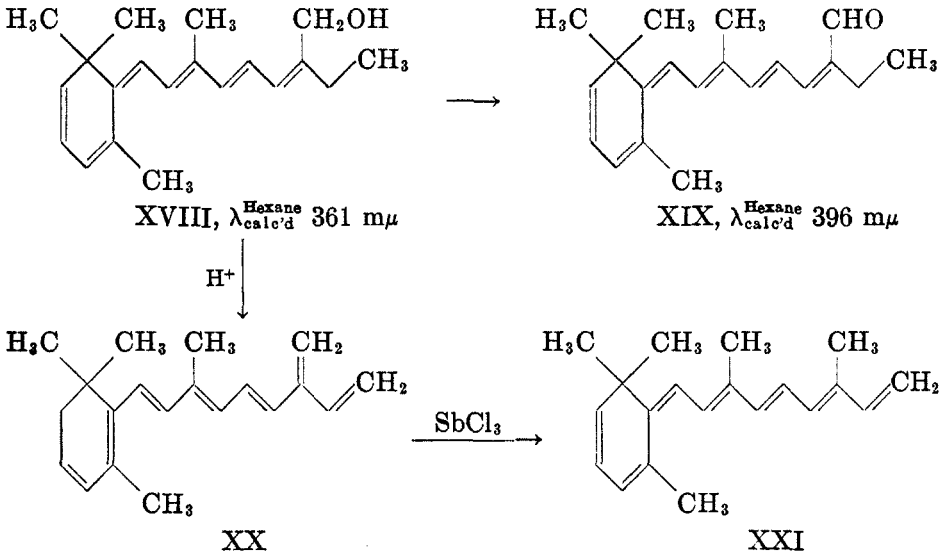


XVII, $\lambda_{calc'd}^{Hexane}$ 354.5 mμ

and Lederer (20) and favored by Gray (16). Retinene$_2$ would then have the formula XIII, above, which accounts adequately for the spectrum, and it would be identical with the C_{20}-aldehyde resulting from oxidation of retinene$_1$. Since the alcohol XVII represents the dehydro derivative of vitamin A_1, the hypsochromic R_i effect can be assumed to be operative as in A_1, and the maximum calculated from equation 4 (354.5 mμ) is close to that found (351 mμ). Karrer and Bretscher (18) rejected formula XVII because the substance yielded no α,α-dimethylsuccinic acid on ozonization, but since ozonization follows an anomalous course to the extent of yielding formaldehyde and acetone the validity of the negative evidence cited is open to some question. Another objection to the formula is that dehydration would be expected to proceed exactly as with A_1 by elimination of water across the conjugated system to give a heptaene, whereas anhydro A_2 appears to contain only a hexaene system.

The alternate formula XVIII accounts for the absence of α,α-dimethylsuccinic acid from the products of ozonization and offers a possible explanation of the

difference between A_2 and A_1 in their behavior on dehydration. In XVIII the carbon atom adjacent to the end of the polyenic alcoholic system carries no hydrogen atom and hence direct dehydration across the conjugated system is



not possible. An alternate sequence of reactions might lead to an anhydro compound of structure XX. This structure has a cross-conjugated system and would be expected to have the absorption characteristics of a hexaene rather than a heptaene. Calculation presents the same uncertainties as in the case of formula XIV for anhydro A_1 and the conclusions are practically the same: the maxima expected for XX if the R_i effect is operative and non-operative, respectively, are 349.5 and 366 mμ (found, 370 mμ). In any case XIV and XX should have very similar absorption spectra and hence are possible representations of anhydro A_1 and anhydro A_2. The difference in the maxima of the antimony chloride complexes is also accounted for on the assumption that XX is isomerized by the reagent to XXI, which has a normal heptaene system.

The calculation of the maximum for XVIII is subject to the uncertainties discussed with reference to XVII and the value given (361 mμ) thus appears close enough to the actual value (351 mμ) to admit the formula as a possibility. A substance of the alternate structure XVII could yield the anhydro compound XX by 1,4-elimination of water across the terminal double bond, but it would then be difficult to see why A_2 should behave any differently from A_1. Formula XVIII for vitamin A_2 thus seems to offer a better general account of the properties of the alcohol and its transformation products than any of the alternate formulas. The interpretation suggested implies that retinene$_2$ (XIX) and the C_{20}-aldehyde for vitamin A_1 (XIII) have similar absorption characteristics but are not identical, in spite of the mixed melting point evidence of identity. It discounts also the mixed melting point evidence of an open-chain structure. Perhaps the most serious objection is that the cyclic formula is consistent with only one of three available analyses. A final decision thus awaits further evidence.

Acknowledgement. This paper was conceived and completed in the course of a visit of the author to Israel as a guest of the Weizmann Institute. I am indebted to Dr. Chaim Weizmann, Dr. E. Bergmann, and associates for helpful discussions and for providing facilities for the study both at the Institute and in transit.

Note added in proof. Since this paper was written, Karrer and Schneider, *Helv. Chim. Acta*, **33**, 38 (1950), have reported the preparation by the method of Shantz (4) of a sample of vitamin A_2 phenylazobenzoate melting somewhat higher than Shantz's sample. They report an analysis of the derivative that agrees better with the cyclic than with the open-chain formula and state that neither the derivative nor the vitamin A_2 obtained from it afforded any acetone on ozonization.

SUMMARY

Empirical equations have been developed for calculation of the absorption maxima of all types of natural carotenoid pigments; maxima calculated for over sixty-five compounds are in substantial agreement with the values found.

The magnitude of the displacements of the spectra of a series of compounds in different solvents is proportional to the number of conjugated double bonds.

Analysis of the spectrographic data regarding the properties and transformations of vitamins A_1 and A_2 has led to consideration of new formulas for vitamin A_2 and derived compounds.

REHOVOTH, ISRAEL

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[CONTRIBUTION FROM THE GATES AND CRELLIN LABORATORIES OF CHEMISTRY, CALIFORNIA INSTITUTE OF TECHNOLOGY[1]]

SYNTHESIS OF CERTAIN ETHYL, PHENYL, AND NITROPHENYL DERIVATIVES OF UREA[2]

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Received December 13, 1949

As part of an investigation (1) of the derivatives which are formed from centralite (1,3-diethyl-1,3-diphenylurea) during the accelerated aging of double base smokeless powder, it was necessary to synthesize a considerable number of derivatives of centralite and of urea. Since certain of these compounds, or the intermediates which are required for their synthesis, apparently have not been described in the literature, we present in this paper methods which we have found to be successful for their synthesis. With one exception, in which a nitration was used, all of the compounds were prepared by the reaction of an amine with either an isocyanate or a substituted carbanilyl chloride. Because only small quantities of the compounds were required, no attempts were made to improve yields or to refine the procedures; however, experience suggested certain possibilities for improvement which are briefly discussed.

EXPERIMENTAL PART

Stem corrections were applied to melting points all of which were taken in melting-point tubes in an electrically-heated copper block. Micro-analyses were made by the late Dr. G. Oppenheimer and Mr. G. Swinehart. 1,3-Diethyl-1-phenylurea was synthesized by Mr. Floyd Preston.

1,1-Diphenyl-3-ethylurea. 1,1-Diphenyl-3-ethylurea was prepared by the reaction of ethyl isocyanate with diphenylamine. Ethyl isocyanate[4] was obtained by the method of Boehmer (2) in which propionyl chloride is reacted with activated sodium azide (3). This reaction may become vigorous unless carefully controlled. An 8-g. portion of recrystallized diphenylamine (Eastman White Label) and an equivalent amount of ethyl isocyanate in 30 ml. of toluene were heated for 13 hrs. in a sealed tube at 150° since the reaction seemed to be sluggish in refluxing toluene. The cooled reaction mixture was boiled with 100 ml. of benzene in order to remove unreacted isocyanate and when the volume had been reduced to 25 ml., 400 ml. of ligroin (60–70°) was added and the solution was cooled. The pink needles which separated were recrystallized 6 times from ligroin to yield a colorless product, m.p. 74.8–75.3°. The yield of purified compound was 4 g. or 37%.

Anal. Calc'd for $C_{15}H_{16}N_2O$: C, 74.97; H, 6.71; N, 11.66.

Found: C, 75.04; H, 6.55; N, 11.61.

1,3-Diethyl-1-phenylurea. The reaction between N-ethylcarbanilyl chloride and ethylamine was used to prepare 1,3-diethyl-1-phenylurea. A 12-g. portion of N-ethylcarbanilyl chloride which had been synthesized by the method of Price (4) was dissolved in 50 ml. of toluene and 11 g. of cold ethylamine (Eastman White Label) was slowly added at 0°. Heat

[1] Contribution No. 1366.

[2] This paper is based in whole on work done for the Office of Scientific Research and Development under Contract OEMsr-881 with the California Institute of Technology. Professor Linus Pauling was Official Investigator.

[3] Present address: Harvard Medical School, Boston, Massachusetts.

[4] Dr. C. E. Schweitzer (private communication) recommends the method of Slotta and Lorenz, *Ber.*, **58**, 1320 (1925) as a more convenient one for the preparation of ethyl isocyanate. Ethyl sulfate, potassium cyanate, and sodium carbonate are heated with caution.

was evolved and a gelatinous precipitate of ethylamine hydrochloride formed immediately. After 15 hrs. at room temperature, the reaction mixture was refluxed for one hr. The solution was separated from the ethylamine hydrochloride and washed 5 times with 50 ml. of water to remove dissolved ethylamine hydrochloride. After the solvent had been removed, the crystalline residue was recrystallized 5 times from ligroin (60–70°) and twice from ethyl ether; Norit was used during two of the recrystallizations from ligroin. The final product was colorless, free of halogen, and melted at 62.5–62.8°. The yield was 1.5 g. (12%).

Anal. Calc'd for $C_{11}H_{16}N_2O$: C, 68.71; H, 8.39; N, 14.58.

Found: C, 68.59; H, 8.20; N, 14.54.

The yield probably could be improved if dissolved ethylamine hydrochloride were removed from the solution with a paste of sodium carbonate rather than by washing with water because, as was determined later, the compound is appreciably soluble in water.

1-Phenyl-1,3,3-triethylurea. This compound was prepared from 12 g. of N-ethylcarbanilyl chloride (4) and 11 g. of diethylamine (Eastman White Label), each of which was dissolved in 50 ml. of anhydrous toluene. When the solutions were mixed at 0°, heat was evolved and diethylamine hydrochloride precipitated. The temperature was permitted to rise to 60° and after the reaction had slowed, the mixture was refluxed for 30 min. After the filtered solution had been washed once with 3 *N* hydrochloric acid and twice with water, the solvent was evaporated under reduced pressure. The 14.3 g. of yellowish residual oil was then distilled under reduced pressure in an all-glass apparatus and 12.5 of product (yield 88%) was obtained; b.p. 166–167°/27 mm. and m.p.−7 to −8°.

Anal. Calc'd for $C_{13}H_{20}N_2O$: C, 70.84; H, 9.17; N, 12.72.

Found: C, 71.18; H, 9.19; N, 12.77.

The anomalous melting point of 1-ethyl-1,3,3-triphenylurea. This substituted urea has been prepared by Michler (5) who heated N,N-diphenylcarbamyl chloride with 2 equivalents of N-ethylaniline at 130° and by Kaufmann (6) who melted together N-ethylcarbanilyl chloride and diphenylamine in the presence of zinc dust. Kaufmann's product melted at 80° and it is stated in his paper that Michler's material also had this melting point, while Dains, *et al.* (7) report m.p. 79°.

An initial attempt to prepared the compound by the method of Michler resulted in the isolation of a viscous oil which could not be induced to crystallize. Trial experiments then showed that a purer product could probably be obtained by the following procedure. An 8-g. portion of N,N-diphenylcarbamyl chloride (Eastman White Label recrystallized), 5 g. of redistilled N-ethylaniline, and 5 g. of zinc dust were heated at 110° until the reaction began with the evolution of gas and then at 90–100° for 12 hrs. The viscous reaction mixture was dissolved in 100 ml. of ether, the solid was filtered off, and the solution was washed with two 100-ml. portions of 3 *N* hydrochloric acid and three 100-ml. portions of water. However, the viscous, light yellow liquid which remained after evaporation of the solvent could not be made to crystallize.

Crystals were first obtained from a sample which was distilled in a high vacuum; the fraction which distilled at 137–138° at a pressure of 10–20 microns crystallized when a solution in ligroin (60–70°) was cooled to the temperature of Dry Ice. It is interesting to note that, once these crystals had formed, crude and distilled fractions from the various preparations began to crystallize slowly at their different places in the laboratory even though they were not consciously seeded. However, the solid product was somewhat amorphous in nature and the melting point and character of the solid were not improved by recrystallization. A pure product was finally obtained by dissolving the material from several preparations in anhydrous ether and saturating at 0° with hydrogen chloride gas. The precipitate which formed (probably diphenylamine hydrochloride) was filtered off, excess hydrogen chloride was removed with moist sodium bicarbonate, and the solvent was evaporated. Several recrystallizations were carried out from methanol by adding water at room temperature until a trace of oil separated, seeding, and cooling to 0°. The final product was composed of well-formed, colorless needles which had a constant melting point of 66.0–66.5° and gave the following analysis.

Anal. Calc'd for $C_{21}H_{20}N_2O$: C, 79.70; H, 6.39; N, 8.86; M.W., 316.
Found: C, 79.94; H, 6.41; N, 9.14; M.W., 325 (Rast micromethod in exaltone).

Because of the complicated series of purifications from several preparations, the calculation of a yield is meaningless.

The melting point 66.0–66.5° is very different than that of 80° which is reported by Michler (5) and Kaufmann (6) and of 79° by Dains, Roberts, and Brewster (7). However, the method of preparation, the analysis, and the molecular weight lead us to believe that our product actually is 1-ethyl-1,3,3-triphenylurea and that the difference in melting points probably is due to polymorphism.

N-Ethyl-2-nitrocarbanilyl chloride. N-Ethyl-2-nitrocarbanilyl chloride was required as an intermediate in the synthesis of 2-nitrocentralite.[5] A 15-g. sample of 2-nitro-N-ethylaniline[6] and 10 g. of triethylamine (Eastman White Label) were dissolved in 300 ml. of dry distilled benzene. Phosgene which had been washed with unsaturated cottonseed oil and conc'd sulfuric acid was passed into the solution at 0° for 15 min. At the end of this time, the solution was removed from the ice-bath, allowed to warm to 40°, and then, after the reaction had slowed and the temperature had fallen to 30°, warmed to 60° for 20 min. Phosgene was passed into the solution throughout this time and 5 g. of triethylamine was added during the course of the reaction to replace any which had been lost by vaporization. A white precipitate of triethylamine hydrochloride formed in the solution during the reaction. The benzene solution was washed with three 200-ml. portions of 6 *N* hydrochloric acid and four 200-ml. portions of water and then dried with calcium chloride. Evaporation of the solvent left a residue of 24 g. of dark yellow oil which solidified slowly when 100 ml. of ligroin (60–70°) was added and the mixture was cooled to 0°. Recrystallization from 50 ml. of warm ether to which 150 ml. of ligroin was added yielded 15.5 g. (yield 75%) of light yellow product, m.p. 46.5–47.5°. A small portion was recrystallized three times to m.p. 47.5–48.0° and this material gave the following analysis.

Anal. Calc'd for $C_9H_9ClN_2O_3$: C, 47.27; H, 3.94; N, 12.24; Cl, 15.53.
Found: C, 47.13; H, 4.16; N, 11.86, 11.84; Cl, 15.62.

While phosgene was being passed into the solution during the above preparation, a white solid formed in the air above the solution and, indeed, the first reaction in the solution was the formation of a white solid at a rate much more rapid than the main reaction which resulted in the formation of hydrogen chloride and the eventual formation of triethylamine hydrochloride. It seems probable that this white substance is a *complex of phosgene and triethylamine:* the literature apparently does not contain information about such a complex although some data are available concerning complexes or reaction products of phosgene and other tertiary amines. We have not had occasion to study the properties of this material further but we should like to point out that if it is a reasonably stable complex, it might prove useful in organic syntheses as a convenient, solid, concentrated source of phosgene. Its formation during the preparation of N-ethyl-2-nitrocarbanilyl chloride apparently did not interfere with the main reaction.

2-Nitrocentralite. When the solution of 8 g. of N-ethyl-2-nitrocarbanilyl chloride and 10 g. of N-ethylaniline (Eastman White Label) in 25 ml. of dried benzene was refluxed for 2 hrs., it became very dark red in color and both a red-black and a colorless precipitate formed. The mixture was diluted with 100 ml. of benzene and the nearly black solution was washed successively with 100 ml. of water, 100 ml. of 3 *N* hydrochloric acid, and three 100-ml. portions of water. The final washings were almost colorless and the brownish-orange benzene solution, after drying and treatment with 2 g. of Norit, became bright yellow-orange in color. The oil which remained after removal of the solvent could not be induced to crystallize until it had been purified chromatographically. The general chromatographic procedures have been described elsewhere (8) but the specific details of this purification will

[5] In the convention of *Chemical Abstracts*, "Centralite" refers to 1,3-diethyl-1,3-diphenylurea. Hence, 2-nitrocentralite is 1,3-diethyl-3-(2-nitrophenyl)-1-phenylurea.

[6] Obtained from Dr. R. L. Shriner.

be given. The 2.2 g. of crude 2-nitrocentralite was dissolved in 80 ml. of 1:4 benzene-ligroin[7] and placed on a 7 × 25-cm. column of 2:1 silicic acid-Celite (by weight) which had been pre-washed with V ml.[8] of ether and 2 V ml. of ligroin (60–70°). By development with 2 V ml. of a 5% solution of ether in ligroin, a dark yellow impurity, probably 2-nitro-N-ethylaniline, was washed into the filtrate. After the receiver had been changed, the 2-nitrocentralite was washed into the filtrate with 2 V ml. of 1:1 ether-ligroin. The solvent was evaporated and the residual red oil was taken up in 50 ml. of boiling ligroin (30–60°). The crystals which were formed when the solution was cooled in an ice-salt bath and the vessel was scratched were recrystallized three times to give one gram (yield 9%) of light yellow stubby needles which had a constant melting point of 56–57°. The following analysis was obtained.

Anal. Calc'd for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.06; N, 13.42; M.W., 313.

Found: C, 65.41, 65.44; H, 6.09, 6.17; N, 13.67, 13.65; M.W., 322 (Rast micromethod in exaltone).

The yield of 2-nitrocentralite was small because the main reaction took another course which produced a highly colored red compound. Although the compound which melted at 56–57° was not the main product, there was little doubt that it was 2-nitrocentralite because of the excellent agreement of the analysis and molecular weight determination with the calculated value. Furthermore, the physical and chromatographic properties were those which would be expected of 2-nitrocentralite on the basis of the behavior of related compounds (1).

N-Ethyl-4-nitrocarbanilyl chloride. N-Ethyl-4-nitrocarbanilyl chloride was required as an intermediate in the preparation of 4-nitrocentralite. A 25-g. sample of 4-nitro-N-ethylaniline[9] which had been prepared by the methods of Weller (11) and Nölting and Collin (12) and 20 g. of dimethylaniline (Eastman White Label) were dissolved in 400 ml. of dry, distilled benzene and phosgene was passed through the solution essentially as in the preparation of N-ethyl-2-nitrocarbanilyl chloride. At the end of the reaction, the clear red benzene solution was decanted from a second phase which was then dissolved in benzene. Both solutions were washed thoroughly with 6 *N* hydrochloric acid and with water, dried, and combined, and the solvent was then removed under reduced pressure. The yellow crystalline residue was dissolved in 50 ml. of hot acetone and crystallized by the addition of 50 ml. of ligroin (60–70°) and subsequent cooling to 5°. The yellow crystals weighed 15 g. and melted at 115–116°; the mother liquor yielded 6.5 g. of somewhat darker material, a total yield of 63%. Recrystallization of the lighter-colored sample produced a material which melted at 115.8–116.5° and gave the following analysis.

Anal. Calc'd for $C_9H_9ClN_2O_3$: C, 47.27; H, 3.94; N, 12.24; Cl, 15.53.

Found: C, 48.27; H, 4.48; N, 12.33; Cl, 14.34.

The analytical results were not entirely satisfactory but the product was a satisfactory intermediate for the preparation of 4-nitrocentralite and hence was not purified further.

Probably it would be better to use triethylamine instead of dimethylaniline to remove hydrogen chloride during the reaction of phosgene with 4-nitro-N-ethylaniline since dimethylaniline can react with phosgene to form Michler's ketone. Triethylamine was used in the preparation of N-ethyl-2-nitrocarbanilyl chloride as a result of the experience with this preparation.

4-Nitrocentralite. Lécorché and Jovinet (13) have prepared a mononitrocentralite by

[7] The compositions of solvents are in terms of the ratios of the volumes of the constituents.

[8] "V ml." is defined as the volume of solvent which is required to wet completely the column of adsorbent.

[9] N-Ethylacetanilide which is required as an intermediate in the preparation of 4-nitro-N-ethylaniline is much more easily prepared by the acetylation of N-ethylaniline by general procedures as described by Shriner and Fuson (9) than by ethylation of acetanilide (10).

nitration of centralite. Since a less ambiguous procedure was desired, the compound has been prepared by the reaction of N-ethyl-4-nitrocarbanilyl chloride with N-ethylaniline. An attempt to prepare 4-nitrocentralite by the reaction of N-ethylcarbanilyl chloride with 4-nitro-N-ethylaniline was unsuccessful.

The mixture of 6 g. of N-ethyl-4-nitrocarbanilyl chloride and 9 g. of distilled N-ethylaniline (Eastman White Label) in 25 ml. of purified xylene was refluxed for 2 hrs. About 100 ml. of ether and 100 ml. of water were added to the cooled reaction mixture, the phases were separated, and the organic phase was thoroughly washed with 3 *N* hydrochloric acid and with water. After evaporation of the solvent under reduced pressure the 4-nitrocentralite was in the form of a yellow oil which could not be induced to crystallize from benzene, ligroin, ether, acetone, or chloroform and consequently it was purified by recrystallization in the form of the ethanol complex as suggested by Lécorché and Jovinet (13). The entire material was dissolved in 35 ml. of absolute ethanol, 40 ml. of ligroin (30–60°) was added, and crystallization was induced by seeding and vigorous scratching of the vessel. Three similar recrystallizations yielded 4 g. of pale yellow, superficially dry needles which quickly lost alcohol in air and became sticky. When the complex was heated under vacuum at 70°, a honey-like oil of 4-nitrocentralite was obtained which could not be crystallized although Lécorché and Jovinet did obtain crystals which melted at 43°. The oil gave the following analysis.

Anal. Calc'd for $C_{17}H_{19}N_3O_3$: C, 65.18; H, 6.06; N, 13.42.

Found: C, 65.19; H, 6.22; N, 13.66.

2,4,4'-Trinitrocentralite. [*1,3-Diethyl-1-(4-nitrophenyl)-3-(2,4-dinitrophenyl)urea*]. It was necessary to prepare 2,4,4'-trinitrocentralite by nitration since experience with the preparation of 4-nitrocentralite gave little hope that the compound could be prepared unambiguously by reaction of nitro-N-ethylcarbanilyl chlorides with nitro-N-ethylanilines. A 5-g. portion of 4,4'-dinitrocentralite[6] was dissolved in 8.2 ml. of conc'd sulfuric acid. To this solution, 5.6 ml. of a mixture of 25 ml. of conc'd sulfuric acid, 3.4 ml. of water, and 5.0 ml. of 70% nitric acid was slowly added in the course of 30 min. so that the temperature did not rise above 45°. After the addition was complete, the red solution was warmed to 55°, allowed to stand for 10 min. (during which time gas began to be evolved), cooled in an ice-bath, and then poured onto 300 g. of crushed ice. The yellow solid which separated was filtered, washed well with water, and dried. After digestion of the crude material with 100 ml. of boiling 95% ethanol, an undissolved portion remained which proved to be 2,2',4,4'-tetranitrocentralite and when the solution was cooled to room temperature, the first crystals were mainly tetranitrocentralite. These crystals were filtered off and the solution was allowed to stand overnight during which time 2.8 g. of yellow platelets were deposited. Two recrystallizations of the platelets from 95% ethanol gave a product which melted at 147.5–148.5°. 4,4'-Dinitrocentralite melts at 147–148° (14) but a mixture of the product and 4,4'-dinitrocentralite melted at 125–135°. Five recrystallizations from absolute ethanol raised the melting point to a nearly constant value of 151.5–152.3°. The yield of purified material was 0.5 g. or 9% and from it the following analytical results were obtained.

Anal. Calc'd for $C_{17}H_{17}N_5O_7$: C, 50.60; H, 4.27; N, 17.36; M.W., 403.

Found: C, 50.87; H, 4.36; N, 17.44; M.W., 394 (in camphor).

In addition to the analysis, other experiments were made to show that the compound actually is trinitrocentralite. After hydrolysis with 65% sulfuric acid, the hydrolytic products were separated chromatographically and determined spectrophotometrically. By this means, 112% of the expected 4-nitro-N-ethylaniline and 85% of the expected 2,4-dinitro-N-ethylaniline were found. Further experimentation showed that the low yield of the dinitro compound is caused by some destruction during the hydrolysis and to a somewhat incomplete chromatographic separation from 4-nitro-N-ethylaniline which in turn causes an apparent yield of this compound which is greater than the theoretical. In addition, the chromatographic properties of 2,4,4'-trinitrocentralite on silicic acid-Celite were found to be different from those of 4,4'-dinitrocentralite and 2,2',4,4'-tetranitrocentralite. Hence, it is probable that the compound which melts at 151.5–152.3° is 2,4,4'-trinitrocentralite.

1-Ethyl-1-(4-nitrophenyl)-3-phenylurea. (4-Nitro-N-ethylcarbanilide). Since the reaction between phenyl isocyanate and 4-nitro-N-ethylaniline did not proceed in refluxing benzene or even when the compounds were heated together, 1-ethyl-1-(4-nitrophenyl)-3-phenylurea was prepared by refluxing the solution of 5 g. of N-ethyl-4-nitrocarbanilyl chloride and 4.1 g. of aniline (General Chemical Co.) in 25 ml. of chloroform for 3 hrs. A 50-ml. portion of chloroform was added to the cooled reaction mixture and the solution was washed twice with 100 ml. of 3 *N* hydrochloric acid and twice with 50 ml. of water. After the chloroform phase had been dried, it was heated to boiling, 75 ml. of ligroin (60–70°) was added, and the solution was cooled to 0°. The pale yellow needles which separated were recrystallized once from a mixture of 70 ml. of ethanol and 25 ml. of water and twice from a mixture of 60 ml. of chloroform and 50 ml. of ligroin. The final product had a constant melting point of 156.0–156.7°, weighed 2.5 g. (yield 40%), and gave the following analysis.

Anal. Calc'd for $C_{15}H_{15}N_3O_3$: C, 63.11; H, 5.33; N, 14.73.
Found: C, 63.00, 63.24; H, 5.41, 5.17; N, 14.83, 15.00.

1-Ethyl-3-(4-nitrophenyl)-1-phenylurea. (4-Nitro-N'-ethylcarbanilide). Since the reaction between 4-nitrophenyl isocyanate and N-ethylaniline took place readily, the compound was prepared by refluxing for 2 hrs. a solution of 4 g. of 4-nitrophenyl isocyanate (recrystallized Eastman Practical) and 3 g. of N-ethylaniline in 25 ml. of chloroform. The oil which remained after removal of the solvent under vacuum was crystallized by dissolving in a mixture of 75 ml. of methanol and 15 ml. of water and cooling. Recrystallization from a mixture of 75 ml. of isopropyl ether and 75 ml. of ethyl ether after treatment with Norit yielded 4.4 g. (64%) of large pale yellow prisms which melted at 79.5–80.5°.

Anal. Calc'd for $C_{15}H_{15}N_3O_3$: C, 63.11; H, 5.33; N, 14.73.
Found: C, 63.05; H, 5.31; N, 15.01.

SUMMARY

A number of new ethyl, phenyl, and nitrophenyl derivatives of urea and several intermediate compounds have been synthesized.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. VI. POLYSUBSTITUTED 1,2-BENZOCARBAZOLES, 1,2,5,6- AND 1,2,7,8-DIBENZOCARBAZOLES[1]

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In continuation of the investigation which is being carried out in this Institute under Professor A. Lacassagne upon the relationship between chemical constitution and carcinogenicity in the carbazole series (1), the synthesis of a number of polysubstituted 1,2-benzocarbazoles, 1,2,5,6- and 1,2,7,8-dibenzocarbazoles is now reported. The method of preparation used throughout this work was the one already outlined in previous paper: cyclization of arylhydrazones of properly substituted 1-tetralones to polycyclic 3,4-dihydrocarbazoles, and dehydrogenation of the latter by chloranil; the introduction of methyl groups in position 9 was easily achieved by treatment with methyl sulfate of the organomagnesium compound corresponding to the non-methylated carbazole involved.

The substituted 1-tetralones used in this work were: 6,7-dimethyl-(I), 5,7-dimethyl- (II), 7-methoxy-(III), 6-methyl-7-methoxy-(IV), 8-methyl-5-methoxy- (V), and 6,7-dimethoxy-1-tetralone (VI). They were prepared from the appropriate hydrocarbons or phenol ethers by the routine succinic anhydride method (2). Among them, the ketones (IV) and (V) were unknown; the preparation of those already described has in some instances been greatly improved, and the many new substances prepared in connection with this are reported in the experimental part. The arylhydrazines used were: phenylhydrazine, *p*-tolylhydrazine, *p*-xylylhydrazine, *p*-chloro- and *p*-bromo-phenylhydrazine, and α- and β-naphthylhydrazine.

Among the substituents dealt with, methyl groups are known in the parent series (*viz.* 1,2-benzanthracene, 1,2- and 3,4-benzacridine, etc.) to enhance generally the carcinogenicity of the basic molecules (3); the influence of methoxyl groups is less known, but in a few definite instances they have been found to enhance the action (4), as has chlorine (5), whereas the effect of bromine has been to decrease carcinogenicity.

The new carbazoles reported are listed in the chart given below; they are at present under biological examination by Professor Lacassagne and Dr. Zajdela.

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EXPERIMENTAL[2]

I. PREPARATION OF INTERMEDIATES

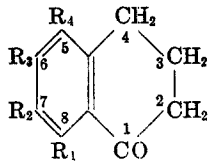
Friedel-Crafts reaction of succinic anhydride with hydrocarbons and phenol ethers. In all the cases considered here, the best yields of β-aroylpropionic acids (up to 95%) were ob-

[1] Paper V in this series: Buu-Hoï, Hoán, Khôi, and Xuong, *J. Org. Chem.*, **15**, 511 (1950).

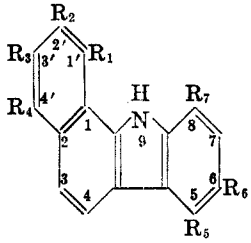
[2] All melting points are uncorrected and were taken with a Maquenne block.

tained when the reaction was performed in redistilled tetrachloroethane (b.p. 144–145°), the aluminum chloride (1.3 moles) being added in small portions to the ice-cooled and well-stirred solution of succinic anhydride (1 mole), the hydrocarbon or the phenol ether (1.5 to 2 moles), and the solvent. The mixture was kept at room temperature for 24 to 48 hours with occasional shaking, then poured into ice, the solvent and the hydrocarbon or the phenol

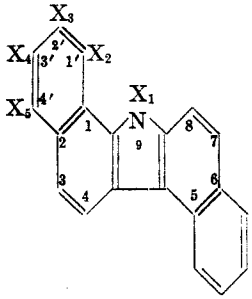
CHART I



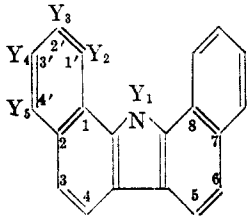
I: $R_1 = R_4 = H$, $R_2 = R_3 = CH_3$
II: $R_1 = R_3 = H$, $R_2 = R_4 = CH_3$
III: $R_1 = R_3 = R_4 = H$, $R_2 = OCH_3$
IV: $R_1 = R_4 = H$, $R_2 = OCH_3$, $R_3 = CH_3$
V: $R_1 = CH_3$, $R_2 = R_3 = H$, $R_4 = OCH_3$
VI: $R_4 = R = H$, $R_2 = R_3 = OCH_3$



VII: $R_1 = R_3 = R_4 = R_5 = R_7 = H$, $R_2 = OCH_3$, $R_6 = CH_3$
VIII: $R_1 = R_3 = R_4 = R_6 = H$, $R_2 = OCH_3$, $R_5 = R_7 = CH_3$
IX: $R_1 = R_3 = R_4 = R_5 = R_7 = H$, $R_2 = OCH_3$, $R_6 = Br$
X: $R_1 = R_3 = R_5 = R_6 = R_7 = H$, $R_2 = R_4 = CH_3$
XI: $R_1 = R_3 = R_6 = H$, $R_2 = R_4 = R_5 = R_7 = CH_3$
XII: $R_1 = R_3 = R_5 = R_7 = H$, $R_2 = R_4 = CH_3$, $R_6 = Cl$
XIII: $R_1 = R_4 = R_5 = R_6 = R_7 = H$, $R_2 = OCH_3$, $R_3 = CH_3$
XIV: $R_1 = R_4 = R_5 = R_7 = H$, $R_2 = OCH_3$, $R_3 = R_6 = CH_3$
XV: $R_1 = R_4 = R_5 = R_7 = H$, $R_2 = OCH_3$, $R_3 = CH_3$, $R_6 = Cl$
XVI: $R_1 = R_4 = R_5 = R_7 = H$, $R_2 = OCH_3$, $R_3 = CH_3$, $R_6 = Br$
XVII: $R_1 = CH_3$, $R_2 = R_3 = R_5 = R_6 = R_7 = H$, $R_4 = OCH_3$



XVIII: $X_1 = X_2 = X_4 = H$, $X_3 = X_5 = CH_3$
XIX: $X_1 = X_3 = X_5 = CH_3$, $X_2 = X_4 = H$
XX: $X_1 = X_2 = X_5 = H$, $X_3 = X_4 = CH_3$
XXI: $X_1 = X_3 = X_4 = CH_3$, $X_2 = X_5 = H$
XXII: $X_1 = X_3 = X_4 = H$, $X_2 = CH_3$, $X_5 = OCH_3$
XXIII: $X_1 = X_2 = X_5 = H$, $X_3 = OCH_3$, $X_4 = CH_3$
XXIV: $X_1 = X_2 = X_5 = H$, $X_3 = X_4 = OCH_3$



XXV: $Y_1 = Y_2 = Y_4 = H$, $Y_3 = Y_5 = CH_3$
XXVI: $Y_1 = Y_3 = Y_5 = CH_3$, $Y_2 = Y_4 = H$
XXVII: $Y_1 = Y_2 = Y_5 = H$, $Y_3 = Y_4 = CH_3$
XXVIII: $Y_1 = Y_3 = Y_4 = CH_3$, $Y_2 = Y_5 = H$
XXIX: $Y_1 = Y_3 = Y_4 = H$, $Y_2 = CH_3$, $Y_5 = OCH_3$
XXX: $Y_1 = Y_2 = Y_5 = H$, $Y_3 = OCH_3$, $Y_4 = CH_3$
XXXI: $Y_1 = Y_2 = Y_5 = H$, $Y_3 = Y_4 = OCH_3$

ether in excess removed by steam-distillation, and the crude acid purified in the usual way by means of its sodium salt.

Reduction of β-aroylpropionic acids to γ-arylbutyric acids. The Clemmensen-Martin procedure (5) was found satisfactory in all instances, except that the time of refluxing had to be at least 72 hours. The following acids were prepared:

γ-(3,4-Dimethylphenyl)butyric acid (7): b.p. 192–193°/12 mm.; yield: 90%.

γ-(2,4-Dimethylphenyl)butyric acid (7): b.p. 198°/16 mm.; yield: 87%.

γ-Anisylbutyric acid (6): b.p. 205–206°/13 mm.; yield: 90%.

γ-(3-Methyl-4-methoxyphenyl)butyric acid (8): b.p. 210°/14 mm.; yield: 87%.

γ-(5-Methyl-2-methoxyphenyl)butyric acid (8): b.p. 200°/12 mm.; yield: 85%.

γ-(3,4-Dimethoxyphenyl)butyric acid (9): b.p. 228–230°/14 mm.; yield: 70%.

γ-Arylbutyryl chlorides and amides. The foregoing acids were converted into their fluid, pale yellow, liquid *chlorides* by thionyl chloride in chloroform solution. The corresponding *amides* were prepared with cold aqueous ammonia. The following substances had not hitherto been isolated:

(a) *γ-(3,4-Dimethylphenyl)butyryl chloride*, b.p. 155–157°/15 mm.; the corresponding *γ-(3,4-dimethylphenyl)butyramide* formed glinting colorless prisms, m.p. 127° from benzene.

Anal. Calc'd for $C_{12}H_{17}NO$: N, 7.3. Found: N, 7.2.

(b) *γ-(2,4-Dimethylphenyl)butyryl chloride*, b.p. 153–155°/13 mm. *γ-(2,4-dimethylphenyl)-butyramide* formed silky colorless needles m.p. 129° from benzene (Found: N, 7.1).

(c) *γ-Anisylbutyryl chloride*, b.p. 165°/13 mm.; *γ-anisylbutyramide* formed lustrous silky needles from benzene, m.p. 119°.

Anal. Calc'd for $C_{11}H_{15}NO_2$: N, 7.2. Found: N, 7.0.

(d) *γ-(3-Methyl-4-methoxyphenyl)butyryl chloride*, b.p. 170–172°/14 mm.; *γ-(3-methyl-4-methoxyphenyl)butyramide* crystallized from benzene in lustrous colorless leaflets, m.p. 125°.

Anal. Calc'd for $C_{12}H_{17}NO_2$: N, 6.9. Found: N, 7.0.

(e) *γ-(5-Methyl-2-methoxyphenyl)butyryl chloride*, b.p. 168–170°/11 mm.; *γ-(5-Methyl-2-methoxyphenyl)butyramide* formed fine glinting needles from benzene, m.p. 103°. (Found: N, 6.8).

(f) *γ-(3,4-Dimethoxyphenyl)butyryl chloride* underwent spontaneous cyclization during vacuum-distillation.

Substituted 1-tetralones. These were best prepared by cyclization of the corresponding γ-arylbutyryl chlorides (1 mole) with aluminum chloride (1.2 moles), either in benzene or in tetrachloroethane (at −10° during addition of the catalyst and then 24 hours at room temperature).

(a) *6-Methyl-7-methoxy-1-tetralone* (IV). From 28 g. of γ-(3-methyl-4-methoxyphenyl)-butyryl chloride, were obtained 20 g. of a ketone, b.p. 165° at 10 mm., which crystallized from ligroin in colorless prisms, m.p. 46°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{12}H_{14}O_2$: C, 75.7; H, 7.3.
Found: C, 75.4; H, 7.5.

The corresponding *semicarbazone* crystallized from ethanol in fine colorless needles, m.p. 220°.

(b) *8-Methyl-5-methoxy-1-tetralone* (V). This ketone, b.p. 180–182° at 14 mm., crystallized from ligroin in colorless prisms, m.p. 108°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{12}H_{14}O$: C, 75.7; H, 7.3.
Found: C, 75.5; H, 7.5.

The *semicarbazone* crystallized from ethanol in fine colorless needles m.p. 200°.

II. 1,2-BENZOCARBAZOLES

The preparation of the arylhydrazones of the various 1-tetralones, their indolization by acetic acid saturated with hydrogen chloride, and the chloranil-treatment of the dihydrocarbazoles thus obtained, were performed in the way described previously (1); the yields at each step were also similar to those recorded.

6-Methyl-2'-methoxy-3,4-dihydro-1,2-benzocarbazole. Obtained from the *p*-tolylhydrazone of ketone III, it formed (from benzene) pale yellow prisms m.p. 159°, giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.3. Found: N, 5.2.

6-Methyl-2'-methoxy-1,2-benzocarbazole (VII). Crystallized from benzene in colorless needles m.p. 207°, also giving with sulfuric acid an orange-yellow coloration.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.4. Found: N, 5.2.

5,8-Dimethyl-2'-methoxy-3,4-dihydro-1,2-benzocarbazole. Obtained from the *p*-xylylhydrazone of ketone III, it formed pale yellow needles, m.p. 157° from benzene; yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{19}H_{19}NO$: N, 5.0. Found: N, 4.9.

5,8-Dimethyl-2'-methoxy-1,2-benzocarbazole (VIII). Formed yellowish microcrystals, m.p. 216° from benzene, giving with sulfuric acid the same coloration as the above.

Anal. Calc'd for $C_{19}H_{17}NO$: N, 5.0. Found: N, 4.9.

6-Bromo-2'-methoxy-3,4-dihydro-1,2-benzocarbazole. From the *p*-bromophenylhydrazone of ketone III; crystallized from benzene in colorless needles, m.p. 136°.

Anal. Calc'd for $C_{17}H_{14}BrNO$: N, 4.2. Found: N, 4.0.

6-Bromo-2'-methoxy-1,2-benzocarbazole (IX). Cream-yellow microcrystals (from benzene) m.p. 220°; orange coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{12}BrNO$: N, 4.2. Found: N, 4.0.

2',4'-Dimethyl-3,4-dihydro-1,2-benzocarbazole. From the phenylhydrazone of ketone II; formed (from benzene) colorless needles m.p. 186°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{17}N$: N, 5.6. Found: N, 5.4.

2',4'-Dimethyl-1,2-benzocarbazole (X). Glistening slightly gray-tinged needles (from benzene), m.p. 229°, giving with sulfuric acid a yellow coloration.

Anal. Calc'd for $C_{18}H_{15}N$: N, 5.7. Found: N, 5.6.

2',4',9-Trimethyl-1,2-benzocarbazole. Prepared from the magnesium compound of X with methyl sulfate (1b); formed (from methanol) glistening colorless needles m.p. 175°.

Anal. Calc'd for $C_{19}H_{17}N$: N, 5.4, Found: N, 5.1.

5,8,2',4'-Tetramethyl-3,4-dihydro-1,2-benzocarbazole. From the *p*-xylylhydrazone of ketone II; colorless needles (from benzene) m.p. 178°; yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{21}N$: N, 5.0. Found: N, 5.2.

5,8,2',4'-Tetramethyl-1,2-benzocarbazole (XI). Slightly gray-tinged needles (from benzene), m.p. 224°.

Anal. Calc'd for $C_{20}H_{19}N$: N, 5.0. Found: N, 4.9.

2',4'-Dimethyl-6-chloro-3,4-dihydro-1,2-benzocarbazole. From the *p*-chlorophenylhydrazone of ketone II; colorless needles (from ligroin) m.p. 205°; yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{16}ClN$: N, 4.9. Found: N, 4.8.

2',4'-Dimethyl-6-chloro-1,2-benzocarbazole (XII). Gray-tinged glinting needles (from benzene) m.p. 239–240°.

Anal. Calc'd for $C_{18}H_{14}ClN$: N, 4.9. Found: N, 4.6.

3'-Methyl-2'-methoxy-1,2-benzocarbazole (XIII). From the phenylhydrazone of ketone IV; formed (from benzene) colorless needles m.p. 222°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.4. Found: N, 5.1.

3',6-Dimethyl-2'-methoxy-3,4-dihydro-1,2-benzocarbazole. From the *p*-tolylhydrazone of ketone IV; formed (from benzene) fine yellowish prisms m.p. 192°.

Anal. Calc'd for $C_{19}H_{19}NO$: N, 5.0. Found: N, 5.1.

3',6-Dimethyl-2'-methoxy-1,2-benzocarbazole (XIV). Slightly gray-tinged microcrystals, m.p. 237°, giving a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{19}H_{17}NO$: N, 5.0. Found: N, 4.8.

3'-Methyl-2'-methoxy-6-chloro-3,4-dihydro-1,2-benzocarbazole. From the *p*-chlorophenylhydrazone of ketone IV; fine colorless needles (from benzene) m.p. 198°.

Anal. Calc'd for $C_{18}H_{16}ClNO$: N, 4.7. Found: N, 4.8.

3'-Methyl-2'-methoxy-6-chloro-1,2-benzocarbazole (XIV). Fine colorless needles (from benzene) m.p. 220°; orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{14}ClNO$: N, 4.7. Found: N, 4.6.

3'-Methyl-2'-methoxy-6-bromo-3,4-dihydro-1,2-benzocarbazole. From the *p*-bromophenylhydrazone of ketone IV; almost colorless microcrystals (from benzene) m.p. 209°.

Anal. Calc'd for $C_{18}H_{16}BrNO$: N, 4.1. Found: N, 4.0.

3'-Methyl-2'-methoxy-6-bromo-1,2-benzocarbazole (XV). Colorless lustrous leaflets (from benzene) m.p. 222°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{14}BrNO$: N, 4.1. Found: N, 4.0.

1'-Methyl-4'-methoxy-3,4-dihydro-1,2-benzocarbazole. From the phenylhydrazone of ketone V; formed (from benzene) colorless microcrystals, m.p. 189°.

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.3. Found: N, 5.3.

1'-Methyl-4'-methoxy-1,2-benzocarbazole (XVII). Colorless microcrystals (from benzene) m.p. 232°, giving an orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.4. Found: N, 5.3.

III. 1,2,5,6-DIBENZOCARBAZOLES

2',4'-Dimethyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. Obtained from the β-naphthylhydrazone of ketone II; formed (from benzene) colorless needles m.p. 240°, giving a deep red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.5.

2',4'-Dimethyl-1,2,5,6-dibenzocarbazole (XVIII). Crystallized from benzene in gray-tinged prisms, m.p. 273°, giving a deep brownish-red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.5.

2',4',9-Trimethyl-1,2,5,6-dibenzocarbazole (XIX). Obtained from the magnesium-compound of XVIII with methyl sulfate; crystallized from methanol in colorless needles, m.p. 210°.

Anal. Calc'd for $C_{23}H_{19}N$: N, 4.5. Found: N, 4.4.

2',3'-Dimethyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone I; formed (from benzene) colorless needles, m.p. 223°, giving with sulfuric acid a deep brown-red coloration.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.4.

2',3'-Dimethyl-1,2,5,6-dibenzocarbazole (XX). Formed (from xylene) fine colorless needles, m.p. 285°; same coloration with sulfuric acid as the above.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.5.

2',3',9-Trimethyl-1,2,5,6-dibenzocarbazole (XXI). Crystallized from methanol in colorless lustrous needles m.p. 226°.

Anal. Calc'd for $C_{23}H_{19}N$: N, 4.5. Found: N, 4.5.

1'-Methyl-4'-methoxy-3,4-dihydro-1,2-dibenzocarbazole. From the β-naphthylhydrazone of ketone V; formed (from benzene) colorless microcrystals, m.p. 231°, giving with sulfuric acid a deep red coloration.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.5. Found: N, 4.4.

1'-Methyl-4'-methoxy-1,2,5,6-dibenzocarbazole (XXII). Gray-tinged microcrystals (from benzene) m.p. 268°; deep red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{17}NO$: N, 4.5. Found: N, 4.3.

3'-Methyl-2'-methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone IV; colorless prisms (from benzene) m.p. 219°, giving with sulfuric acid a deep brown-red coloration.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.5. Found: N, 4.4.

3'-Methyl-2'-methoxy-1,2,5,6-dibenzocarbazole (XXIII). Formed (from xylene) a grayish microcrystalline powder, m.p. 283°.

Anal. Calc'd for $C_{22}H_{17}NO$: N, 4.5. Found: N, 4.3.

2',3'-Dimethoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone VI; crystallized from xylene in colorless needles, m.p. 275°.

Anal. Calc'd for $C_{22}H_{19}NO_2$ N, 4.2. Found: N, 4.2.

2',3'-Dimethoxy-1,2,5,6-dibenzocarbazole (XXIV). Crystallized from xylene in fine colorless needles m.p. 307°.

Anal. Calc'd for $C_{22}H_{17}NO_2$: N, 4.2. Found: N, 4.3.

IV. 1,2,7,8-DIBENZOCARBAZOLES

2',4'-Dimethyl-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone II; formed (from benzene) colorless microcrystals, m.p. 107–108°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.8.

2',4'-Dimethyl-1,2,7,8-dibenzocarbazole (XXV). Crystallized from benzene in colorless needles, m.p. 182°.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.6.

2',4',9-Trimethyl-1,2,7,8-dibenzocarbazole (XXVI). From the magnesium-compound of XXV with methyl sulfate; colorless needles (from methanol) m.p. 206°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{23}H_{19}N$: N, 4.5. Found: N, 4.2.

2',3'-Dimethyl-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone I; iridescent colorless leaflets (from ligroin) m.p. 193°, giving a deep brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.6.

2',3'-Dimethyl-1,2,7,8-dibenzocarbazole (XXVII). Crystallized from benzene in colorless needles, m.p. 247°.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.6.

2',3',9-Trimethyl-1,2,7,8-dibenzocarbazole (XXVIII). Formed (from methanol) colorless microcrystals, m.p. 184°, giving a deep brown-red coloration with sulfuric acid.

Anal. Calc'd for $C_{23}H_{19}N$: N, 4.5. Found: N, 4.4.

1'-Methyl-4'-methoxy-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone V; colorless microcrystals (from benzene), m.p. 178°, giving a deep red coloration with sulfuric acid.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.5. Found: N, 4.3.

1'-Methyl-4'-methoxy-1,2,7,8-dibenzocarbazole (XXIX). Formed (from benzene) fine gray-tinged needles, m.p. 253°.

Anal. Calc'd for $C_{22}H_{17}NO$: N, 4.5. Found: N, 4.6.

3'-Methyl-2'-methoxy-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone IV; fine colorless needles (from benzene), m.p. 189°, giving with sulfuric acid a deep brown-red coloration.

Anal. Calc'd for $C_{22}H_{19}NO$: N, 4.5. Found: N, 4.4.

3'-Methyl-2'-methoxy-1,2,7,8-dibenzocarbazole (XXX). Formed (from xylene) fine colorless needles, m.p. 225°; the violet-red *picrate* had m.p. 200°.

Anal. Calc'd for $C_{22}H_{17}NO$: N, 4.5. Found: N, 4.3.

2',3'-Dimethoxy-1,2,7,8-dibenzocarbazole (XXXI). Formed (from benzene) colorless needles, m.p. 274°, giving with sulfuric acid a deep brown-red coloration. The dark violet *picrate* had m.p. 252°.

Anal. Calc'd for $C_{22}H_{17}NO$: N, 4.2. Found: N, 3.9.

SUMMARY

A large number of new polysubstituted 1,2-benzocarbazoles, and 1,2,5,6- and 1,2,7,8-dibenzocarbazoles have been synthesized by known methods for biological studies.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. VII. POLYCYCLIC CARBAZOLES BEARING ETHYL GROUPS, AND THIOPHENE ISOSTERS THEREOF[1]

NG. PH. BUU-HOÏ NG. HOÁN, AND NG. H. KHOI

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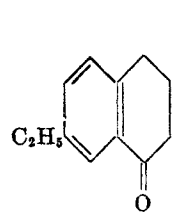
There is ample evidence that the introduction of ethyl groups into the molecule of polycyclic hydrocarbons may result in potent carcinogenic substances. Thus, according to Badger and coworkers (1), 5-ethyl-1,2-benzanthracene and 2-ethyl-3,4-benzphenanthrene readily evoke skin tumors, and Shear and Leiter (2) found 10-ethyl-1,2-benzanthracene to be a potent agent in the production of sarcomas. Similarly, 3-ethylcholanthrene (3) has been found to be fairly carcinogenic, though less than the lower homolog.

In the field of experimental inhibition of tumor-growth by chemical compounds, the activity of some ethyl derivatives has also been recorded (4), and it is of interest to note that in one instance (2-ethyl-3,4-benzphenanthrene), the ethyl compound was found considerably more active than the methyl homolog.

These considerations led us to the preparation, for biological experimentation, of various polycyclic carbazoles bearing ethyl radicals; some thiophene compounds isosteric with the latter were also included in this study.

The modified Fischer-Borsche synthesis of carbazoles as described in previous



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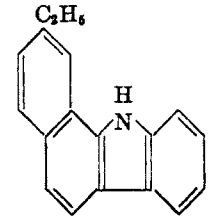

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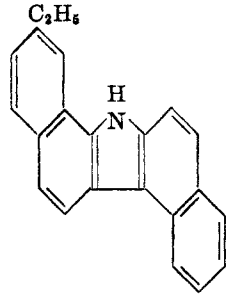

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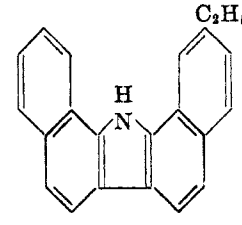
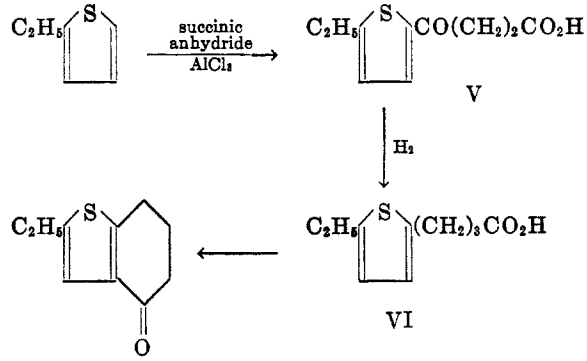


IV

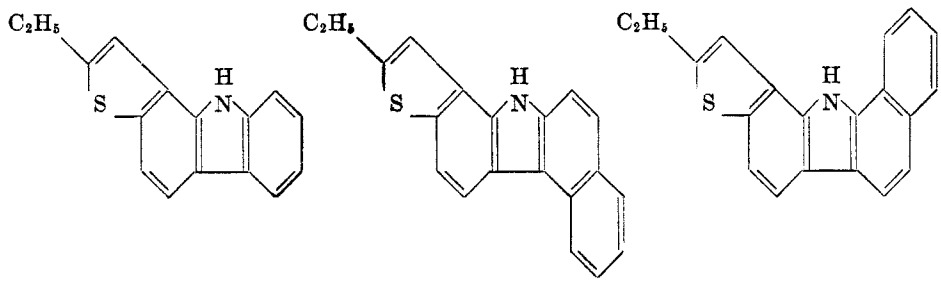
[1] Paper VI in this series: Buu-Hoï, Cagniant, Hoán, and Khôi, *J. Org. Chem.*, preceding article.

papers of this series, could readily be applied to the known 7-ethyl-1-tetralone (I). Thus were obtained, *via* the corresponding 3,4-dihydro compounds: 2′-ethyl-1,2-benzocarbazole (II), 2′-ethyl-1,2,5,6-dibenzocarbazole (III), and 2′-ethyl-1,2,7,8-dibenzocarbazole (IV).

In the thiophene series, 2-ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene (VII), a previously unknown compound, was prepared as follows: succinoylation of 2-ethylthiophene (readily prepared from 2-acetothienone hydrazone by means of the Wolff-Kishner method), reduction of β-(2-ethyl-5-thenoyl)propionic acid (V) to γ-(2-ethyl-5-thienyl)butyric acid (VI) through the same reaction, and cyclization of γ-(2-ethyl-5-thienyl)butyryl chloride by means of stannic chloride.



2-Ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene readily underwent carbazole syntheses, and thus were obtained, *via* the corresponding dihydro compounds: 5′-ethyl-3′,2′:1,2-thiophenocarbazole (VIII), 5′-ethyl-3′,2′:1,2-thiopheno-5,6-benzocarbazole (IX), and 5′-ethyl-3′,2′:1,2-thiopheno-7,8-benzocarbazole (X).



VIII IX X

The new compounds described here are under biological examination by Professor A. Lacassagne.

Acknowledgement. This work was carried out with the financial aid of the U. S. Public Health Service (Federal Security Agency); the authors express their thanks to the authorities concerned.

EXPERIMENTAL[2]

2-Acetothienone. Several methods for the preparation of this compound have recently been proposed (5); we found the following modification of the Biedermann procedure (6) especially convenient: into an ice-cooled solution of 170 g. of thiophene (2 moles) and 173 g. of acetyl chloride (2.1 moles) in one liter of dry carbon disulphide, 300 g. of finely powdered aluminum chloride was stirred in small portions. Stirring was continued for one hour at room temperature, and the mixture was poured onto ice; the organic layer was washed with small portions of a dilute aqueous solution of sodium hydroxide and then with a little water, dried over sodium sulfate, the solvent distilled off, and the residue fractionated. Yield: 80–85%.

2-Ethylthiophene. This compound has been prepared by means of the Wurtz-Fittig reaction (7), by the Clemmensen reduction of 2-acetothienone (8), and recently by the Wolff-Kishner reduction of 2-acetothienone hydrazone in ethylene glycol medium (9). We found the following adaptation of Huang-Minlon's general technique (10) to be very convenient, and it could be extended to various thiophene ketones: a mixture of 2-acetothienone (50 g.) 50% hydrazine hydrate (50 g.), potassium hydroxide (35 g.), and diethylene glycol (200 ml.) was slowly heated up to 185–190° in a flask fitted with a fractionating-column. The distillate was collected, washed with dilute hydrochloric acid, then with water, dried over calcium chloride, and fractionated; 38 g. (80%) of 2-ethylthiophene were obtained, b.p. 134–135°.

β-(2-Ethyl-5-thenoyl)propionic acid (V). Into an ice-cooled mixture of 2-ethylthiophene (56 g.), succinic anhydride (56 g.), and nitrobenzene (350 ml.), finely powdered aluminum chloride (150 g.) was stirred in small portions. After 16 hours at room temperature, the mixture was poured onto ice, and the nitrobenzene was removed by steam-distillation. After cooling, the solid product was purified by dissolution in aqueous sodium carbonate and reprecipitation with dilute hydrochloric acid (yield, 97 g.). After crystallization from toluene, fine colorless needles m.p. 96° were obtained.

Anal. Calc'd for $C_{10}H_{12}O_3S$: C, 56.6; H, 5.6.
Found: C, 56.3; H, 5.8.

γ-(2-Ethyl-5-thienyl)butyric acid (VI). A mixture of the foregoing acid (90 g.), 75% hydrazine hydrate (90 g.), potassium hydroxide (80 g.), and diethylene glycol (300 ml.) was heated, and water removed until the temperature reached 190–195°; the greater part of the solvent then was removed in a vacuum. The residue was dissolved in water and acidified with dilute hydrochloric acid. The reaction-product was extracted with ether and the ether solution dried over calcium chloride. After removal of the solvent, vacuum-distillation of the residue yielded 46 g. of the acid (VI) in the form of a fluid, pale green-yellow oil, b.p. 190–192°/18 mm.

Anal. Calc'd for $C_{10}H_{14}O_2S$: C, 65.5; H, 7.7.
Found: C, 65.5; H, 7.9.

γ-(2-Ethyl-5-thienyl)butyryl chloride. A mixture of the foregoing acid (46 g.), freshly redistilled thionyl chloride (33 g.), and anhydrous ether (100 ml.) was gently refluxed for four hours with 12 drops of pyridine. The solvent and the excess of thionyl chloride were removed in a vacuum, and the residue fractionated. Yield, 50 g. of a pale yellow, fluid oil, b.p. 167–174°/18 mm.

Anal. Calc'd for $C_{10}H_{13}ClOS$: C, 55.4; H, 6.0.
Found: C, 55.2; H, 6.3.

2-Ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene (VII). To an ice-cooled solution of the foregoing chloride (49 g.) in carbon disulfide (150 ml.), was added dropwise with stirring a solution of stannic chloride (80 g.) in carbon disulfide (300 ml.). After the addition, the mixture was gently refluxed for two hours, then poured onto ice and some ether added. The organic layer was washed with water, dried over sodium sulfate, the solvents removed and the residue vacuum-fractionated. Yield, 98% of a pale yellow liquid *ketone*, b.p. 161°/16 mm.

[2] All melting points are uncorrected and were taken with a Maquenne block.

Anal. Calc'd for $C_{16}H_{12}OS$: C, 66.6; H, 6.6.
Found: C, 66.5; H, 6.8.

The corresponding *semicarbazone* formed (from methanol) fine colorless shiny needles m.p. 219°.

7-Ethyl-1-tetralone (I). This compound was obtained according to Bachmann and Edgerton (11), except that β-(4-ethylbenzoyl)propionic acid (prepared in benzene) was reduced as follows by means of the Wolff-Kishner—Huang-Minlon method: a mixture of that crude acid (70 g.), 75% hydrazine hydrate (70 g.), potassium hydroxide (80 g.), and diethylene glycol (200 ml.) was heated to 190–195° with removal of water, most of the solvent vacuum-distilled, and the residue treated in the usual way. Yield, 50 g. of *γ-(4-ethylphenyl)butyric acid*, b.p. 200°/20 mm., melting at 68° after crystallization from ligroin.

2'-Ethyl-3,4-dihydro-1,2-benzocarbazole. Obtained by indolization of the phenylhydrazone of ketone I in the previously described way (12); formed (from petroleum ether) colorless microcrystalline prisms, m.p. 110°.

Anal. Calc'd for $C_{18}H_{17}N$: N, 5.6. Found: N, 5.9.

2'-Ethyl-1,2-benzocarbazole (II). Obtained by refluxing a xylene solution of the *dihydro* compound (1.5 g.) with chloranil (1.6 g.) for three hours, removing the tetrachlorohydroquinone formed with aqueous sodium hydroxide, and crystallizing the residue from a mixture of benzene and ligroin. Yield, 1.2 g. of gray-tinged shiny prisms, m.p. 142°; sulfuric acid produced a greenish coloration, rapidly turning blue.

Anal. Calc'd for $C_{18}H_{15}N$: N, 5.7. Found: N, 5.5.

2'-Ethyl-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone I; formed (from a mixture of benzene and ligroin) gray-tinged microscopic needles, m.p. 173°. Orange-red coloration with sulfuric acid, turning green.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.6.

2'-Ethyl-1,2,5,6-dibenzocarbazole (III). Crystallized from benzene in gray-tinged microscopic needles, m.p. 190°, giving with sulfuric acid a blood red coloration.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.5.

2'-Ethyl-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone I; formed (from ligroin) colorless microcrystals, m.p. 109°, giving with sulfuric acid an orange-red coloration, turning green.

Anal. Calc'd for $C_{22}H_{19}N$: N, 4.7. Found: N, 4.8.

2'-Ethyl-1,2,7,8-dibenzocarbazole (IV). Formed (from ligroin) colorless microcrystals, m.p. 121°, giving with sulfuric acid a blood red coloration.

Anal. Calc'd for $C_{22}H_{17}N$: N, 4.7. Found: N, 4.6.

5'-Ethyl-3,4-dihydro-3',2':1,2-thiophenocarbazole. Obtained by smooth indolization of the phenylhydrazone of ketone VII, formed (from benzene) cream microscopic prisms, m.p. 125°.

Anal. Calc'd for $C_{16}H_{15}NS$: N, 5.5. Found: N, 5.3.

5'-Ethyl-3',2':1,2-thiophenocarbazole (VIII). Formed (from benzene) gray-tinged microcrystals, m.p. 187°; the *picrate* is violet.

Anal. Calc'd for $C_{16}H_{13}NS$: N, 5.6. Found: N, 5.4.

5'-Ethyl-3,4-dihydro-3',2':1,2-thiopheno-5,6-benzocarbazole. From the β-naphthylhydrazone of ketone VII; crystallized from benzene in shiny colorless needles, m.p. 175°, giving with sulfuric acid a red coloration.

Anal. Calc'd for $C_{20}H_{17}NS$: N, 4.8. Found: N, 4.9.

5'-Ethyl-3',2':1,2-thiopheno-5,6-benzocarbazole (IX). Formed (from benzene) shiny colorless needles, m.p. 209°, giving with sulfuric acid a brown-red coloration.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.8. Found: N, 4.6.

5'-Ethyl-3,4-dihydro-3',2':1,2-thiopheno-7,8-benzocarbazole. From the α-naphthylhydrazone of ketone VII; formed (from benzene) cream microneedles, m.p. 140°.

Anal. Calc'd for $C_{20}H_{17}NS$: N, 4.8. Found: N, 4.6.

5'-Ethyl-3',2':1,2-thiopheno-7,8-benzocarbazole (X). Formed (from benzene) gray-tinged needles, m.p. 170°; red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{15}NS$: N, 4.8. Found: N, 4.6.

SUMMARY

1. The synthesis of 2-ethyl-4-keto-4,5,6,7-tetrahydrothianaphthene is reported.

2. From that ketone and from its isolog, 7-ethyl-1-tetralone, several new polycyclic carbazoles were prepared.

PARIS Ve, FRANCE

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, RADIUM INSTITUTE, UNIVERSITY OF PARIS]

POTENTIAL NITROGEN-HETEROCYCLE CARCINOGENS. VIII. POLYCYCLIC CARBAZOLES WITH PHENOLIC GROUPS[1]

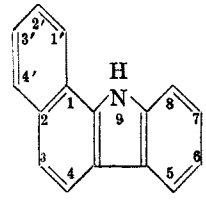
NG. PH. BUU-HOÏ, NG. HOÁN, NG. H. KHÔI, AND NG. D. XUONG

Received December 28, 1949

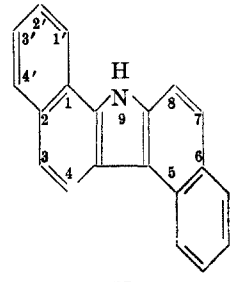
Hydroxylation has been found to be a biochemical process involved in the metabolism of many carcinogenic compounds by the animal body. For instance, 4′-hydroxy-1,2-benzanthracene (1) and 4′-hydroxy-9,10-dimethyl-1,2-benzanthracene (2) are formed from the corresponding hydrocarbons, and 1,2,5,6-dibenzanthracene is oxidized to the 4′,8′-dihydroxy derivative (3). Even carcinogenic nitrogen-compounds seem to be metabolized along a similar path, 2-acetaminofluorene being thus converted into 7-hydroxy-2-acetaminofluorene (4).

In view of the carcinogenic activity dispalyed by some polycyclic carbazoles (5), and in anticipation of metabolism studies upon these, the synthesis of some hydroxy derivatives of 1,2-benzocarbazole (I), 1,2,5,6- (II) and 1,2,7,8-dibenzocarbazole (III) was deemed worthy of consideration.

The literature concerning compounds of this series is scanty: 4′-hydroxy-1,2-benzocarbazole (6) and 1′-hydroxy-3,4-benzocarbazole (7) are mentioned in patents in connection with their potential use in the preparation of azo and indigoid dyes. Both were prepared by alkaline fusion of the corresponding sulfonic acids, but their properties were not recorded, nor were those of some hydroxy- and aminohydroxy-benzocarbazole sulfonic acids also mentioned in patents (8). We have found that demethylation of benzo- and dibenzo-carbazoles bearing methoxyl groups is readily brought about by a short heating with pyridine hydrochloride. This offers a convenient route for the preparation of substances bearing hydroxyl groups in known positions. The methoxy compounds we have thus treated were previously known, with the exception of those derived from 6-methoxy-1-tetralone (IV).

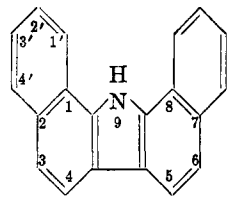


I



II

[1] Paper VII in this series: Buu-Hoï, and Hoán, and Khôi: *J. Org. Chem.*, preceding article.



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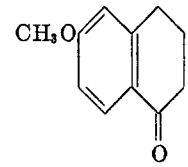

IV

The often described routine carbazole synthesis (9), applied to the latter ketone and the appropriate arylhydrazines, gave 3′-methoxy-1,2-benzocarbazole, 3′-methoxy-6-methyl-1,2-benzocarbazole, 3′-methoxy-1,2,5,6-dibenzocarbazole, and 3′-methoxy-1,2,7,8-dibenzocarbazole.

All of the hydroxy compounds prepared are colorless alkali-soluble substances, now under biological investigation by Professor A. Lacassagne; in view of the high bactericidal activity of 3,4,5,6-dibenzocarbazole against staphylococci (10), they are also being tested for potential antibiotic properties.

Acknowledgment. This work was financially aided by the U. S. Public Health Service (Federal Security Agency); the authors wish to thank the authorities concerned.

EXPERIMENTAL[2]

6-Methoxy-1-tetralone. This ketone was synthesized from tetralin according to the literature (11). It melted at 79°, and its *semicarbazone* formed (from ethanol) silky lustrous needles, m.p. 244°. Papa (12) gave m.p. 75–77° for the ketone, and m.p. 235.5–236.5° for the semicarbazone.

3′-Methoxy-3,4-dihydro-1,2-benzocarbazole. Prepared in the usual way by indolization of the phenylhydrazone of ketone IV; crystallized from benzene in colorless needles, m.p. 169°; light yellow coloration with sulfuric acid, and violet *picrate.*

Anal. Calc'd for $C_{17}H_{15}NO$: N, 5.6. Found: N, 5.5.

3′-Methoxy-1,2-benzocarbazole. Formed from benzene in colorless needles m.p. 245°; deep yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.4.

3′-Hydroxy-1,2-benzocarbazole. A solution of 0.5 g. of the foregoing compound in 3 g. of redistilled pyridine hydrochloride was gently boiled for five minutes; water was added after cooling, and the precipitate thus obtained filtered off and recrystallized from xylene. Yield, 0.35 g. of colorless prisms m.p. 265°, slightly soluble in water; deep yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{11}NO$: N, 6.0. Found: N, 5.9.

3′-Methoxy-6-methyl-3,4-dihydro-1,2-benzocarbazole. From the *p*-tolylhydrazone of ketone IV; formed from benzene colorless needles, m.p. 191°; yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{17}NO$: N, 5.3. Found: N, 5.2.

3′-Methoxy-6-methyl-1,2-benzocarbazole. Crystallized from xylene in shiny colorless prisms, m.p. 285°; orange-yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.3. Found: N, 5.2.

3′-Hydroxy-6-methyl-1,2-benzocarbazole. Shiny colorless leaflets, m.p. 295°; this compound and the eight following ones gave an orange-yellow coloration with sulfuric acid.

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[2] All melting points are uncorrected and were taken with a Maquenne block.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.3.

2'-Hydroxy-6-methyl-1,2-benzocarbazole. Gray-tinged shiny leaflets (from xylene), m.p. 275°.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.4.

2'-Hydroxy-3'-methyl-1,2-benzocarbazole. Shiny colorless leaflets (from xylene), m.p. 297°.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.6.

1'-Methyl-4'-hydroxy-1,2-benzocarbazole. Slightly yellowish needles (from toluene), m.p. 224–225°.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.3.

2'-Hydroxy-5,8-dimethyl-1,2-benzocarbazole. Slightly gray-tinged needles (from water), m.p. 227–228°.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.3. Found: N, 5.2.

2'-Hydroxy-3,6-dimethyl-1,2-benzocarbazole. Shiny colorless leaflets (from xylene), m.p. 330°.

Anal. Calc'd for $C_{18}H_{15}NO$: N, 5.3. Found: N, 5.0.

2'-Methoxy-3,4-dihydro-1,2-benzocarbazole. Obtained from the phenylhydrazone of 7-methoxy-1-tetralone; formed (from benzene) in colorless needles, m.p. 131°.

Anal. Calc'd for $C_{17}H_{15}NO$: N, 5.6. Found: N, 5.4.

2'-Methoxy-1,2-benzocarbazole. Crystallized from benzene in colorless microscopic needles, m.p. 190°.

Anal. Calc'd for $C_{17}H_{13}NO$: N, 5.6. Found: N, 5.5.

2'-Hydroxy-1,2-benzocarbazole. Formed (from water) colorless leaflets, m.p. 246°; this compound and the two preceding ones gave a yellow coloration with sulfuric acid.

Anal. Calc'd for $C_{16}H_{11}NO$: N, 6.0. Found: N, 5.8.

3'-Methoxy-3,4-dihydro-1,2,5,6-dibenzocarbazole. From the β-naphthylhydrazone of ketone IV; colorless needles from benzene, m.p. 190–191°, giving with sulfuric acid an orange coloration.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.5.

3'-Methoxy-1,2,5,6-dibenzocarbazole. Formed from xylene graytinged microcrystals, m.p. 293°; orange-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.6.

3'-Hydroxy-1,2,5,6-dibenzocarbazole. Microscopic colorless needles from xylene, m.p. 303°; same coloration with sulfuric acid as the above.

Anal. Calc'd for $C_{20}H_{13}NO$: N, 4.9. Found: N, 4.6.

2'-Hydroxy-3'-methyl-1,2,5,6-dibenzocarbazole. Shiny colorless leaflets from xylene, m.p. 309–310°; brownish-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.5.

1'-Methyl-4'-hydroxy-1,2,5,6-dibenzocarbazole. Colorless microscopic needles from xylene, m.p. 265°; violet-red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.4.

3'-Methoxy-3,4-dihydro-1,2,7,8-dibenzocarbazole. From the α-naphthylhydrazone of ketone IV; colorless needles from benzene, m.p. 169°, giving an orange coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{17}NO$: N, 4.7. Found: N, 4.6.

3'-Methoxy-1,2,7,8-dibenzocarbazole. Formed from benzene colorless microscopic needles, m.p. 235°; red coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.5.

3'-Hydroxy-1,2,7,8-dibenzocarbazole. Colorless needles from xylene, m.p. 255°; deep red coloration with sulfuric acid.

Anal. Calc'd for $C_{20}H_{13}NO$: N, 4.9. Found: N, 4.8.

1'-Methyl-4'-hydroxy-1,2,7,8-dibenzocarbazole. Colorless needles from xylene, m.p. 311°; brown coloration with sulfuric acid.

Anal. Calc'd for $C_{21}H_{15}NO$: N, 4.7. Found: N, 4.8.

SUMMARY

1. Several carbazole syntheses from 6-methoxy-1-tetralone have been performed.

2. A series of polycyclic carbazoles bearing phenolic groups has been prepared by demethylation of the corresponding methoxy compounds with pyridine hydrochloride.

PARIS V^e^ FRANCE

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[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, UNIVERSITY OF CHICAGO]

REACTIONS OF ATOMS AND FREE RADICALS IN SOLUTION. XXII. THE ADDITION OF POLYHALOMETHANES TO ALKYNES

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Under visible illumination, or in the presence of thermally-decomposing acyl peroxides, bromotrichloromethane reacts additively with 1-octyne to form the one-to-one adduct exclusively. With phenylacetylene or 2-octyne, however, bromotrichloromethane forms, not only the one-to-one adducts, but products that result from the condensation of one molecule of the halide with two molecules of the respective alkynes. Under the experimental conditions imposed in this study these one-to-two adducts comprise, respectively, 20 and 16 per cent of the total products. The reaction scheme proposed to account for the observed products may be outlined as follows:

(Ia) $BrCCl_3 + h\nu \rightarrow Br\cdot + Cl_3C\cdot$ *or*

(Ib) $BrCCl_3 + R\cdot$ (from acyl peroxide) $\rightarrow RBr + Cl_3C\cdot$

(II) $R'C{\equiv}CH + Cl_3C\cdot \rightarrow Cl_3CCH{=}R'C\cdot$

(III) $Cl_3CCH{=}R'C\cdot + BrCCl_3 \rightarrow Cl_3CCH{=}CR'Br + Cl_3C\cdot$

(IV) $Cl_3CCH{=}R'C\cdot + HC{\equiv}CR' \rightarrow Cl_3CCH{=}R'CCH{=}R'C\cdot$

(V) $Cl_3CCH{=}R'CCH{=}R'C\cdot + BrCCl_3 \rightarrow Cl_3CCH{=}R'CCH{=}CR'Br + Cl_3C\cdot$

When carbon tetrachloride is substituted for bromotrichloromethane in analogous reactions of 1-octyne and 2-nonyne the yields of one-to-one adducts are extremely small.[1] The reaction products consist chiefly of high-boiling materials that decompose even under very low-pressure distillation. From the apparent molecular weights and the chlorine contents of admittedly impure fractions it is possible to surmise that these products consist of: (a) some material of the composition $R'CCl{=}CHCl$, or perhaps more probably, $R'CH{=}C{=}CCl_2$,[2] (b) a small amount of the one-to-one adduct, and (c) a mixture of higher condensates containing many molecules of alkyne and many chlorine atoms.

Under similar conditions phenylacetylene yields a short-chain "polymer" containing chlorine.

Whereas the alkenes (except styrene) corresponding to the alkynes used in this study produce good yields of one-to-one carbon tetrachloride adducts (1), it is evident that with respect to the over-all addition reaction the alkynes constitute the less reactive class. It is of interest to determine whether the relative unreactivity of the alkynes must be referred to the first step of the addition

[1] It should be noted that in photochemical reactions involving carbon tetrachloride ultraviolet irradiation is necessary.

[2] The product here suggested might result from the loss of a chlorine atom (perhaps through disproportionation) from the product of the first additional step [$Cl_3CCH{=}(n\text{-}C_6H_{13})C\cdot$], accompanied by a hydrogen-atom shift. Evidence for such processes has been obtained in other work in this laboratory (Kharasch and Büchi, unpublished work).

(corresponding to equation II), to the second step (corresponding to equation III), to or both.

Because both bromotrichloromethane and carbon tetrachloride generate the same primary free radical ($Cl_3C\cdot$), and because the alkenes concerned in this study produce good yields of one-to-one adducts with both bromotrichloromethane (2) and carbon tetrachloride, whereas alkynes produce comparable yields of one-to-one adducts only with the former, it may be concluded that in the second step of the carbon tetrachloride addition the alkyne intermediate is less reactive than the corresponding alkene intermediate. Specifically, the free radical derived by the addition of a trichloromethyl radical to an alkyne is less reactive with respect to its ability to attack carbon tetrachloride (equation IIIa) than is the free radical derived by the addition of a trichloromethyl radical to the corresponding alkene (equation IIIb).

(IIIa) $$Cl_3CCH{=}R'C\cdot + CCl_4 \rightarrow Cl_3CCH{=}CR'Cl + Cl_3C\cdot$$

(IIIb) $$Cl_3CCH_2R'CH\cdot + CCl_4 \rightarrow Cl_3CCH_2R'CHCl + Cl_3C\cdot$$

In order to establish a basis for comparison of reactivities in the first step of the carbon tetrachloride addition (corresponding to equation II), carbon tetrachloride, 1-octene, 1-octyne, and acetyl peroxide, in the molecular proportions 110:20:5:1, were caused to react in the usual way. In such experiments the yield of one-to-one halide-1-octene adduct (64–69 per cent) is only a little lower than in similar experiments in which 1-octyne is omitted (72–74 per cent). It may therefore be inferred that the addition of a trichloromethyl radical to 1-octene takes place more readily than does the similar addition to the corresponding alkyne, 1-octyne.

In consideration of the range of reactivities (with respect to the reaction represented by equation II) displayed by variously substituted ethenes (3), there is a reasonable supposition that variously substituted ethynes might also vary widely in reactivity. It by no means follows from the observations already recorded that *any* alkyne is less reactive than *any* alkene.

Evidence that this is not the case is supplied by an experiment similar to the one just described in which phenylacetylene is substituted for 1-octyne. It was found that phenylacetylene completely inhibits the formation of the halide-1-octene adduct, although the one-to-one halide-phenylacetylene adduct is not formed either. This observation is interpreted as indicating that phenylacetylene undergoes the first step of the addition reaction (corresponding to equation II) much more readily than does 1-octene. Phenylacetylene therefore captures virtually all the trichloromethyl radicals liberated, thus blocking 1-octene out of the reaction. The intermediate free radical formed by the addition of a trichloromethyl radical to a phenylacetylene molecule is, however, incapable of undergoing the second step of the addition reaction (equation IIIa) at a rate competitive with that of the condensation reaction ("polymerization," equation IV). The net effect is the preponderant formation of chlorine-containing phenylacetylene "polymers."

To facilitate further comparisons of relative reactivities of alkynes and alkenes

with respect to the first step of the addition reaction bromotrichloromethane was chosen as the addendum for the reason that it readily undergoes the second step of the addition reaction (corresponding to equation III) with all the intermediates formed in the first step.

When a competitive reaction is conducted in this way with styrene and phenylacetylene, the one-to-one adduct of the former was formed to the total exclusion of that of the latter. It would thus seem a safe conclusion that, although some alkynes react with trichloromethyl radicals more readily than do some alkenes, any given alkene is more reactive in this respect than is the *corresponding* alkyne.

Several other competitions which do not bear so directly on this point, but which are, nevertheless, of incidental interest were studied. 1-Octyne and allyl chloride were found to react with bromotrichloromethane at comparable rates. Phenylacetylene reacts much more rapidly than either allyl or methallyl chloride.

Identification of one-to-one addition products. The expected one-to-one addition products were tentatively identified by their apparent molecular weights (cryoscopic, benzene) and halogen contents (silver equivalents).[3] Confirmations of tentative identifications were obtained by ozonolytic degradations:

$$\text{(a)}\quad n\text{-}C_6H_{13}CBr{=}CHCCl_3 + O_3 \xrightarrow{H_2O} n\text{-}C_6H_{13}CO_2H + Cl_3CCHO$$

$$\text{(b)}\quad C_6H_5CBr{=}CHCCl_3 + O_3 \xrightarrow{H_2O} C_6H_5CO_2H + Cl_3CCHO$$

Details of the procedures are described in the experimental part.

EXPERIMENTAL

Apparatus and procedure. The apparatus and the general method of operation employed have been described previously (3). Any significant deviations from the general method are noted at the appropriate points hereafter.

Photochemical reaction of 1-octyne with bromotrichloromethane. A solution of 31.9 g. (0.29 mole) of 1-octyne (n_D^{20} 1.4182) in 360.0 g. (1.79 mole) of bromotrichloromethane (n_D^{20} 1.5062), maintained at 65° by an oil-bath, was internally illuminated with a neon-type glass coil containing mercury vapor for a period of 4½ hours. Residual starting materials were removed from the reaction mixture under reduced pressure, and the crude product (28.0 g.) was subjected to "molecular" distillation. The following fractions were collected: fraction 1 (8.4 g.), n_D^{20} 1.5093, mol. wt., 281, Ag equiv. 82.7; fraction 2 (8.4 g.), n_D^{20} 1.5117, mol. wt., 288, Ag equiv. 89.0; fraction 3 (9.3 g.), n_D^{20} 1.5136, mol. wt., 309, Ag equiv. 79.4; fraction 4 (0.8 g.), mol. wt., 362, Ag equiv. 83.3.

Fraction 3 consisted essentially of the one-to-one adduct, 1,1,1-trichloro-3-bromo-2-nonene (calc'd mol. wt., 308.5; calc'd Ag equiv., 77.1).

Peroxide-induced reaction of 1-octyne with bromotrichloromethane. A solution of 0.94 g. (0.008 mole) of acetyl peroxide in a small portion of a total of 27.5 g. (0.25 mole) of 1-octyne was added slowly over a two-hour period to a solution of the greater part of the 1-octyne in 198.5 g. (1.0 mole) of bromotrichloromethane, maintained at a temperature of 100°. One hour after completion of the addition heating was discontinued and residual reactants

[3] The term silver equivalent is defined as the number of grams of the halogen-containing compound which react with one mole of silver nitrate in accordance with the equation: $Ag^+ + X^- \rightarrow AgX$.

were removed under reduced pressure. "Molecular" distillation of the product effected the separation of 61.2 g. (80%) of material identical in properties with that of fraction 3 of the photochemical reaction product. Less than a gram of material of higher molecular weight was present.

Identification of the bromotrichloromethane-1-octyne addition product (1,1,1-trichloro-3-bromo-2-nonene). The oily and aqueous layers resulting from ozonolysis of the addition product and hydrolytic cleavage of the ozonide were separated.

The aqueous layer was extracted with ether, and solvent was evaporated from the extract. Sulfuric acid was added to the residue, and the mixture was subjected to distillation. The distillate yielded a 2,4-dinitrophenylhydrazone which melted at 125–127° in agreement with the melting point reported for the derivative of chloral (4). There was no depression of melting point upon mixture with a sample prepared from chloral hydrate.

The oily layer was taken up in aqueous sodium hydroxide, and the alkaline solution was extracted with ether to remove neutral impurities. Acidification of the extracted aqueous solution yielded an acid which was converted to the *p*-bromophenacyl ester by the method of Reid and Judefind (5). The melting point of this derivative (70–71°) was not depressed by mixture with a sample of ester similarly prepared from authentic heptanoic acid (6).

The identity of the one-to-one bromotrichloromethane-1-octyne adduct as 1,1,1-trichloro-3-bromo-2-nonene is thus established.

Photochemical reaction of 2-octyne with bromotrichloromethane. A solution of 16.7 g. (0.15 mole) of 2-octyne (n_D^{20} 1.4278) in 366.4 g. (1.85 mole) of bromotrichloromethane was internally illuminated for a period of 26 hours. Removal of unchanged reactants under reduced pressure yielded 19.0 g. of crude product, which was separated by "molecular" distillation into distillate (15.6 g.) and relatively non-volatile residue (3.1 g.). By the cryoscopic method in benzene, the distillate had an apparent molecular weight of 308.0, consistent with that calculated for the one-to-one halide-2-octyne adduct, $C_9H_{14}BrCl_3$ (308.5).

Peroxide-induced reaction of 2-octyne with bromotrichloromethane. A solution of 0.59 g. (0.005 mole) of acetyl peroxide in 27.5 g. (0.25 mole) of 2-octyne and 198.5 g. (1.0 mole) of bromotrichloromethane was allowed to react at 100° for 2½ hours. After removal of the solvents the product was distilled with the aid of a short Vigreaux column, yielding 6.3 g. of relatively low-boiling fractions and 15.2 g. of material (n_D^{20} 1.5185) boiling at 92–95° under 2 mm. The principal distillate had a halogen content (Ag equiv., 80.1) consistent with that calculated for the one-to-one halide-2-octyne adduct, $C_9H_{14}BrCl_3$ (Ag equiv., 77.1).

Photochemical reaction of phenylacetylene with bromotrichloromethane. A solution of 50.0 g. (0.49 mole) of phenylacetylene (n_D^{20} 1.5482) in 500.0 g. (2.52 moles) of bromotrichloromethane, maintained at 60° by means of an oil-bath, was internally illuminated for a period of 19 hours. Unchanged reactants were removed under reduced pressure, and the product was subjected to "molecular" distillation. The following fractions were collected: fraction 1 (14.5 g.), n_D^{20} 1.5961, mol. wt., 275, Ag equiv. 78.3; fraction 2 (15.4 g.), n_D^{20} 1.5968, mol. wt., 279, Ag equiv. 75.9; fraction 3 (15.1 g.), n_D^{20} 1.5983, mol. wt., 270, Ag equiv. 74.3; fraction 4 (7.6 g.), n_D^{20} 1.6014, mol. wt., 293, Ag equiv. 75.1; fraction 5 (9.2 g.), n_D^{20} 1.6100, mol. wt., 299, Ag equiv. 77.8; fraction 6 (16.0 g.), mol. wt., 376, Ag equiv. 95.2.

Although obviously impure, or modified by secondary reactions, fractions 1 to 4 inclusive must be derived principally from the one-to-one halide-octyne adduct.

The apparent molecular weight (299) and the halogen content (Ag equiv., 77.8) of fraction 5 agree fairly well with those calculated (mol. wt., 300.5; Ag equiv., 75.1) for the one-to-one halide-alkyne adduct, 1-bromo-1-phenyl-3,3,3-trichloropropene.

Anal. Calc'd for $C_9H_6BrCl_3$: C, 36.0; H, 2.0.

Found: C, 35.8; H, 2.2.

The apparent molecular weight (376) and the halogen content (Ag equiv., 95.2) of fraction 6 correspond roughly to these calculated for a product derived from one molecule of halide and two molecules of octyne (mol. wt., 402.5; Ag. equiv., 100.6). Assuming that fraction 6 consists essentially of the two-to-one adduct, contaminated with one-to-one

adduct, the halogen analysis and the molecular weight determination would indicate a 78–74% content of the former to 22–26% of the latter.

Peroxide-induced reaction of phenylacetylene with bromotrichloromethane. A solution of 0.94 g. (0.008 mole) of acetyl peroxide in a small portion of a total of 198.5 g. (1.0 mole) of bromotrichloromethane was added gradually over a two-hour period to a solution of 25.5 g. (0.25 mole) of phenylacetylene in the greater part of the halide, maintained at a temperature of 105°. One hour after completion of the addition heating was discontinued and residual reactants were removed under reduced pressure. "Molecular" distillation of the product yielded the following fractions: fraction 1 (7.0 g.), n_D^{20} 1.6110, mol. wt., 278; fraction 2 (6.4 g.), n_D^{20} 1.6150, mol. wt., 287; fraction 3 (14.9 g.), n_D^{20} 1.6114, mol. wt., 280; residue (28.2 g.).

From the residue were isolated small amounts of white crystals (m.p., 176–177°; Ag equiv., 80) and of orange crystals (m.p., 203–205°).

Identification of the bromotrichloromethane-phenylacetylene addition product (1-bromo-1-phenyl-3,3,3-trichloropropene). Ozonolysis of the supposed one-to-one adduct and hydrolytic cleavage of the ozonide yielded benzoic acid (m.p. and mixture m.p., 122–123°) and chloral, identified through its 2,4-dinitrophenylhydrazone (m.p. and mixture m.p., 123.5–124.0°). In a second ozonolytic experiment trichloracetic acid, identified through its *p*-nitrobenzyl ester (m.p. and mixture m.p., 82°), rather than chloral, was obtained.

The identity of the one-to-one bromotrichloromethane-phenylacetylene adduct as 1-bromo-1-phenyl-3,3,3-trichloropropene is thus established.

Peroxide-induced reaction of 1-octyne with carbon tetrachloride. By the usual experimental procedure, already described, a total of 8.26 g. (0.07 mole) of acetyl peroxide was gradually (over a period of 16 hours) added to and decomposed in a total of 73.8 g. (0.67 mole) of 1-octyne and 838.3 g. (5.4 moles) of carbon tetrachloride, maintained at the reflux temperature of the reaction mixture. Unchanged reactants were removed under reduced pressure and the product was distilled, yielding the following fractions: fraction 1, 48–56°/4 mm., 4.3 g.; fraction 2, 55–60°/3 mm., 3.0 g.; fraction 3, 91–92°/4 mm., 8.6 g.; residue.

The residue from the original distillation, subjected to "molecular" distillation, yielded the following fractions: fraction 4, 5.0 g.; fraction 5, 4.5 g.; residue 18.4 g., apparent mol. wt., 982, Cl, 34.6%.

Anal. Calc'd for $C_8H_{14}Cl_2$ (n-$C_6H_{13}CCl{=}CHCl$): Cl, 39.2; mol. wt., 181.0.
Calc'd for $C_9H_{14}Cl_2$ (n-$C_6H_{13}CH{=}C{=}CCl_2$): Cl, 36.8; mol. wt., 193.0.
Found (fraction 1): Cl, 37.0; mol. wt., 187; (fraction 2): Cl, 38.3; mol. wt., 196.
Calc'd for $C_9H_{14}Cl_4$ (1:1 adduct): Cl, 53.7; mol. wt., 264.0.
Found (fraction 3): Cl, 46.3; mol. wt., 228; (fraction 4): Cl, 49.3; mol. wt., 283; (fraction 5): Cl, 47.3; mol. wt., 321.

In the final residue there are, on the average, at least nine chlorine atoms and six molecules of octyne per "polymer" molecule.

Peroxide-induced reaction of phenylacetylene with carbon tetrachloride. By the usual experimental procedure, already described, a total of 13.1 g. (0.11 mole) of acetyl peroxide was decomposed, over a period of four hours, in 23.2 g. (0.23 mole) of phenylacetylene and 154.0 g. (1.0 mole) of carbon tetrachloride, maintained at the reflux temperature of the reaction mixture. Removal under reduced pressure of the unchanged reactants left a black, tarry residue which had an apparent molecular weight of 436 and a chlorine content of 16.0%.

The reaction product was dissolved in ether. The addition of methanol to the ethereal solution precipitated a yellow curd-like material. Attempts to crystallize this precipitate from ligroin and other solvents did not affect its color, physical appearance, or melting point range (155–160°). The apparent molecular weight was 2037, and the chlorine content 12.0%.

The material recovered from the carbon-decolorized ether-methanol solution had an apparent molecular weight of 450 and a chlorine content of 12.5%.

Peroxide-induced reaction of 2-nonyne with carbon tetrachloride. In the usual manner,

2.0 g. (0.016 mole) of acetyl peroxide was decomposed in 38.3 g. (0.29 mole) of 2-nonyne (n_D^{20} 1.4325) and 320 g. (2.1 moles) of carbon tetrachloride. After separation from residual reactants the product was distilled at reduced pressure: fraction 1, 44–60°/0.2 mm., Cl, 36.5%; 0.6 g.; fraction 2, 60–90°/0.2 mm., 2.1 g. During the distillation of fraction 2 gas evolution, indicative of decomposition, was noted.

Anal. Calc'd for $C_{10}H_{16}Cl_4$ (1:1 adduct): Cl, 49.0; mol. wt., 288.

Found (fraction 2): Cl, 38.2; mol. wt., 232.

1-Octyne-inhibition of the peroxide-induced reaction of 1-octene with carbon tetrachloride. In duplicate experiments, conducted in the usual way, acetyl peroxide, 1-octyne, 1-octene, and carbon tetrachloride, in the relative molecular proportions 1:5:20:110, were allowed to interact for periods of 21 and 24 hours, respectively. The yields of the known (1) one-to-one carbon tetrachloride-1-octene adduct, identified by its boiling point (67–74°/1 mm.) and refractive index (n_D^{20} 1.4770), were 64.0% and 69.0%, respectively.

Otherwise comparable experiments with reaction mixtures from which the 1-octyne had been omitted yielded 74.0% and 71.5%, respectively, of the one-to-one adduct (1,1,1,3-tetrachlorononane).

Phenylacetylene-inhibition of the peroxide-induced reaction of 1-octene with carbon tetrachloride. In duplicate experiments similar to those just described, but in which phenylacetylene was substituted for 1-octyne, the mixtures were allowed to interact for 21½ and 24½ hours, respectively. The yields of one-to-one halide-1-octene adduct obtained were only 3.8% and 4.1%, respectively. Quantities of "polymeric" material (*ca.* 10 g.) approximated those obtained in uninhibited reactions in which the yields of addition product were much larger.

Competition of styrene with phenylacetylene in the photochemical reaction with bromotrichloromethane. A solution of 11.0 g. (0.11 mole) of styrene, 10.0 g. (0.10 mole) of phenylacetylene, and 324.6 g. (1.64 mole) of bromotrichloromethane was internally illuminated by a neon-type mercury-vapor coil for a half-hour. Unchanged reactants were removed under reduced pressure and the residue was subjected to "molecular" distillation. Virtually the whole of the product was thus converted into a crystalline sublimate. Recrystallized from methanol, the material melted at 53–55° and did not depress the melting point of an authentic sample of the known (2) styrenebromo-trichloromethane adduct (1,1,1-trichloro-3-bromo-3-phenylpropane).

Competition of phenylacetylene with allyl chloride in the photochemical reaction with bromotrichloromethane. A solution of 30.0 g. (0.25 mole) of phenylacetylene, 19.1 g. (0.25 mole) of allyl chloride, and 397.0 g. (2.0 moles) of bromotrichloromethane was internally illuminated by a neon-type mercury-vapor coil for two hours. Removal of unchanged reactants under reduced pressure yielded 2.9 g. of residue.

Anal. Calc'd for $C_4H_5BrCl_4$: Ag equiv., 55.0.

Calc'd for $C_9H_6BrCl_3$: Ag equiv., 75.1. Found: Ag equiv., 80.0.

It is concluded the product consists principally of the one-to-one phenylacetylene-bromotrichloromethane adduct (1-bromo-1-phenyl-3,3,3-trichloropropene).

Competition of phenylacetylene with methallyl chloride in the photochemical reaction with bromotrichloromethane. A solution of 30.0 g. (0.25 mole) of phenylacetylene, 24.5 g. (0.25 mole) of methallyl chloride, and 401.0 g. (2.0 moles) of bromotrichloromethane was internally illuminated by a neon-type mercury-vapor coil for two hours. Removal of unchanged reactants under reduced pressure yielded 10.4 g. of residue.

Anal. Calc'd for $C_5H_7BrCl_4$: Ag equiv., 57.8.

Calc'd for $C_9H_6BrCl_3$: Ag equiv., 75.1. Found: Ag equiv., 83.1.

It is concluded that the product consists principally of the one-to-one phenylacetylene-bromotrichloromethane adduct (1-bromo-1-phenyl-3,3,3-trichloropropene).

Competition of 1-octyne with allyl chloride in the photochemical bromotrichloromethane reaction. A solution of 27.5 g. (0.25 mole) of 1-octyne, 19.1 g. (0.25 mole) of allyl chloride, and 397.0 g. (2.0 moles) of bromotrichloromethane was internally illuminated by a neon-type mercury-vapor coil for three hours, at which time approximately 25% of the hydro-

carbons had reacted. After removal of unchanged reactants at reduced pressure, the residue (28.2 g.) was subjected to "molecular" distillation: fraction 1 (5.6 g.), n_D^{20} 1.5254, mol. wt., 275, Ag equiv., 58.0, Cl/Br 3.4; fraction 2, (8.0 g.), n_D^{20} 1.5232, mol. wt., 285, Ag equiv., 59.7, Cl/Br 2.8; fraction 3 (8.5 g.), n_D^{20} 1.5208, mol. wt., 287, Ag equiv., 62.4, Cl/Br 3.2; fraction 4 (3.6 g.), n_D^{20} 1.5151, mol. wt., 301, Ag equiv. 78.2, Cl/Br 1.4; residue (1.2 g.), mol. wt., 339, Ag equiv., 71.3, Cl/Br 1.8.

The calculated and observed constants for the respective one-to-one adducts are: Allyl chloride adduct ($C_4H_5BrCl_4$): n_D^{20} 1.5337, mol. wt., 275.0, Ag equiv., 55.0, Cl/Br 4; 1-Octyne adduct ($C_9H_{14}BrCl_3$): n_D^{20} 1.5180, mol. wt., 308.1, Ag equiv., 77.1, Cl/Br 3.

In view of the known tendency of such adducts to undergo decomposition upon distillation it may be inferred from the data recorded only that very little "polymeric" material was formed in the course of the experiment, and that both adducts were present in quantities sufficient to justify the conclusion that the over-all rates of the two addition reactions are comparable.

SUMMARY

1. In photochemical or peroxide-induced reactions with 1-alkynes bromotrichloromethane yields one-to-one adducts and polymerization-addition products.

2. Any 1-alkyne is less reactive than the corresponding 1-alkene, both in ability to add free trichloromethyl radicals and in the ability of the free radical thus formed to react with bromotrichloromethane.

3. Phenylacetylene is less reactive than styrene in so far as the ability to add a free trichloromethyl radical is concerned but more reactive than 1-octene.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY[1]]

MIXED ESTERS OF LACTIC AND CARBONIC ACIDS. *n*-ALKYL CARBONATES OF *n*-ALKYL LACTATES

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Previous papers in this series described a group of miscellaneous carbonates of lactates (1) and three homologous families (2), and also indicated the usefulness of some of these esters as plasticizers for vinyl chloride resins (3). This paper describes two additional series of esters having the formula ROCOOCH (CH_3)COOR′. In one homologous series, R is ethyl and R′ is *n*-alkyl. In the other, R and R′ are identical *n*-alkyl groups. Each series consists of six members, one compound being common to both (Table I).

The esters were prepared, and physical properties were determined as described in a previous paper (2). The preparation and physical properties of the lactates used have been described recently (4).

Although the lowest members of each series have been prepared (2), they are not included in this paper because, as is usual in homologous series, their physical properties deviate from the orderly sequence shown by the higher members of the series.

Boiling points and vapor pressures. Figures 1 and 2 show the boiling points of the esters as a function of the pressure. In these modified Cox charts, pressure is plotted logarithmically, and the temperature scale is laid off as a linear function of $1/(t+193)$, where t is in °C. The lines showed considerable curvature (convex upward) when plotted on the usual types of Cox paper having temperature scales determined by $1/(t+273)$ or $1/(t+230)$, although the curvature was less with the latter type paper. The scales determined by $1/(t+193)$ were straight lines, and charts having this scale were conveniently prepared from commercial Cox chart paper having a scale linear with $1/(t+273)$ by adding 80° to each temperature designated on the chart. The mathematical proof of this transformation has been published elsewhere (5).

In each homologous series, the logarithm of the vapor pressure at any fixed temperature is a linear function of the number of carbon atoms in the ester. Tables II and III show equations for these lines at various temperatures. For each series, these lines constitute a family having a common point of intersection located as follows:

For the ethyl carbonate series: $x = -18$, $\log P = 7.5$.
For the alkyl carbonate series: $x = -14.5$, $\log P = 6.5$.

Also, within each family, the slopes (a) of these lines vary with the absolute temperature:

For the ethyl carbonate series: $a = -113/T + 0.055$.
For the alkyl carbonate series: $a = -130/T + 0.103$.

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TABLE I

n-ALKYL CARBONATES OF *n*-ALKYL LACTATES: $ROCOOCH(CH_3)COOR'$

R	R'	YIELD, %	n_D^{20}	n_D^{40}	d_4^{20}	d_4^{40}	MOL. REFR. 20°		VISCOSITY, CPS.		C, %		H, %	
							Calc'd	Found	20°	40°	Calc'd	Found	Calc'd	Found
Ethyl	Ethyl	72	1.4112	1.4032	1.0742	1.0523	44.10	43.98	4.11	2.45	50.5	50.5	7.4	7.5
Ethyl	Butyl[a]	54	1.4181	1.4102	1.0325	1.0138	53.33	53.28	5.16	2.95	55.0	54.8	8.3	8.3
Ethyl	Hexyl	80	1.4242	1.4167	1.0021	0.9828	62.57	62.75	7.46	3.79	58.5	58.5	9.0	8.9
Ethyl	Octyl[b]	49	1.4281	1.4212	0.9846	0.9664	71.80	71.70	8.96	4.61	61.3	61.3	9.6	9.6
Ethyl	Dodecyl	48	1.4366	1.4295	0.9569	0.9406	90.27	90.41	15.64	7.51	65.4	65.4	10.4	10.5
Ethyl	Hexadecyl	90	1.4422	1.4352	0.9390	0.9235	108.75	108.97	25.48	11.57	68.4	68.6	10.9	10.9
Propyl	Propyl	70	1.4189	1.4110	1.0338	1.0136	53.33	53.31	5.88	3.20	55.0	55.0	8.3	8.2
Butyl	Butyl[a]	73	1.4240	1.4162	1.0049	0.9864	62.57	62.75	6.51	3.64	58.5	59.1	9.0	9.2
Amyl	Amyl[c]	67	1.4290	1.4214	0.9848	0.9670	71.80	71.82	8.74	4.57	61.3	61.3	9.6	9.4
Hexyl	Hexyl[c]	64	1.4327	1.4250	0.9654	0.9483	81.04	81.34	11.59	5.65	63.5	63.4	10.0	10.1
Decyl	Decyl[c]	25	1.4440	1.4358	0.9315	0.9157	117.98	118.22	25.66	11.68	69.5	69.8	11.2	11.1

[a] These compounds have been described previously (2), but are included here for comparison with their homologs. [b] Some of the data on this compound have been published previously (1). [c] Certain data on these compounds have been reported previously (3).

By use of these equations for the slopes, and the common points given above, equations for vapor pressures at any desired temperature may be readily calculated.

FIG. 1 BOILING POINTS OF ETHYL CARBONATES OF n-ALKYL LACTATES

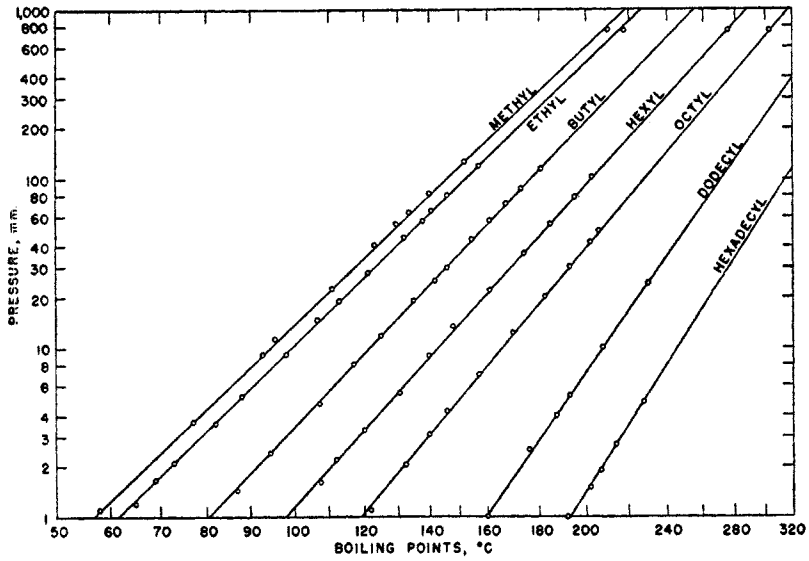
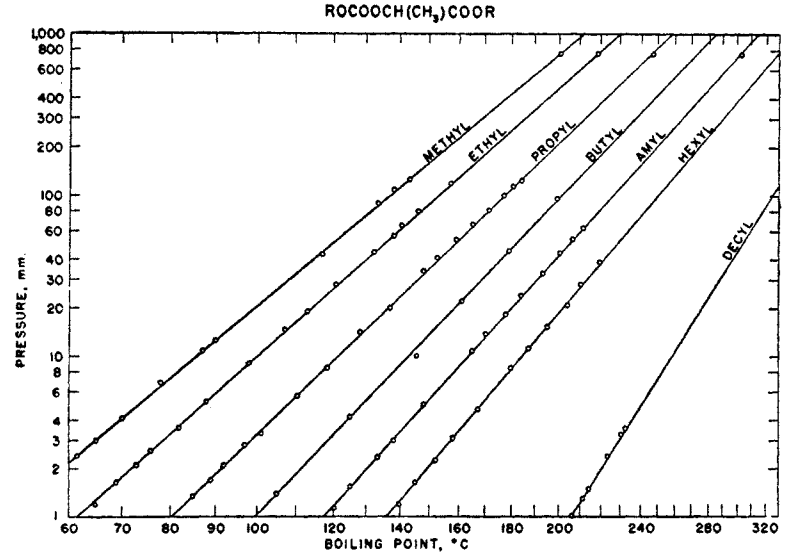


FIG. 2 BOILING POINTS OF n-ALKYL CARBONATES OF n-ALKYL LACTATES: ROCOOCH(CH_3)COOR



At any chosen fixed pressure, the squares of the boiling points (°K) vary directly with the number of carbon atoms in the esters of either series. Equations in Tables II and III show these relationships. Within each family, these lines determined at different pressures pass through a common point.

TABLE II

BOILING POINTS (T = °K.) AND VAPOR PRESSURES (P = PRESSURE, MM.) OF ETHYL CARBONATES OF *n*-ALKYL LACTATES AS RELATED TO NUMBER OF CARBON ATOMS (x)

CONST. TEMP., °C., OR PRESSURE, MM.	a	b	DEVIATIONS[a]	
			Max.	Average
Boiling Points: $10^{-4}T^2 = ax + b$				
760 mm.	1.56	11.30	3	1.2
100	1.18	8.50	1	0.7
10	0.918	6.50	3	1.8
1	0.746	5.18	4	2.0
Vapor Pressures: Log P = $ax + b$				
300°	−0.143	4.92	19	14
250	−0.161	4.57	9	7
200	−0.184	4.17	6	2
150	−0.212	3.67	2	1
100	−0.248	3.00	6	4

[a] Temperature deviations are in °C. Pressure deviations are in percentages. A deviation of 1° is equivalent to a pressure deviation of about 5%.

TABLE III

BOILING POINTS (T = °K.) AND VAPOR PRESSURES (P = PRESSURE, MM.) OF COMPOUNDS ROCOOCH(CH_3)COOR (R = *n*-ALKYL) AS RELATED TO NUMBER OF CARBON ATOMS (x)

CONSTANT TEMP., °C. OR PRESSURE, MM.	a	b	DEVIATIONS[a]	
			Max.	Average
Boiling Points: $10^{-4}T^2 = ax + b$				
760 mm.	1.51	11.95	2	0.6
100	1.15	8.80	5	1.7
10	0.896	6.60	2	1.0
1	0.734	5.12	2	1.3
Vapor Pressures: Log P = $ax + b$				
300°	−0.127	4.66	11	7
250	−0.145	4.35	7	4
200	−0.171	4.02	3	2
150	−0.202	3.57	4	2
100	−0.245	2.95	4	3

[a] Temperature deviations are in °C. Pressure deviations are in percentages. A deviation of 1° is equivalent to a pressure deviation of about 5%.

For ethyl carbonates: $x = -7.5$, $10^{-4}T^2 = -0.4$.
For alkyl carbonates: $x = -9.0$, $10^{-4}T^2 = -1.5$.

The slopes (a) of these lines vary inversely with the logarithm of the pressure (P):

For the ethyl carbonates: Log P = $-4.21/a + 5.59$.

For the alkyl carbonates: Log P = $-4.21/a + 5.69$.

By use of these equations for the slopes and the common points given above, equations may be calculated for boiling points at any desired pressure.

Densities, refractive indices, and viscosities. These physical properties were measured at 20° and at 40° (Table I). As reported in the previous paper (2), linear relationships were found between certain functions of these physical constants and the number of carbon atoms in the esters. Table IV shows equations for these relationships. These equations are highly useful, not only for calculating the properties of homologs not prepared but for checking the purity

TABLE IV

EQUATIONS RELATING REFRACTIVE INDICES, DENSITIES, AND VISCOSITIES TO THE NUMBER OF CARBON ATOMS IN CARBONATES OF LACTATES ROCOOCH(CH$_3$)COOR′

R	R′	EQUATION	DEVIATIONS[a]	
			Max.	Average
Ethyl	*n*-Alkyl	$1/(x + 10) = -0.773\ n_D^{20} + 1.1462$	0.0007	0.0002
Ethyl	*n*-Alkyl	$1/(x + 10) = -0.741\ n_D^{40} + 1.095$	0.0005	0.0002
Ethyl	*n*-Alkyl	$1/x = 0.583\ d_4^{20} - 0.5019$	0.0017	0.0008
Ethyl	*n*-Alkyl	$1/x = 0.618\ d_4^{40} - 0.5253$	0.0020	0.0009
Ethyl	*n*-Alkyl	$\text{Log } \eta_{20} = 0.0566\ x + 0.161$	6.7[b]	2.3[b]
Ethyl	*n*-Alkyl	$\text{Log } \eta_{40} = 0.0495\ x - 0.030$	3.3[b]	1.6[b]
R = R′ =	*n*-Alkyl	$1/(x + 8) = -0.954\ n_D^{20} + 1.4088$	0.0005	0.0002
	n-Alkyl	$1/(x + 8) = -0.954\ n_D^{40} + 1.4012$	0.0005	0.0002
	n-Alkyl	$1/(x + 1) = 0.498\ d_4^{20} - 0.4238$	0.0005[c]	0.0002[c]
	n-Alkyl	$1/(x + 1) = 0.521\ d_4^{40} - 0.4371$	0.0002[c]	0.0002[c]
	n-Alkyl	$\text{Log } \eta_{20} = 0.0500\ x + 0.240$	7.3[b]	5.4[b]
	n-Alkyl	$\text{Log } \eta_{40} = 0.0424\ x + 0.065$	3.8[b]	2.6[b]

[a] Difference between calculated and observed values of the physical constants; methyl esters excluded. [b] Percentage deviation from the observed value. [c] Hexyl carbonate of hexyl lactate excluded; its deviation was .0037 at 20° and .0035 at 40°.

of those studied and the accuracy of physical measurements made on them. When such correlations of physical properties with molecular structure have been made for a sufficient number of families of compounds, broader and more fundamental relationships may become demonstrable.

Acknowledgment. The authors are grateful to C. O. Willits, C. L. Ogg, and their associates for analyses, and to H. L. Fisher, U. S. Industrial Chemicals Corporation, for hexyl and decyl chloroformates.

SUMMARY

Two homologous series of *n*-alkyl carbonates of *n*-alkyl lactates, ROCOOCH(CH$_3$)COOR′, were prepared, and several physical properties were determined. In one series R is ethyl and R′ is *n*-alkyl; in the other R and R′ are identical *n*-alkyl groups.

Equations were developed which relate vapor pressures, boiling points, refractive indices, densities, and viscosities to the number of carbon atoms in the members of each series.

PHILADELPHIA 18, PA.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

REACTIONS OF NITROPARAFFINS WITH IMINES AND PSEUDO BASES

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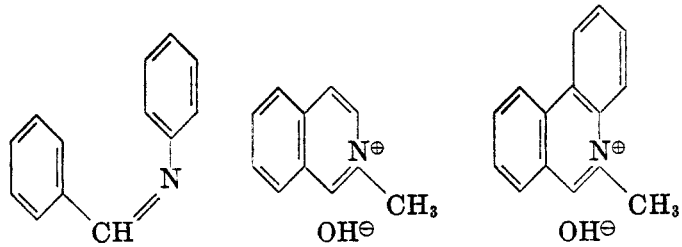
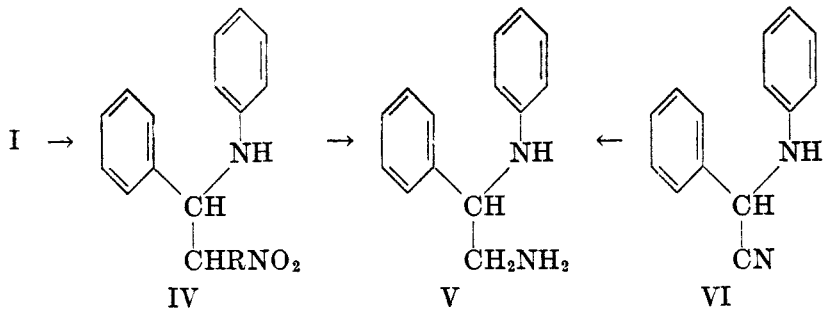
As an adjunct to our study of the reactions of certain isoquinoline compounds (1, 2), the structural similarities of benzalaniline (I) and isoquinoline, 10-methylphenanthridinium hydroxide (II) and 2-methylisoquinolinium hydroxide (III) led us to investigate the condensation products of nitroparaffins with I and II. Optimum conditions have now been found for the condensation of nitroparaffins with benzalaniline (I), 10-methylphenanthridinium hydroxide (II), and the isomeric 10-methylacridinium hydroxide (IX).[4]



I III II

The addition of nitromethane to benzalaniline to give 1-anilino-2-nitro-1-phenylethane (IVa) was previously reported by Mayer (3), but the details of the preparation, such as proportion of reactants and yield obtained, were lacking. It has been possible to effect a 79% yield of the adduct IVa by heating an ethanol solution of benzalaniline with three mole-equivalents of nitromethane under reflux for six hours. The structure of the adduct (IVa) was established



IV V VI

a. R = H; b. R = CH_3;
c. R = C_2H_5

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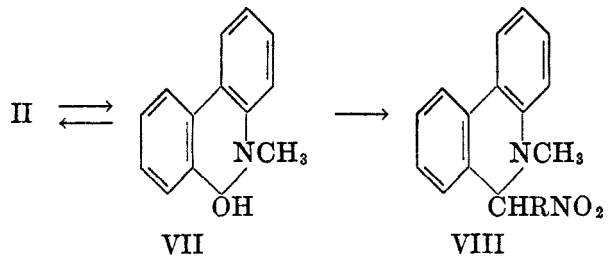
[3] Present address: Sherwin-Williams Company, Chicago, Illinois.
[4] The latter two probably as the pseudo base forms, VII and X.

by its reduction, both by catalytic hydrogenation and by chemical means, to 2-anilino-2-phenylethylamine (V), identical with the product of similar reduction of anilinophenylacetonitrile (VI). Addition of the homologous nitroethane and 1-nitropropane to benzalaniline did not proceed very satisfactorily in the absence of a catalyst, and we were dissuaded from the use of an acidic catalyst since Snyder, Kornberg, and Romig (4) found, in a study of the addition of active methylene compounds to benzalaniline in the presence of boron trifluoride, that nitromethane failed to give a solid product. By contrast, the use of a basic catalyst such as diethylamine was found to facilitate the addition to benzalaniline of nitroethane to give 1-anilino-2-nitro-1-phenylpropane (IVb) and of 1-nitropropane to give 1-anilino-2-nitro-1-phenylbutane (IVc). The method employing diethylamine possesses an advantage over others in that the adducts are readily isolated in pure form.

The nitroparaffins were found not to add readily to the analogous imine system of phenanthridine itself, but the combination of the two moieties was effected by condensation of 10-methylphenanthridinium iodide in ethanolic potassium hydroxide solution [essentially, therefore, the pseudo base form of II, 9-hydroxy-10-methyl-9,10-dihydrophenanthridine (VII) (5)] with nitroethane and with 1-nitropropane. The products, 9-(α-nitroethyl)-10-methylphen-

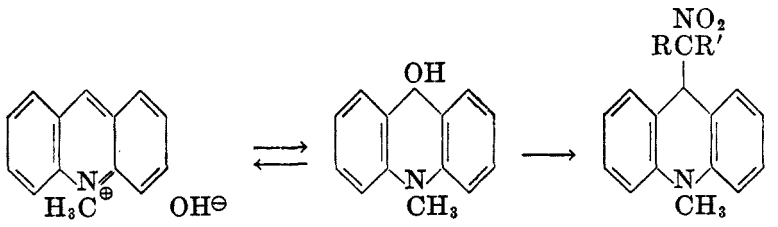


VII VIII

a. R = CH_3; b. R = C_2H_5

anthridan (VIIIa) and 9-(α-nitropropyl)-10-methylphenanthridan (VIIIb), were obtained in 54% yield in both examples.

The study of nitroparaffin condensation with a pseudo base (VII) was then extended to the vinylog of a pseudo base, as represented by the isomeric 9-hydroxy-10-methyl-9,10-dihydroacridine (X) (5). It was found that selected nitroparaffins (nitromethane, nitroethane, 1-nitropropane, and 2-nitropropane)



IX X XI { a. R = R′ = H; b. R = CH_3, R′ = H; c. R = C_2H_5, R′ = H; d. R = R′ = CH_3 }

reacted readily with a solution of 10-methylacridinium iodide made alkaline with potassium hydroxide. The condensation products, which were assigned the general structure of 9-substituted-10-methylacridans (XI), were obtained in yields of 62% (XIa), 68% (XIb), 50% (XIc), and 35% (XId).

EXPERIMENTAL[5]

1-Anilino-2-nitro-1-phenylethane (IVa). The method employed for the preparation of this compound was essentially that of Mayer (3), but since Mayer provided no details as to proportion of reactants used or yield obtained, the following directions are reported as giving the desired product in optimum yield. A solution of 100 g. (0.55 mole) of benzalaniline, 100 g. (1.64 mole) of nitromethane, and 50 ml. of absolute ethanol was heated at the reflux temperature for six hours. The solvent and excess nitromethane were evaporated at room temperature with the aid of a stream of dry air. The resulting mixture of rhombohedral prisms and oil was crushed and stirred with 95% ethanol, and the solid was collected. Several washings with cold 95% ethanol followed by air-drying gave 106 g. (79%) of product, m.p. 85–87°. Recrystallization from 95% ethanol raised the melting point of the light yellow prisms to 86–87.5° [reported by Mayer (3), 90°; reported by Worrall (6), who prepared it by a different method, 86–87°].

Anal. Calc'd for $C_{14}H_{14}N_2O_2$: C, 69.40; H, 5.82.
Found: C, 69.62; H, 5.91.

The *hydrochloride* was prepared by saturating an ether solution of the amine with anhydrous hydrogen chloride; m.p. 126–127° [reported (6), 126–127°]. The hydrochloride dissociated immediately on contact with water to give the free amine.

1-Anilino-2-nitro-1-phenylpropane (IVb). Five grams (27.6 millimoles) of benzalaniline was dissolved in 6.2 g. (82.6 millimoles) of nitroethane and 5 ml. of 95% ethanol. After the addition of 0.6 g. (8.2 millimoles) of diethylamine, the solution was heated at the reflux temperature for 15 minutes. Evaporation of the solution at room temperature with a stream of dry air gave an orange oil. Crystallization was induced by trituration with 95% ethanol, and the solid obtained was washed with ethanol; yield, 2.1 g. (30%); m.p. 100–102°. Recrystallization from absolute ethanol raised the melting point of the yellow prisms to 103–105°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: C, 70.29; H, 6.29; N, 10.93.
Found: C, 70.30; H, 6.51; N, 10.70.

The employment of a longer reflux time with diethylamine led to impure product. The use of benzyltrimethylammonium hydroxide (Rohm and Haas Company) in 0.05 mole-equivalent quantity and with a reflux time of two hours gave a slightly higher yield (35%), but of less pure product (m.p. 96–100°). In the absence of a basic catalyst, the reactants produced a low-melting mixture (m.p. 78–83°).

1-Anilino-2-nitro-1-phenylbutane (IVc). A method similar to that for 1-anilino-2-nitro-1-phenylpropane was used, with the difference that a two-hour reflux time was employed. The product was obtained in 55% yield as yellow prisms, m.p. 128–130°.

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: C, 71.09; H, 6.71; N, 10.37.
Found: C, 70.93; H, 6.86; N, 10.33.

Anilinophenylacetonitrile (VI). This compound was prepared by the method of Bucher and Grolée (7). The *N-acetyl derivative* was best prepared as follows. Anilinophenylacetonitrile with four mole-equivalents of acetic anhydride and a few drops of sulfuric acid was heated at 100° for one hour or at the reflux temperature for one-half hour. The reaction mixture was poured into water, giving a light yellow solid in quantitative yield (in small runs). Recrystallization from petroleum ether gave colorless prisms, m.p. 75–76°.

Anal. Calc'd for $C_{16}H_{14}N_2O$: C, 76.78; H, 5.64; N, 11.20.
Found: C, 76.57; H, 5.69; N, 11.08.

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[5] All melting points are corrected.

2-Anilino-2-phenylethylamine (V). The method of catalytic reduction employed was that used with analogous compounds by Reihlen and coworkers (8). The most satisfactory results were achieved when 30-g. batches of anilinophenylacetonitrile dissolved in 60 ml. of acetic anhydride were pretreated with Raney nickel at 25° and then hydrogenated over 1.0 g. of platinum oxide catalyst at 2–3 atm. and 60°. Even under these conditions, the usual yield was not over 20% of 2-anilino-2-phenylethylamine. Separation from the by-products of aniline (60%), identified as the picrate, and N-benzylaniline (*ca.* 10%), identified as the phenylthiourea derivative, was accomplished by fractional distillation *in vacuo*; b.p. 119–128° (0.13–0.20 mm.); n_D^{20} 1.6069.

Anal. Calc'd for $C_{14}H_{16}N_2$: C, 79.20; H, 7.60; N, 13.20.
Found: C, 79.42; H, 7.43; N, 12.96.

The *monohydrochloride* of 2-anilino-2-phenylethylamine was formed in ethanol-ether and was recrystallized from 95% ethanol; m.p. 245–248°.

Anal. Calc'd for $C_{14}H_{17}ClN_2$: C, 67.59; H, 6.89; N, 11.26.
Found: C, 67.74; H, 6.88; N, 10.98.

The yield of 2-anilino-2-phenylethylamine was not improved by using N-acetylanilinophenylacetonitrile in the hydrogenation over platinum oxide. When lithium aluminum hydride was employed for the reduction of anilinophenylacetonitrile using the conditions which Nystrom (9) applied for the conversion of nitriles to amines, a 25% yield of 2-anilino-2-phenylethylamine was realized, but N-benzylaniline was the major product (41% yield).

Reduction of 1-anilino-2-nitro-1-phenylethane. The structure of 1-anilino-2-nitro-1-phenylethane was related to that of anilinophenylacetonitrile by reduction to the same product: 2-anilino-2-phenylethylamine. The diamine, b.p. 124–125° (*ca.* 0.3 mm.), n_D^{20} 1.6064, was obtained, but only in low yield, by the hydrogenation of 1-anilino-2-nitro-1-phenylethane over platinum oxide catalyst (8) or by reduction with lithium aluminum hydride (9). Aniline and N-benzylaniline were again formed in larger amount than that of the desired diamine.

9-(α-Nitroethyl)-10-methylphenanthridan (VIIIa). A solution of 1.3 g. (23 millimoles) of potassium hydroxide in 20 ml. of absolute ethanol was added to a boiling suspension of 4.6 g. (14 millimoles) of 10-methylphenanthridinium iodide (5) in 15 ml. of absolute ethanol. To the resulting solution, 7.0 g. (93 millimoles) of nitroethane was added, and the light orange reaction mixture was heated under reflux for 30 minutes. After saturation with carbon dioxide, the reaction mixture was allowed to stand 12 hours at 25°. The solid which separated was recrystallized from 95% ethanol. Yellow rhombic crystals of 9-(α-nitroethyl)-10-methylphenanthridan, m.p. 112.5–113.5°, were thereby obtained; yield, 2.03 g. (54%).

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.45.
Found: C, 71.60; H, 6.25; N, 10.29.

9-(α-Nitropropyl)-10-methylphenanthridan (VIIIb). This product was obtained in the same manner as the lower homolog by the use of 1-nitropropane; m.p. 102–103.5°; yield, 54%.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.92.
Found: C, 72.32; H, 6.55; N, 9.65.

9-Dimethylaminomethylphenanthridine. A solution of 4.0 g. (17 millimoles) of 9-chloromethylphenanthridine (10) and 6.80 g. (150 millimoles) of dimethylamine in 20 ml. of 95% ethanol was placed in a pressure bottle and allowed to stand at 25° for four days. When the reaction mixture was added to 60 ml. of 5% aqueous sodium hydroxide, an oil separated which was extracted with ether. The ether extracts were evaporated and the crude 9-dimethylaminomethylphenanthridine was distilled at 160–170° (2 mm.). The distillate crystallized on cooling and was recrystallized from aqueous methanol; m.p. 86–87°; yield, 2.1 g. (50%).

Anal. Calc'd for $C_{16}H_{16}N_2$: C, 81.32; H, 6.83; N, 11.85.
Found: C, 81.23; H, 6.87; N, 11.81.

9-Diethylaminomethylphenanthridine. A solution of 10.6 g. (140 millimoles) of diethylamine and 10 g. (44 millimoles) of 9-chloromethylphenanthridine in 20 ml. of 95% ethanol

was heated under reflux for two hours. The reaction mixture was worked up in the same manner as that used for the dimethylamine product. The 9-diethylaminomethylphenanthridine was recrystallized from petroleum ether; m.p. 72.5–73°.

Anal. Calc'd for $C_{18}H_{20}N_2$: C, 81.77; H, 7.63; N, 10.59.
Found: C, 81.70; H, 7.90; N, 10.44.

9-(N-Piperidinomethyl)phenanthridine. Prepared by the same method using piperidine, the product crystallized from aqueous methanol as colorless needles, m.p. 98–99° [reported (11), 90–93°]; yield, 57.2%.

Anal. Calc'd for $C_{19}H_{20}N_2$: C, 82.57; H, 7.29; N, 10.14.
Found: C, 82.43; H, 7.23; N, 10.18.

9-Nitromethyl-10-methylacridan (XIa). A solution of 0.45 g. (8 millimoles) of potassium hydroxide in 10 ml. of absolute ethanol was added to a suspension of 2.4 g. (7.5 millimoles) of 10-methylacridinium iodide in 15 ml. of absolute ethanol. To the resulting clear solution was added 2.93 g. (48 millimoles) of nitromethane. The reaction mixture was heated to boiling and then was allowed to stand at 25° for three days. The resulting suspension was saturated with carbon dioxide, heated to boiling, and filtered to remove inorganic salts. Upon cooling, 9-nitromethyl-10-methylacridan separated and was recrystallized from absolute ethanol; plates, m.p. 131–132°; yield, 1.18 g. (62%).

Anal. Calc'd for $C_{15}H_{14}N_2O_2$: C, 70.84; H, 5.55; N, 11.02.
Found: C, 70.80; H, 5.35; N, 10.96.

9-(α-Nitroethyl)-10-methylacridan (XIb). This compound was prepared in 68% yield by the same method, using nitroethane; plates from ethanol, m.p. 144.5–145.5°.

Anal. Calc'd for $C_{16}H_{16}N_2O_2$: C, 71.62; H, 6.01; N, 10.45.
Found: C, 71.72; H, 6.20; N, 10.45.

9-(α-Nitropropyl)-10-methylacridan (XIc), This compound was prepared in 50% yield by the same method, using 1-nitropropane; plates from ethanol, m.p. 134–135°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.92.
Found: C, 72.27; H, 6.65; N, 9.79.

9-(α-Methyl-α-nitroethyl)-10-methylacridan (XId). This compound was prepared in 35% yield by the same method, using 2-nitropropane; needles from ethanol, m.p. 198°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.92.
Found: C, 72.17; H, 6.44; N, 10.06.

SUMMARY

Optimum conditions have been found for the addition of representative nitroparaffins to the imino linkage of benzalaniline and for the condensation of nitroparaffins with the pseudo bases derived from 10-methylphenanthridinium hydroxide and 10-methylacridinium hydroxide.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE INSTITUTE OF PAPER CHEMISTRY]

THE INFRARED ABSORPTION SPECTRA OF TWO ISOMERS OF CONIDENDRIN AND OF THE CORRESPONDING DEMETHYLATION PRODUCTS

WALTER E. SPEARIN[1]

Received February 8, 1950

The isolation of one stereoisomer of conidendrin (now termed α-conidendrin) has been described by Kawamura (1), Emde and Schartner (2), and Erdtman (3). These investigators extracted the material from various softwoods or from sulfite waste liquors of several softwoods. Brauns (4) extracted the same isomer from western hemlock (*Tsuga heterophylla*) and Pearl (5) obtained it from the sulfite waste liquor of western hemlock. Recently, Hearon, Lackey, and Moyer (6) reported the preparation of a second stereoisomer of conidendrin, which has been designated β-conidendrin. In the same papers, Hearon, *et al.* also described the preparation of the demethylation products of the two isomers of conidendrin. These hydroxylated compounds are designated as α- and β-conidendrol, respectively, to correspond with the parent substances.

The infrared spectra of β-conidendrin, α-conidendrol, and β-conidendrol have been determined.[2] The work was carried out using a Perkin-Elmer Infrared Spectrometer Model 12-B with a General Motors breaker-type amplifier and a Brown strip chart recorder. The instrument was operated under conditions similar to those described by Jones (7) who determined the spectrum of α-conidendrin (8). A sodium chloride prism was used to cover the range 3700 cm.$^{-1}$ to 725 cm.$^{-1}$.

Excellent crystalline mats of the compounds were prepared by evaporating the respective acetone solutions on salt plates. The "films" thus formed were strongly adherent to the plates, and showed little tendency to scatter the infrared radiation. Crystal mats were also deposited on salt plates from dioxane-ethanol solutions in order to clarify the regions of the spectrum where absorption resulting from retained acetone might be expected. The mats from the dioxane-ethanol solutions were not as uniform as those from acetone. When satisfactory thicknesses of the compounds were obtained on the salt plates, the "films" were dried *in vacuo* over sulfuric acid, Ascarite, and paraffin for at least 24 hours before the spectrum determination.

The identity of each substance was checked by observing the melting point (Fisher-Johns melting point block) and the optical rotation (Bausch & Lomb half-shadow saccharimeter). Table I is a summary and comparison of the observed and reported values.

The spectra of the three compounds are shown in Figure 1. That of α-conidendrin, as obtained by Jones (8), is included for comparison. The possible band assignments for each of the spectra are given in Table II.

[1] Present address: Combined Locks Paper Co., Combined Locks, Wis.

[2] The samples used were furnished by the Crown Zellerbach Corporation, Camas, Washington.

TABLE I

MELTING POINTS AND OPTICAL ROTATIONS

	MELTING POINT, °C.		OPTICAL ROTATION, $[\alpha]_D^{25}$	
	Obs.	Lit.	Obs.[d]	Lit.[d]
β-Conidendrin	208	210–212[a]	+30.3 (4)	+32.5 (4)[b]
α-Conidendrol	164	165–166[b, c]	−78.1 (2)	−72.5 (2)[b, e]
β-Conidendrol	247	249–251[b]	+13.0 (4)	+15 (5)[b]

[a] Holmberg, *Ber.*, **54**, 2389 (1921). [b] See ref. 6. [c] Anhydrous. [d] Parenthetical numbers are concentrations in grams of solute per 100 g. of acetone. [e] Dihydrate [the dihydrate melts at 102–103°] (6).

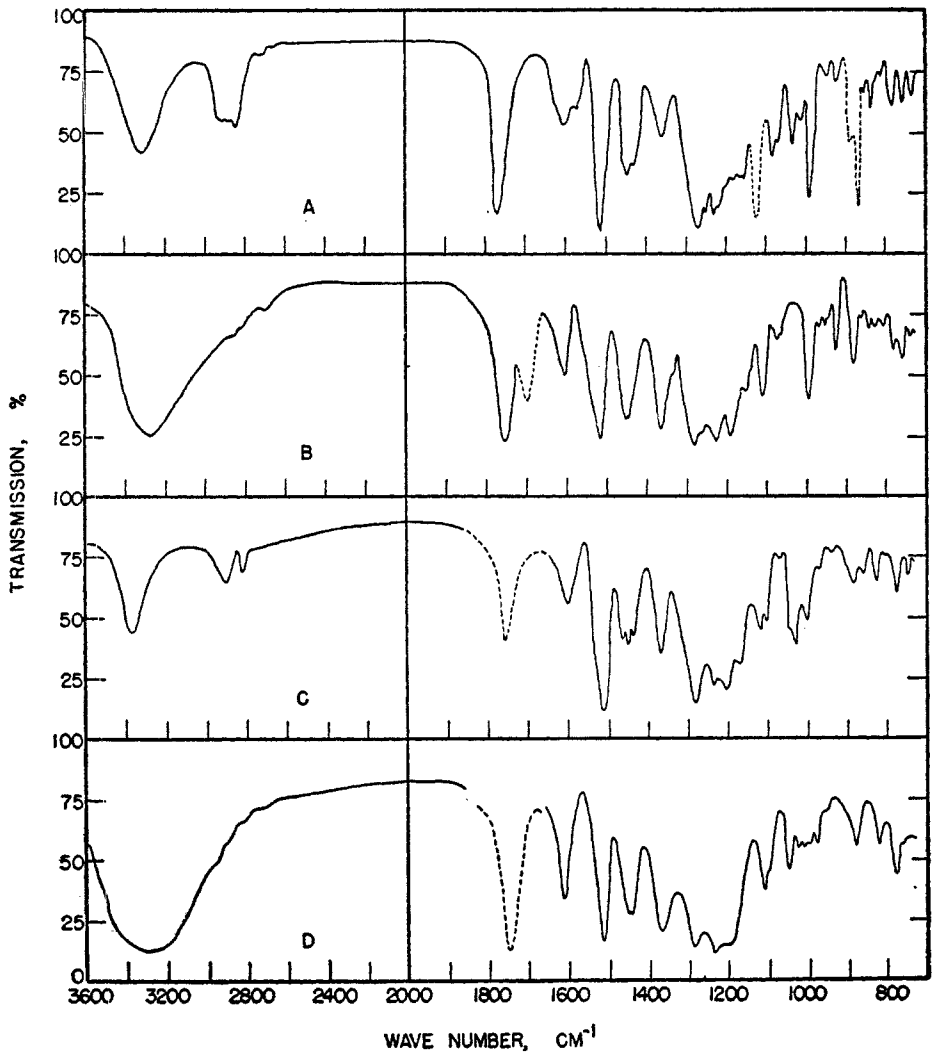

FIGURE 1. INFRARED ABSORPTION SPECTRA

A. α-Conidendrin (film from dioxane-ethanol); B. α-conidendrol (film from acetone); C. β-conidendrin (film from acetone); D. β-conidendrol (film from acetone). Dotted lines refer to absorption attributed to retained solvent and dashed lines refer to films of the respective compounds from dioxane-ethanol solution.

Inspection of Figure 1 reveals that:

1. The conidendrols exhibit a higher hydroxyl content (increased hydroxyl absorption intensity) than the conidendrins. Little difference is found in the hydroxyl absorption strengths of the conidendrols.

2. The hydroxyl groups or at least a portion of them are evidently involved in bridging of some type in each componud. However, the conidendrols show the strongest hydrogen bonding (shift to low frequency of the hydroxyl absorption band) and β-conidendrin the least.

3. The saturated C-H stretching absorption bands are nearly obscured by the strong hydroxyl absorptions in the conidendrols. The saturated C-H stretching frequencies, however, are quite clear in the spectra of the conidendrins.

4. The lactone structure involving the strained ring is clearly indicated by strong absorption occurring in the high-frequency end of the carbonyl absorption range. The intensity of this absorption remains apparently constant for the four compounds. The reasons for the shifts in frequency of the carbonyl bands

TABLE II

TENTATIVE ABSORPTION BAND ASSIGNMENTS

ASSIGNMENT	ABSORPTION MAXIMUM, CM.$^{-1}$			
	α-Conidendrin[a]	β-Conidendrin	α-Conidendrol	β-Conidendrol
Hydroxyl	3310[b]	3370[c]	3270[c]	3280[c]
Saturated C-H	2920; 2870; 2820	2900; 2820	[d]	[d]
Gamma lactone	1771	1762	1754	1744
Phenyl ring	1603; 1511	1599; 1512	1606; 1515	1607; 1515

[a] See ref. 8. [b] Band position determined within ±10 cm.$^{-1}$. [c] Band position determined within ±15 cm.$^{-1}$. [d] These bands are apparently obscured by the strong hydroxyl absorption; absorption maxima could be detected but they were somewhat indefinite.

between the various products are not clear, although the changes could be associated with the corresponding variations in the hydroxyl bands to indicate hydrogen bridging.

5. The aromatic nature of the materials is shown by two strong absorption bands at about 1600 cm.$^{-1}$ and 1515 cm.$^{-1}$, respectively.

6. There are several differences in the lower frequency region of the spectra of these materials. Some of these may be due to stereoisomerism or to demethylation. However, because the low frequency portion of the infrared spectrum obtained gives corroborative evidence only, little can be stated concerning it, except to support the above items.

Because an empirical method is involved, it should be pointed out that the group assignments made in this study are intended only for the compounds in question. Excellent surveys of structure-absorption band correlation in infrared spectroscopy are available; for example, see the review by Barnes, Gore, Liddel, and Williams (9), (in which is incorporated a library of reference curves and a comprehensive bibliography through 1941) and by Rasmussen (10).

SUMMARY

The infrared absorption spectra of two stereoisomers of conidendrin and of the corresponding demethylated products were determined. A tentative correlation of the structure with the absorption bands is given.

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[CONTRIBUTION NO. 196 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY AND ENZYMOLOGY, FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. X. SYNTHESES OF THENAL- AND THENYL-BARBITURIC ACIDS

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Received February 13, 1950

The progress of syntheses in thiophene chemistry has been handicapped by the cumbersome methods of obtaining a pliable starting material. This situation was alleviated with the advent of the one-step preparation of 2-thiophenealdehyde (1). Some recent work (2) in this laboratory has been conducted with the purpose of utilizing this versatile reactant for the preparation of various 2-thienyl-substituted compounds.

In this communication are described the syntheses of several new 2-thenal- and 2-thenyl-substituted barbituric acids.

It was known that 2-thiophenealdehyde, I, can be condensed with malonic acid in the presence of pyridine and piperidine (3), with the formation of 2-thenylacrylic acid. It was found that if milder conditions were employed, this modification could be applied for the synthesis of 2-thenalmalonic acid (II). However, because of the danger of decarboxylation, it was necessary to keep the reaction temperature below 55°. By so doing, the yield of the dicarboxylic acid amounted to 45%. Prolonging the reaction time served to increase only the extent of decarboxylation but not the yields. We found that by employing alcoholic ammonia (4), 2-thenalmalonic acid could be obtained in excellent yield. The successful synthesis of this dicarboxylic acid facilitated the preparation of the new thenyl-substituted barbituric acids.

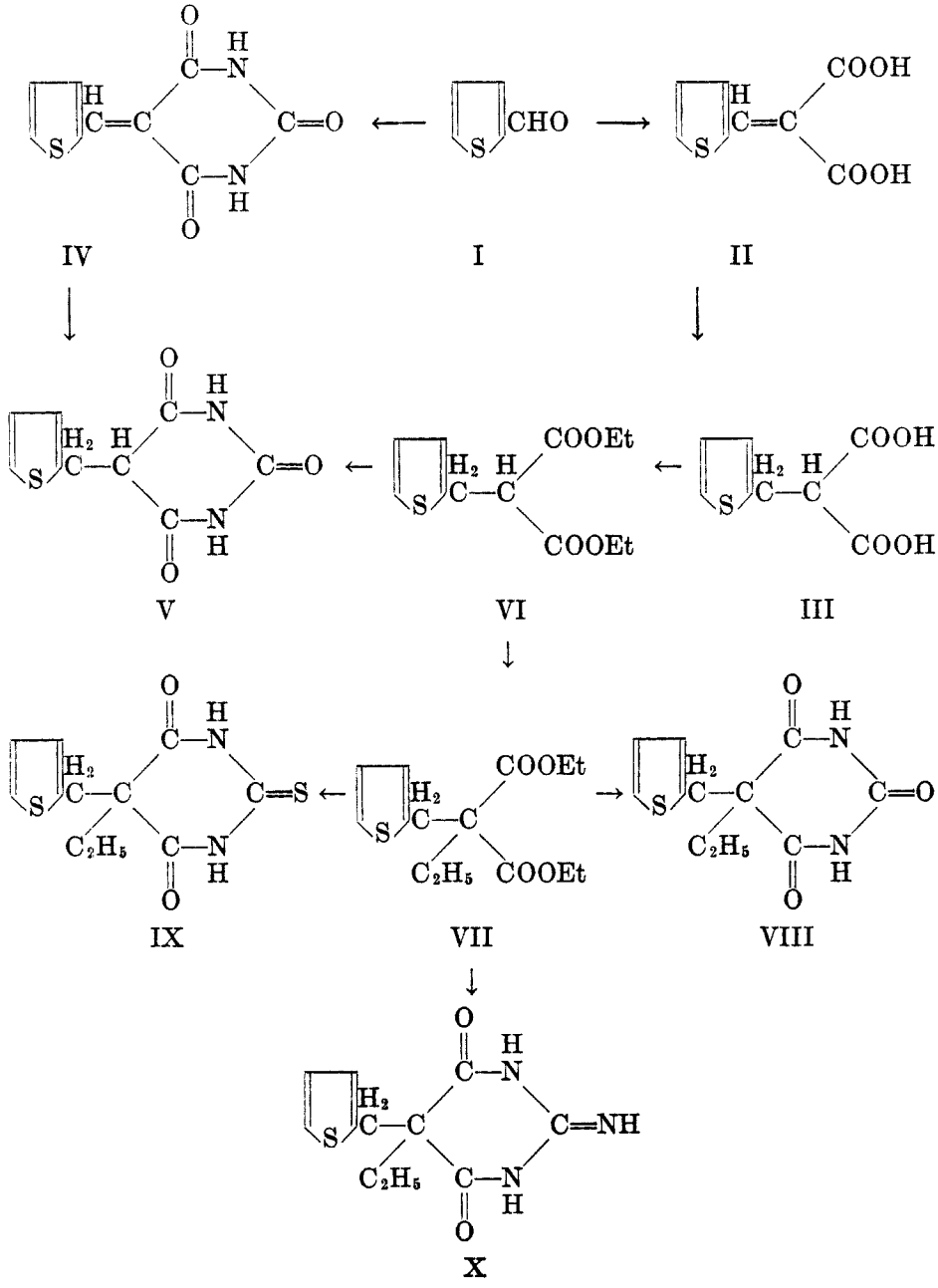
Upon reduction of II with sodium-amalgam in the presence of carbon dioxide, 2-thenylmalonic acid (III) was obtained. Maintaining the *p*H between 8 and 9, in this manner, reduced the reaction time from 72 hours to 24 hours. When mixed with an authentic sample of this saturated dicarboxylic acid, prepared according to an earlier method (5), a mixed melting point showed no depression. Esterification of 2-thenylmalonic acid and subsequent alkylation with ethyl bromide resulted in the formation of diethyl ethyl-(2-thenyl)malonate (VII). Upon condensation of this ester with urea, thiourea, and guanidine (as the carbonate) there was obtained 5-ethyl-5-(2-thenyl)barbituric acid (VIII), 5-ethyl-5-(2-thenyl)-2-thiobarbituric acid (IX), and 5-ethyl-5-(2-thenyl)-2-iminobarbituric acid (X), respectively.

In addition to the above named disubstituted barbituric acids it was found possible to prepare a number of monosubstituted, unsaturated barbituric acids, such as IV, by the direct condensation of 2-thiophenealdehyde with barbituric acid. These barbituric acids, listed in Table I, are yellow solids which melt at

[1] This investigation was carried out under the auspices of the Office of Naval Research. The analyses were obtained through the courtesy of Dr. F. Bühler, formerly of this Department.

[2] For paper No. IX of this series, see Gilsdorf and Nord, *J. Org. Chem.*, **15**, 307 (1950).

SCHEME I



high temperatures with decomposition and are insoluble in most organic solvents (6).

As a corroboration of the structure of these barbiturates, 5-(2-thenal)barbituric

TABLE I

MONOSUBSTITUTED, UNSATURATED THIOPHENE DERIVATIVES OF BARBITURIC ACID[a]

THIOPHENE-2-ALDEHYDES	PRODUCT	M.P., °C.	YIELD, %	ANALYSIS			
				Calc'd		Found	
				C	H	C	H
Thiophene-2-aldehyde	5-(2-Thenal)barbituric acid	330–333	98	48.64	2.72	48.45	2.57
3-Methylthiophene-2-aldehyde	5-(3-Methyl-2-thenal)barbituric acid	283–285	97	50.83	3.41	50.95	3.24
5-Bromothiophene-2-aldehyde[b]	5-(5-Bromo-2-thenal)barbituric acid	364–367	92	35.89	1.67	35.75	1.71
5-Chlorothiophene-2-aldehyde	5-(5-Chloro-2-thenal)barbituric acid	345–348	93	42.11	1.96	42.25	2.09
5-Methylthiophene-2-aldehyde[c]	5-(5-Methyl-2-thenal)barbituric acid	320–323	95	50.83	3.41	50.55	3.42
5-Ethylthiophene-2-aldehyde[c]	5-(5-Ethyl-2-thenal)barbituric acid	288–290	95	52.78	4.02	52.65	4.17
5-Propylthiophene-2-aldehyde[c]	5-(5-Propyl-2-thenal)barbituric acid	275–277	96	54.53	4.58	54.70	4.71

[a] In this series, melting points are not very characteristic, representing temperatures of decomposition that depend upon the rate of heating. [b] Ref. (8). [c] Ref. (9).

TABLE II

PHARMACOLOGICAL ACTIVITY

	COMPOUND	DOSE mg./kg. *per os*	NO. DEAD / NO. TREATED	LD_{50} mg./kg.	REMARKS
I	5-Ethyl-5-(2-thenyl)-barbituric acid	500 1000 1500	1/6 4/6 6/6	770	Light sleep, hyperexcitability, and convulsions
II	5-Ethyl-5-(2-thenyl)-2-thiobarbituric acid	500 1000 1500	2/6 3/6 5/6	950	Light sleep, hyperexcitability, and convulsions
III	5-Ethyl-5-(2-thenyl)-2-iminobarbituric acid	500 1000 1500 2000 3000 4000 5000	0/6 0/6 0/6 0/6 0/6 0/6 0/6	>5000	No hypnosis
IV	5-(5-Methyl-2-thenal)-barbituric acid	500 1000 2000 3000 4000 5000	0/6 0/6 0/6 0/6 0/6 0/6	>5000	No hypnosis

acid was reduced with zinc and acetic acid whereby 5-(2-thenyl)barbituric acid (V), was obtained. This saturated barbiturate was prepared subsequently by the condensation of VI with urea (7).

The data regarding the effectiveness of four of these new barbiturates are recorded in Table II and were obtained in the pharmacology laboratories of Hoffmann-La Roche Inc., Nutley, N. J., through the courtesy of Dr. L. O. Randall.

EXPERIMENTAL[3]

2-Thenalmalonic acid. Freshly distilled 2-thiophenealdehyde (28 g.) and 52.0 g. of malonic acid, previously dried over phosphorus pentoxide and 250 cc. of absolute ethyl alcohol saturated with anhydrous ammonia, were heated at 70–75° for four hours. Then 500 cc. of water was added and the solution was acidified with concentrated hydrochloric acid. The precipitate, recrystallized from dilute alcohol, gave faintly yellow plates of 2-thenalmalonic acid (85%), m.p. 206–207°.

Anal. Calc'd for $C_8H_6O_4S$: C, 48.47; H, 3.05.

Found: C, 48.55; H, 3.41.

2-Thenylmalonic acid. 2-Thenalmalonic acid (19.82 g.) was dissolved in 250 cc. of water with the aid of 10% sodium hydroxide until the solution was neutral. Finely divided 4% sodium-amalgam (400 g.) was added, the entire mixture was vigorously agitated, and a stream of carbon dioxide was passed into the liquid. At the end of 24 hours, the solution was carefully acidified with hydrogen chloride. The acidified solution was extracted three times with 150 cc. of ether, the ether extract washed successively with water and 10% sodium bicarbonate solution, and dried over Drierite. Upon removal of the ether, a yellow oil was obtained which, after cooling and scraping, solidified. Recrystallization from acetone-benzene gave white needles of 2-thenylmalonic acid (85%), m.p. 136–137°.[4]

Anal. Calc'd for $C_8H_8O_4S$: C, 48.20; H, 4.03.

Found: C, 48.25; H, 4.02.

Diethyl 2-thenylmalonate. 2-Thenylmalonic acid (40 g.) was esterified by refluxing gently for four hours with 200 cc. of absolute ethyl alcohol and 6 cc. of sulfuric acid. At the end of this time the excess alcohol was removed *in vacuo* and 250 cc. of water was added. The resulting solution was extracted twice with 150-cc. portions of ether, washed with water and 10% sodium bicarbonate, and dried over Drierite. Fractionation yielded diethyl 2-thenylmalonate (80%), b.p.[5] 125–128°/1–2 mm.

Anal. Calc'd for $C_{12}H_{16}O_4S$: C, 56.22; H, 6.29.

Found: C, 56.10; H, 6.01.

Diethyl ethyl-(2-thenyl)malonate. Diethyl 2-thenylmalonate (128.2 g.) was refluxed gently for one to two minutes in a solution of 14.0 g. of sodium and 500 cc. of absolute ethyl alcohol, and 75.0 g. of ethyl bromide was added dropwise. When the addition was completed, the mixture was refluxed vigorously until the solution was no longer alkaline. Excess ethyl alcohol was removed *in vacuo* and the oil was taken up in ether. Fractionation yielded diethyl ethyl-(2-thenyl)malonate (72%), b.p. 130–135°/1–2 mm.

Anal. Calc'd for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.08.

Found: C, 59.05; H, 7.06.

Ethyl (2-thenyl)malonic acid. Diethyl ethyl-(2-thenyl)malonate (3 g.) was refluxed for two hours with 20.0 g. of potassium hydroxide pellets, 40.0 g. of ethyl alcohol, and 40.0 g. of water. After acidification with sulfuric acid, the acid was treated in the manner described for 2-thenylmalonic acid, m.p. 127.5–128.5°.

Anal. Calc'd for $C_{10}H_{12}O_4S$: C, 52.62; H, 5.30.

Found: C, 52.80; H, 5.43.

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[3] Melting points were obtained with the Fischer-John apparatus.

[4] Blicke and Leonard reported 138–139°.

[5] Blicke and Leonard reported 149–152°/6 mm.

5-Ethyl-5-(2-thenyl)barbituric acid. Diethyl ethyl-(2-thenyl)malonate (10 g.), 2.43 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 10.55 g. of urea were refluxed gently for 18 hours. The alcohol was removed *in vacuo*, the residue was dissolved in water and acidified with 2 *N* hydrochloric acid. The precipitate was filtered and recrystallized from toluene. The white needles of 5-ethyl-5-(2-thenyl)barbituric acid (62%) melted at 207–208°.

Anal. Calc'd for $C_{11}H_{12}N_2O_3S$: C, 52.36; H, 4.79.
Found: C, 52.55; H, 4.67.

5-Ethyl-5-(2-thenyl)-2-thiobarbituric acid. Ten grams of diethyl ethyl-(2-thenyl)malonate, 2.43 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 13.35 g. of thiourea were treated as in the procedure described for the preparation of 5-ethyl-5-(2-thenyl)barbituric acid. After recrystallization from *o*-xylene the yellow plates of 5-ethyl-5-(2-thenyl)-2-thiobarbituric acid (49.5%) melted at 216–217°.

Anal. Calc'd for $C_{11}H_{12}N_2O_2S_2$: C, 49.26; H, 4.50.
Found: C, 49.55; H, 4.53.

5-Ethyl-5-(2-thenyl)-2-iminobarbituric acid. Ten grams of diethyl ethyl-(2-thenyl)-malonate, 7.29 g. of sodium dissolved in 150 cc. of absolute ethyl alcohol, and 15.00 g. of guanidine carbonate were treated as described in the two proceding sections. Purification was accomplished by repeated acidifications from alkaline solutions, m.p. 365–368°. The yield was 58%.

Anal. Calc'd for $C_{11}H_{13}N_3O_2S$: C, 52.57; H, 5.21.
Found: C, 52.55; H, 5.59.

GENERAL PROCEDURE FOR THE PREPARATION OF THENALBARBITURIC ACIDS

The procedure utilized was identical for all the thenalbarbituric acids.

5-(2-Thenal)barbituric acid. Barbituric acid (13 g.) was vigorously shaken with 2 liters of water at room temperature until solution was effected (usually from one to two hours). At the end of this time, 11.22 g. (0.1 mole) of freshly distilled 2-thiophenealdehyde was added and shaking was resumed. Within a short time, a lustrous, yellow solid was formed, but shaking was continued for an hour to insure the completeness of the reaction. After the addition of 250 g. of sodium chloride, the mixture was shaken for an additional one-half hour. After 12 hours in the refrigerator, the yellow, amorphous 5-(2-thenal)barbituric acid was filtered, washed with water to remove any unreacted barbituric acid, and washed with ether to remove any unreacted 2-thiophenealdehyde. The product (98%) was recrystallized from glacial acetic acid.

5-(2-Thenyl)barbituric acid. a. 5-(2-Thenal)barbituric acid (10 g.) was dissolved in 250 cc. of hot glacial acetic acid. An excess of zinc dust was added and the temperature was maintained at 70–75° until the intense, yellow color no longer persisted (usually from 10–20 minutes). The solution was cooled, filtered, and evaporated *in vacuo* yielding a faintly yellow mixture of zinc acetate and 5-(2-thenyl)barbituric acid. Upon recrystallization from water, there was obtained 8.8 g. of 5-(2-thenyl)barbituric acid, m.p. 214–215°.

Anal. Calc'd for $C_9H_8N_2O_3S$: C, 48.20; H, 3.59.
Found: C, 48.15; H, 3.71.

b. Diethyl 2-thenylmalonate (25.6 g.), 2.2 g. of sodium, and 6.0 g. of urea were refluxed for 7 hours in 100 cc. of absolute ethyl alcohol. The resulting crystals were dissolved in 80 cc. of hot water and acidified with concentrated hydrochloric acid. Upon recrystallization from water there was obtained 5-(2-thenyl)barbituric acid in 55% yield, m.p. 214–215°.

Anal. Calc'd for $C_9H_8N_2O_3S$: C, 48.20; H, 3.59.
Found: C, 48.25; H, 3.45.

SUMMARY

The syntheses of several 2-thenal- and 2-thenyl-barbituric acids are reported.

NEW YORK 58, N. Y.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

STUDIES CONCERNING WATER-SOLUBLE ORGANOTIN COMPOUNDS

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Received February 20, 1950

Although organotin compounds have shown little promise in the field of chemotherapy, the possibility that certain types may exhibit marked therapeutic properties is not precluded since so few of these compounds have been investigated. By sufficiently "masking" the tin and providing water-solubility, it is possible that the toxicity of these compounds might be reduced and their absorption in the body enhanced so that a more accurate estimate of their effectiveness in chemotherapy would be possible. This study was undertaken in an attempt to introduce water-solubilizing groups into organotin compounds, or to provide these compounds with reactive groups that might be utilized in subsequent reactions leading to water-soluble tin compounds.

Halogen-metal interconversion reactions (1) have opened up a new field in which organolithium compounds containing certain functional groups may be prepared in satisfactory yields (2, 3). These organolithium compounds may be used to introduce organic radicals containing functional groups into organotin compounds of the R_4Sn type. However, when compounds of the $R_3R'Sn$, $R_2R'_2Sn$, etc. types are to be prepared, it is desirable to convert these organolithium compounds into the corresponding organomagnesium compounds by means of anhydrous magnesium bromide to avoid formation of side products, probably by a redistribution reaction. The following new compounds were prepared by the use of the halogen-metal interconversion reaction: triphenyl-*o*-hydroxyphenyltin, triphenyl-*p*-hydroxyphenyltin, di-*o*-hydroxyphenyldiphenyltin, triphenyl-*o*-hydroxymethylphenyltin, and triphenyl-*p*-hydroxymethylphenyltin.

The halogen-metal interconversion reactions with the halogen-substituted phenols and benzyl alcohols give the lithium salts of the hydroxyphenyllithiums and hydroxymethylphenyllithiums. These can then be reacted directly, or, after conversion to the corresponding organomagnesium compounds, with the organotin halide to form the hydroxyl-containing organotin compound (I).

$$o\text{-}BrC_6H_4OH + 2\ n\text{-}C_4H_9Li \rightarrow o\text{-}LiC_6H_4OLi + 2\ n\text{-}C_4H_{10}$$

$$o\text{-}LiC_6H_4OLi + MgBr_2 \rightarrow o\text{-}BrMgC_6H_4OLi + LiBr$$

$$o\text{-}BrMgC_6H_4OLi + (C_6H_5)_3SnCl \rightarrow (C_6H_5)_3Sn(o\text{-}LiOC_6H_4) + MgBrCl$$

$$(C_6H_5)_3Sn(o\text{-}LiOC_6H_4) \xrightarrow{NH_4Cl\ (aqueous)} (C_6H_5)_3Sn(o\text{-}HOC_6H_4)$$

I

Attempts to prepare triphenyl-*p*-aminophenyltin by this method were unsuccessful. The reaction led to the formation of a red tar from which no definite compounds could be isolated. In one case, however, a small amount of material

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melting at 167–169° was obtained by resorting to purification through the hydrochloride. The tin content of this material approximated that of triphenyl-*p*-aminophenyltin but was not close enough to be conclusive.

Triphenyl-β-hydroxyethyltin (II) was prepared by the reaction of triphenyltin-sodium and ethylene oxide in liquid ammonia. This reaction proceeded smoothly, giving a 59% yield of (II).

$$(C_6H_5)_3SnCl + Na \xrightarrow{NH_3(l)} (C_6H_5)_3SnNa$$

$$(C_6H_5)_3SnNa + \underset{\backslash\,/\\ O}{CH_2CH_2} \longrightarrow (C_6H_5)_3SnCH_2CH_2ONa$$

$$(C_6H_5)_3SnCH_2CH_2ONa \xrightarrow{NH_4Cl\ (aqueous)} \underset{II}{(C_6H_5)_3SnCH_2CH_2OH}$$

The Grignard reagent or the organolithium compound can be prepared directly from the dimethylaminophenyl bromides. Therefore, triphenyl-*o*-dimethylaminophenyltin and triphenyl-*p*-dimethylaminophenyltin were prepared for subsequent studies in this manner without resorting to the halogen-metal interconversion reaction.

Potassium permanganate oxidation of triphenyl-*p*-hydroxymethylphenyltin (III) gave the expected triphenyl-*p*-carboxyphenyltin (IV), whereas oxidation

$$\underset{III}{(C_6H_5)_3Sn(p\text{-}C_6H_4CH_2OH)} + KMnO_4 \rightarrow (C_6H_5)_3Sn(p\text{-}C_6H_4COOK) \xrightarrow{H^+} \underset{IV}{(C_6H_5)_3Sn(p\text{-}C_6H_4COOH)}$$

of triphenyl-*o*-hydroxymethylphenyltin (V) in an analogous manner gave entirely unexpected results. The product after acidification from the oxidation of V was probably the inner salt of diphenyl-*o*-carboxyphenyltin hydroxide (VI), although its exact structure was not definitely established. This product (VI) after conversion to what was supposedly diphenyl-*o*-carboxyphenyltin chloride (VII) was esterified with diazomethane to give a product which was probably diphenyl-*o*-carbomethoxyphenyltin chloride (VIII). The tin contents of VI and VIII corresponded closely to those calculated for their assumed compositions. One possible set of reactions for the oxidation of V and subsequent reactions is given below.

$$3\,\underset{V}{(C_6H_5)_3Sn(o\text{-}C_6H_4CH_2OH)} + 4\,KMnO_4 \longrightarrow$$

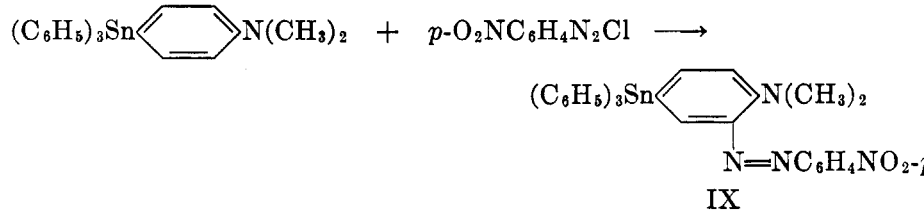
$$3\,(C_6H_5)_2Sn(o\text{-}C_6H_4COOK)OH + 3\,C_6H_6 + 4\,MnO_2 + KOH + H_2O$$

$$(C_6H_5)_2Sn(o\text{-}C_6H_4COOK)OH + HCl(dilute) \longrightarrow \underset{VI}{(C_6H_5)_2Sn(o\text{-}C_6H_4CO)}$$

$$(C_6H_5)_2Sn(o\text{-}C_6H_4CO) + HCl(6\,N) \longrightarrow (C_6H_5)_2Sn(o\text{-}C_6H_4COOH)Cl$$
$$\text{VII}$$

$$(C_6H_5)_2Sn(o\text{-}C_6H_4COOH)Cl + CH_2N_2 \longrightarrow (C_6H_5)_2Sn(o\text{-}C_6H_4COOCH_3)Cl + N_2$$
$$\text{VIII}$$

The coupling reaction between organotin compounds containing functional groups which facilitate azo compound formation and diazonium chlorides was studied. Apparently the diazonium chloride solution causes cleavage of the organotin compound. Of the numerous different coupling reactions attempted, only in the case of triphenyl-*p*-dimethylaminophenyltin could a pure tin-containing azo compound be isolated and then only after repeated recrystallization. The azo compound which was isolated was triphenyl-4-dimethylamino-3-(4′-nitrophenylazo)phenyltin (IX) from the reaction of triphenyl-*p*-dimethylaminophenyltin and *p*-nitrobenzenediazonium chloride.



IX

Several additional reactions were investigated as possible means for introducing functional groups into organotin compounds. Attempts to introduce the sulfonyl chloride group directly into tetraphenyltin gave only cleavage products even at −75°. No apparent reaction between phenylboric acid and stannic chloride was observed; therefore, substituted phenylboric acids containing functional groups were not investigated. Tetraphenyltin was not affected by prolonged heating with an alkaline solution, but triphenyl-*o*-hydroxyphenyltin was cleaved, thereby excluding the Reimer-Tiemann reaction as a possible method for the introduction of an aldehyde group in organotin compounds.

EXPERIMENTAL

Triphenyltin chloride from tetraphenyltin and stannic chloride. Triphenyltin chloride was prepared from tetraphenyltin and stannic chloride by a method similar to that described by Kocheshkov and co-workers (4).

Triphenyltin iodide. Triphenyltin iodide was prepared according to the method described by Chambers and Scherer (5) for the preparation of triphenyltin bromide with triphenyltin iodide as an intermediate which was not isolated.

After the iodine was added, the chloroform and iodobenzene were removed by distillation, the latter under reduced pressure. A Soxhlet extractor was then employed to extract the crude triphenyltin iodide from the unreacted tetraphenyltin with ether. After crystallization from petroleum ether (b.p. 77–117°), there was obtained a 70% yield of pure triphenyltin iodide melting at 119–121°.

Tetraethyltin. Tetraethyltin was prepared by the reaction of ethyl bromide and an alloy

of tin, sodium, and zinc according to the method described by Harada (6). The "large excess" of ethyl bromide to which Harada refers is greater than 60% since a smaller excess results in a violent reaction which takes place several hours after the reactants are mixed and gives very poor yields of tetraethyltin.

Triethyltin bromide. Triethyltin bromide was prepared by slowly adding 11.2 g. (0.070 mole) of bromine to 16.4 g. (0.070 mole) of tetraethyltin which was stirred and cooled in an ice-salt bath. By fractional distillation of the resulting liquid there was collected 17.6 g. (88%) of triethyltin bromide boiling at 105–107° (15 mm.), n_D^{20} 1.5240.

Diphenyltin dichloride. Diphenyltin dichloride was prepared in a manner similar to that described by Kocheshkov (7).

Anhydrous magnesium bromide. Bromine was added slowly to a large excess of magnesium turnings in ether. The large excess of magnesium was used to prevent the formation of small fragments of magnesium which are difficult to remove when the solution is filtered through glass wool. Both layers which form during the preparation were used since the ether layer contains some magnesium bromide in solution.

Triphenyl-o-hydroxyphenyltin. To a cold solution of 0.246 mole of *n*-butyllithium in 490 cc. of ether was added rapidly 21.3 g. (0.123 mole) of *o*-bromophenol in 25 cc. of ether. After 40 minutes 0.25 mole of anhydrous magnesium bromide in approximately 100 cc. of ether was added. Then 47.4 g. (0.123 mole) of triphenyltin chloride was added and after the mixture had stirred for two hours, it was hydrolyzed with a cold solution of ammonium chloride and the ether layer was dried over sodium sulfate. The ether was removed by distillation and the residue boiled for ten minutes with 100 cc. of ethanol to remove unreacted materials. After the mixture was cooled, it was filtered and the residue, which consisted of crude triphenyl-*o*-hydroxyphenyltin, was crystallized from chloroform. Yield, 31 g. (57%) of pure triphenyl-*o*-hydroxyphenyltin which melted with decomposition between 176–182°, depending on the rate of heating. When the temperature was raised from 170° to 176° over a period of nine minutes the compound melted with decomposition at 176–177°.

Anal. Calc'd for $C_{24}H_{20}OSn$: Sn, 26.81. Found: Sn, 26.70.

Triphenyl-p-hydroxyphenyltin, di-o-hydroxyphenyldiphenyltin, triethyl-o-hydroxyphenyltin, triphenyl-o-hydroxymethylphenyltin, and triphenyl-p-hydroxymethylphenyltin. These compounds were all prepared in essentially the same manner as described for triphenyl-*o*-hydroxyphenyltin. Tables I and II contain the details of their preparation and their physical properties.

Reaction of triphenyltin iodide and p-aminophenyllithium. A solution of 0.190 mole of *n*-butyllithium in 240 cc. of ether was added to 10.9 g. (0.063 mole) of *p*-bromoaniline in 50 cc. of ether. After the mixture had been stirred for one hour, during which time a yellow precipitate formed, a slight excess of anhydrous magnesium bromide in ether was added. Then 21.2 g. (0.0444 mole) of triphenyltin iodide was added, and the mixture was stirred for 15 minutes before it was hydrolyzed with ice-water. After the ether layer was dried over sodium sulfate the solvent was removed. The red residue which resulted was boiled with ethanol and then recrystallized from chloroform-methanol yielding a red solid melting between 185° and 200°.

Attempts to purify this material invariably led to the formation of a considerable amount of red tar. A portion of this impure red solid was dissolved in ether and precipitated as the hydrochloride with dry hydrogen chloride gas. The hydrochloride was quickly filtered and the free amine was regenerated with dilute ammonium hydroxide. The dark yellow material thus obtained melted at 167–169°. Purification of this material thru the hydrochloride was not very successful since less than 20% was recovered. Cleavage of the tin-carbon linkage by hydrogen chloride undoubtedly occurred to a large extent during the time required to precipitate the hydrochloride. The values for the tin content of the material melting at 167–169° were too high for triphenyl-*p*-aminophenyltin to be conclusive.

Anal. Calc'd for $C_{24}H_{21}NSn$: Sn, 26.85. Found: Sn, 27.7 and 27.7.

Triphenyl-β-hydroxyethyltin. Triphenyltin-sodium was prepared by adding slowly 2.76 g. (0.12 gram-atom) of sodium to a stirred solution of 23.1 g. (0.06 mole) of triphenyltin

TABLE I

ORGANOTIN COMPOUNDS CONTAINING HYDROXYL GROUPS

NO.	ORGANOTIN COMPOUND	FORMULA	YIELD, %	M.P., °C.	ANALYSIS, Sn, %	
					Calc'd	Found
1	Triphenyl-*p*-hydroxyphenyltin	$(C_6H_5)_3Sn(p\text{-}C_6H_4OH)$	10	201–203[a]	26.81	27.2, 27.4
2	Di-*o*-hydroxyphenyldiphenyltin	$(C_6H_5)_2Sn(o\text{-}C_6H_4OH)_2$	68	136–138[a]	25.88	26.2, 26.35
3	Triethyl-*o*-hydroxyphenyltin[b]	$(C_2H_5)_3Sn(o\text{-}C_6H_4OH)$	54	155–156/15 mm.	39.74	39.85
4	Triphenyl-*o*-hydroxymethylphenyltin	$(C_6H_5)_3Sn(o\text{-}C_6H_4CH_2OH)$	64	158–159	25.99	26.4, 26.4
5	Triphenyl-*p*-hydroxymethylphenyltin	$(C_6H_5)_3Sn(p\text{-}C_6H_4CH_2OH)$	66	98–100	25.99	26.0, 26.2

[a] Melting points depend on rate of heating. Rates used: (1) 190–201°/10 min., (m.p. 210–211° by heating 190–210°/5 min.); (2) 120–136°/5 min. [b] Density, d_4^{25} 1.3150, refractive index n_D^{25} 1.5379.

TABLE II

PREPARATION DETAILS OF ORGANOTIN COMPOUNDS CONTAINING HYDROXYL GROUPS

NO.	ORGANIC HALIDE SOLN.			*n*-C_4H_9Li SOLN.		STIR. TIME (min.)	$MgBr_2$[a] (moles)	$(C_6H_5)_3SnCl$ (moles)	STIR. TIME (min.)	RECRYSTALLIZATION MEDIUM
	RX	(moles)	ETHER (cc.)	*n*-C_4H_9Li (moles)[b]	ETHER (cc.)					
1	*p*-BrC_6H_4OH	0.098	50	0.196	245	75	0.225[c]	0.054	120	Methanol; $CHCl_3$-pet. ether (77–117°)
2	*o*-BrC_6H_4OH[d]	.105	25	.21	250	50	.27[c]	.042[e]	90	Ether-pet. ether (28–380°)
3	*o*-BrC_6H_4OH	.0565	50	.113	290	45	.12	.0565[f]	[g]	Fractionally distilled
4	*o*-$BrC_6H_4CH_2OH$[d,h]	.0965	50	.193	240	60	.22	.0835[i]	60	Ethanol; $CHCl_3$-pet. ether (77–117°)
5	*p*-$BrC_6H_4CH_2OH$[d,j]	.107	50	.214	240	60	.225	.0856	60	Ethanol-H_2O; benzene-pet. ether (60–68°)

[a] Approximate concentration 1 mole $MgBr_2$/500 cc. ether. Stirred with *n*-C_4H_9Li approximately 15 min. [b] Determined by the analytical procedure of Gilman and Haubein (8). [c] The organotin compound could not be prepared when the $MgBr_2$ was omitted. [d] *n*-Butyllithium added to RX. [e] $(C_6H_5)_2SnCl_2$ used instead of $(C_6H_5)_3SnCl$. [f] $(C_2H_5)_3SnBr$ in 25 cc. of ether. [g] Permitted to stand overnight. [h] Prepared in a manner similar to that described for the preparation of *p*-bromobenzyl alcohol by Gilman and Melstrom (3). [i] Enough added to give a negative color test. [j] Prepared as described by Gilman and Melstrom (3).

chloride in 300 cc. of liquid ammonia. The ammonia was then permitted to evaporate until approximately 50 cc. remained. Ether (200 cc.) was added and the remaining ammonia was removed in a vacuum (100 mm.). After this treatment, a yellow amorphous precipitate of triphenyltin-sodium had formed. Then an excess of ethylene oxide (approximately 15 g.) in ether was added to the triphenyltin-sodium which was cooled in an ice-bath. After one hour of stirring, the mixture was hydrolyzed with ice-water and then the ether layer was dried over sodium sulfate. Removal of the ether followed by crystallization of the product from petroleum ether (b.p. 77–117°) gave 19.4 g. of crude β-hydroxyethyltriphenyltin melting at 67–69° (with turbidity). A second crystallization from the same solvent did not change the melting point. From methanol, however, after removal of a small amount of insoluble material from the hot solution by filtration, there was obtained 13.8 g. or a 59% yield of β-hydroxyethyltriphenyltin melting at 65–68° without turbidity. A second recrystallization of a small portion of this material from methanol decreased the melting point range to 67–68°. The chief impurity was probably hexaphenylditin (m.p. 237°).

The analysis was made on the material melting at 67–68°.

Anal. Calc'd for $C_{20}H_{20}OSn$: Sn, 30.05. Found: Sn, 30.35, 30.8.

Triphenyl-o-dimethylaminophenyltin. To a solution of *o*-dimethylaminophenylmagnesium bromide, prepared from 14.0 g. (0.07 mole) of *o*-bromodimethylaniline and 1.8 g. (0.074 gram-atom) of magnesium in 200 cc. of ether, was added 19.9 g. (0.042 mole) of triphenyltin iodide. After the solution had been stirred for 45 minutes, it was hydrolyzed with a cold ammonium chloride solution and the ether layer was dried over sodium sulfate. The ether was removed and to the resulting viscous liquid was added 50 cc. of boiling methanol. The crystals obtained by cooling the methanol solution were recrystallized twice from methanol, by first effecting solution with the minimum amount of chloroform. There was obtained 12.6 g. or a 64% yield, based on the triphenyltin iodide, of triphenyl-*o*-dimethylaminophenyltin melting at 110–112°.

Anal. Calc'd for $C_{26}H_{25}NSn$: Sn, 25.28. Found: Sn, 25.7.

Triphenyl-p-dimethylaminophenyltin. The *p*-dimethylaminophenyllithium used was prepared from 13.0 g. (0.065 mole) of *p*-bromodimethylaniline and 0.98 g. (0.14 gram-atom) of lithium in 250 cc. of ether. The solution was permitted to stand for two hours before the clear liquid was decanted carefully through glass wool. The solution of 0.058 mole of *p*-dimethylaminophenyllithium in 235 cc. of ether was added to 22.3 g. (0.058 mole) of triphenyltin chloride in 100 cc. of ether. The mixture was stirred for three hours and then permitted to stand overnight before it was hydrolyzed with a cold solution of ammonium chloride. The ether layer was dried over sodium sulfate and the solvent was removed. The resulting residue was dissolved in the minimum amount of chloroform and 200 cc. of hot ethanol was added. The solution was concentrated to approximately 200 cc., cooled, and the triphenyl-*p*-dimethylaminophenyltin which separated was removed. Yield, 17 g. (62%) of triphenyl-*p*-dimethylaminophenyltin; m.p. 132–134° after two recrystallizations from petroleum ether (b.p. 77–117°).

Anal. Calc'd for $C_{26}H_{25}NSn$: Sn, 25.28. Found: Sn, 25.7.

Oxidation of triphenyl-p-hydroxymethylphenyltin to triphenyl-p-carboxyphenyltin. Over a period of four hours, 7.37 g. (0.0467 mole) of solid potassium permanganate was added, in small amounts, to 16.0 g. (0.035 mole) of triphenyl-*p*-hydroxymethylphenyltin in 150 cc. of alcohol-free acetone. The mixture was allowed to stir one hour longer or until the potassium permanganate color disappeared, and the precipitate was removed and washed with 20 cc. of acetone. The precipitate, consisting of manganese dioxide and the potassium salt of triphenyl-*p*-carboxyphenyltin, was dried in a vacuum desiccator over calcium chloride and finally was extracted with three 75-cc. portions of boiling 95% ethanol. The ethanol extract was cooled and carefully acidified with dilute hydrochloric acid using Methyl Orange as an indicator. Then a few drops of base were added to render the solution just basic to Methyl Orange. The potassium chloride was separated and the ethanol solution was concentrated under reduced pressure to a volume of 100 cc. The warm solution was then carefully acidified to Methyl Orange and diluted slowly with water until a considerable

amount of crystals had formed. The solution was cooled and 9.1 g. of crude triphenyl-*p*-carboxyphenyltin melting at 164–166° was removed. After one recrystallization from ethanol-water, there was obtained 7.2 g. or a 44% yield of pure triphenyl-*p*-carboxyphenyltin melting at 166–168°.

Anal. Calc'd for $C_{25}H_{20}O_2Sn$: Sn, 25.22; Neut. equiv., 471.

Found: Sn, 25.0, 25.25; Neut. equiv., 470, 472.

Oxidation of triphenyl-o-hydroxymethylphenyltin. To a solution of 16.0 g. (0.035 mole) of triphenyl-*o*-hydroxymethylphenyltin in 150 cc. of alcohol-free acetone was added 7.37 g. (0.0467 mole) of solid potassium permanganate in small portions over a period of five hours. Manganese dioxide was removed and the acetone was evaporated; to the resulting residue was added 30 cc. of 75% ethanol. From this solution, after cooling, there was removed 6.4 g. (40%) of unreacted triphenyl-*o*-hydroxymethylphenyltin. The mother liquor was then acidified (Methyl Orange) with hydrochloric acid and there was obtained 6.6 g. of material which did not melt below 340°. From the manganese dioxide after extraction with alcohol and acidification, there was obtained an additional 0.84 g. of material which did not melt below 340°. The combined portions of material which did not melt were dissolved in a large volume of warm dilute sodium hydroxide and filtered. The filtrate was acidified with acetic acid and the precipitate removed. It was heated with distilled water and then filtered. This material was insoluble in the common organic solvents and did not melt below 340°. No reaction with diazomethane could be detected when this material was suspended in an ether solution of diazomethane. The value for the tin content corresponded closest to that of the inner salt of diphenyl-*o*-carboxyphenyltin hydroxide. The yield of the crude product, assuming it was the inner salt of diphenyl-*o*-carboxyphenyltin hydroxide was 7.44 g. or 54%.

Anal. Calc'd for $C_{19}H_{14}O_2Sn$: Sn, 30.23. Found: Sn, 30.5 and 30.6.

The material which was assumed to be the inner salt of diphenyl-*o*-carboxyphenyltin hydroxide was suspended in ethanol and cold concentrated hydrochloric acid was added until a clear solution resulted after a few minutes. To this clear solution there was added enough 6 *N* hydrochloric acid to precipitate all of the organic material from the alcohol solution. The product, which was assumed to be diphenyl-*o*-carboxyphenyltin chloride, sintered at approximately 200° but did not melt below 340°.

In order to obtain a compound with a melting point this material was dissolved in ether and treated with diazomethane. The product so obtained melted at 168–169° after one crystallization from methanol and was assumed to be diphenyl-*o*-carbomethoxyphenyltin chloride.

Anal. Calc'd for $C_{20}H_{17}ClO_2Sn$: Sn, 26.78. Found: Sn, 27.0 and 27.1.

Triphenyl-4-dimethylamino-3-(4′-nitrophenylazo)phenyltin. A mixture of 7.05 g. (0.05 mole) of triphenyl-*p*-dimethylaminophenyltin in 150 cc. of ethyl acetate and 8.2 g. of sodium acetate in 100 cc. of water was cooled in an ice-bath. To this mixture there was added slowly with vigorous stirring a cold solution of *p*-nitrobenezenediazonium chloride, prepared from 2.07 g. (0.015 mole) of *p*-nitroaniline and 1.04 g. (0.015 mole) of sodium nitrite in 6 cc. of concentrated hydrochloric acid and 15 cc. of water. When the *p*-nitrobenzenediazonium chloride solution was all added the ice-bath was removed and the solution was stirred for two hours, during which a dark red solution was formed. The ethyl acetate was then permitted to evaporate and the amorphous red solid which was left was stirred with 100 cc. of distilled water and then filtered. The red solid was then boiled with 50 cc. of ethanol, cooled, and filtered. The treatment with ethanol was then repeated once more before the red solid was crystallized twice from chloroform-petroleum ether (b.p. 77–117°). After the recrystallizations from chloroform-petroleum ether, there was obtained 1.62 g. (17.5%) of dark yellow material containing tin and nitrogen and melting at 188–190°. The nitrogen content was found to be 10.0% as compared to 9.05% calculated for triphenyl-4-dimethylamino-3-(4′-nitrophenylazo)phenyltin. Since it apparently contained a small amount of azo compound from the cleavage of the organotin compound, another recrystallization was carried out by dissolving in chloroform and adding hot ethanol. From this

recrystallization the *triphenyl-4-dimethylamino-3-(4'-nitrophenylazo)phenyltin* separated as a bright yellow solid melting at 190–192°.

Anal. Calc'd for $C_{32}H_{28}N_4O_2Sn$: Sn, 19.20. Found: Sn, 19.80.

Tetraphenyltin and chlorosulfonic acid. To a suspension of 10.65 g. (0.025 mole) of powdered tetraphenyltin in unsaturate-free petroleum ether (b.p. 28–38°) at −75° was added 5.84 g. (0.050 mole) of chlorosulfonic acid. The mixture was stirred for five minutes, and a thick gum was formed. Liquid ammonia, followed by concentrated ammonium hydroxide, was carefully added to the mixture before it was filtered. The filter cake was extracted and crystallized from chloroform; there was obtained 4.0 g. or a 38% recovery of pure tetraphenyltin. From the mother liquor used to crystallize the tetraphenyltin there was obtained 0.7 g. of diphenylsulfone (mixed m.p.) melting at 122–124°. From the neutralized ammonium hydroxide solution was obtained 1.9 g. of material which would not melt when heated. The physical properties of this material indicated that it was metastannic acid.

Phenylboric acid and stannic chloride. A solution containing 5.21 g. (0.02 mole) of stannic chloride and 12.8 g. (0.10 mole) of phenylboric acid in 30 cc. of water was refluxed for nine hours. During this time no precipitate nor oil separated, indicating that no organotin compound was formed. After the solution was cooled, the unreacted phenylboric acid was removed and recrystallized from water. There was recovered 8.8 g. or 69% of pure phenylboric acid melting at 218–220°. A strong odor of benzene was detected in the reaction mixture, probably from the decomposition of the phenylboric acid by prolonged heating with water.

Tetraphenyltin and alcoholic sodium hydroxide. A mixture of 10 g. of tetraphenyltin and 40 g. of sodium hydroxide in 200 cc. of 95% ethanol was refluxed for three hours. After the mixture was cooled 300 cc. of distilled water was added and the solution was filtered. After one crystallization from chloroform 9.5 g. or 95% of the tetraphenyltin was recovered.

Triphenyl-o-hydroxyphenyltin and alcoholic sodium hydroxide. This reaction was carried out in exactly the same manner as previously described with tetraphenyltin. A strong odor of benzene was noted in the reaction mixture. Since no precipitate formed when it was poured into water, no unreacted triphenyl-*o*-hydroxyphenyltin (insoluble in base), triphenyltin hydroxide, or diphenyltin oxide could be present. Carbon dioxide was then passed into the solution and some amorphous precipitate, which would not melt, separated. The precipitate contained tin but charred only slightly on ignition indicating that it probably consisted of metastannic acid or phenylstannonic acid or a mixture of both.

SUMMARY

The usefulness of halogen-metal interconversion products for the preparation of organotin compounds containing functional groups has been demonstrated in the preparation of triethyl-*o*-hydroxyphenyltin, triphenyl-*o*-hydroxyphenyltin, triphenyl-*p*-hydroxyphenyltin, di-*o*-hydroxyphenyldiphenyltin, triphenyl-*o*-hydroxymethylphenyltin, and triphenyl-*p*-hydroxymethylphenyltin. The desirability of converting these organolithium halogen-metal interconversion products into the Grignard reagents prior to reaction with the organotin compounds was also demonstrated.

The preparation of triphenyl-*p*-aminophenyltin has been attempted but the identity of the small amount of relatively pure product which was isolated could not be established.

Triphenyl-β-hydroxyethyltin has been prepared.

Triphenyl-*o*-dimethylaminophenyltin and triphenyl-*p*-dimethylaminophenyltin have been prepared.

Triphenyl-*p*-carboxyphenyltin has been prepared by the oxidation of triphenyl-*p*-hydroxymethylphenyltin with potassium permanganate.

Oxidation of triphenyl-*o*-hydroxymethylphenyltin by potassium permanganate gives a product which is probably the inner salt of diphenyl-*o*-carboxyphenyltin hydroxide. From this product, two derivatives have been prepared which are probably diphenyl-*o*-carboxyphenyltin chloride and diphenyl-*o*-carbomethoxyphenyltin chloride.

Triphenyl-4-dimethylamino-3-(4′-nitrophenylazo)phenyltin has been prepared from triphenyl-*p*-dimethylaminophenyltin and *p*-nitrobenzenediazonium chloride.

Attempts to introduce the sulfonyl chloride group directly into tetraphenyltin gave cleavage products even at −75°.

There is no apparent reaction between phenylboric acid and stannic chloride in a hot aqueous solution.

Tetraphenyltin is not affected by prolonged heating with alcoholic sodium hydroxide whereas triphenyl-*o*-hydroxyphenyltin is cleaved under the same conditions.

AMES, IOWA

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

THE SYNTHESIS OF MORPHAN (2-AZABICYCLO[3.3.1]NONANE)[1]

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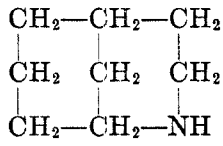
The bicyclic secondary amine morphan (I) is of interest as it constitutes both a portion of the morphine molecule (heavy lines in structure II) and of the strychnine structure in its recently suggested modification (2). It has been synthesized by a sequence of relatively simple transformations.

When ethyl *m*-nitrophenylacetate was reduced in *glacial acetic acid*, using Adams' catalyst, six moles of hydrogen were absorbed, and two compounds isolated: ethyl *cis*-(3-aminocyclohexyl)acetate (III) and—due to cyclisation in the course of distillation—the lactam of *cis*-(3-aminocyclohexyl)acetic acid (IV). Also the reduction of 3-nitrophenylacetic acid in glacial acetic acid yields—at any rate, preponderantly (isolated 75%)—the corresponding *cis*-acid, m.p. 269° (dec.). [Cronyn (1) gives m.p. 272–273°].

Protiva and Sorm (3) obtained a (3-aminocyclohexyl)acetic acid (m.p. 230°) which did not yield a lactam and consequently was considered to have the *trans*-configuration. The *cis*-configuration of III follows from the fact that upon prolonged heating and distillation it yields the lactam (IV) as is often the case with esters of δ- and ϵ-amino acids (4). The *cis*-directing influence of acidic media in such hydrogenation reactions has been observed previously (5, 6).

The lactam (IV) is reduced to morphan (I) by means of lithium aluminum hydride in accordance with similar observations of Ruzicka and co-workers (7).



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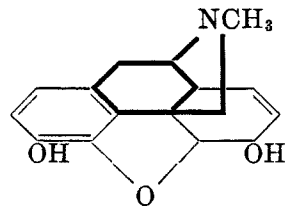

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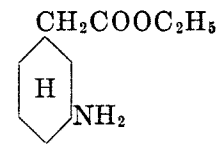
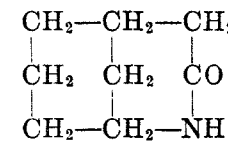


III



IV

[1] The investigation reported here was ready for publication when the paper by Cronyn (1) was received in Rehovoth. The present paper is believed not only to corroborate Cronyn's results, but also to contain a number of interesting observations which seem to warrant its publication.

EXPERIMENTAL[2]

Ethyl m-nitrophenylacetate. This ester was prepared by the following sequence of reactions: *m*-nitrobenzaldehyde $\xrightarrow[92\%]{Al(OC_3H_7)_3}$ *m*-nitrobenzylalcohol $\xrightarrow[100\%]{\text{HBr in benzene}}$ *m*-nitrobenzyl-bromide (8) $\xrightarrow[60\%]{NaCN}$ *m*-nitrophenylacetonitrile (9, 10) $\xrightarrow[90\%]{20\%\ HCl}$ *m*-nitrophenylacetic acid (9, 11, 12) $\xrightarrow[97\%]{\text{azeotropic esterification}}$ ethyl *m*-nitrophenylacetate (12).

The reduction of other nitroaldehydes to the corresponding nitroalcohols by means of aluminum isopropoxide has been observed before (13–15).

Ethyl 3-aminophenylacetate. A mixture of 2.09 g. of ethyl-*m*-nitrophenylacetate, 0.2 g. of Adams' platinum oxide, and 50 ml. of absolute ethanol was hydrogenated at room temperature and 25 p.s.i. of hydrogen. The reduction was complete in five hours. Only three moles of hydrogen were absorbed. The catalyst was removed and the solvent distilled. Distillation of the residue yielded 1.8 g. of ethyl 3-aminophenylacetate, b.p. 118°/0.1 mm.

Anal. Calc'd for $C_{10}H_{13}NO_2$: C, 67.0; H, 7.3; N, 7.8.
Found: C, 67.2; H, 7.3; N, 8.0.

Cronyn (1) reports b.p. 138–140° (3–4 mm.).

Ethyl cis-(3-aminocyclohexyl)acetate (III) *and lactam* (IV). A mixture of 2.09 g. of ethyl *m*-nitrophenylacetate, 0.2 g. of Adams' platinum oxide, and 50 ml. of *glacial acetic acid* was hydrogenated as above at room temperature and 25 p.s.i. of hydrogen. After 2–3 hours, three moles of hydrogen had been absorbed. When the temperature was raised (to 35–40°), the hydrogen uptake continued although somewhat more slowly (four hours), until six moles had been taken up. Treatment as above gave 1.8 g. of an oil, b.p. 132°/37 mm. This was triturated with anhydrous ether and crystallized on prolonged standing in the refrigerator. The ethyl *cis*-(3-aminocyclohexyl)acetate (III) thus obtained melted at 112°.

Anal. Calc'd for $C_{10}H_{19}NO_2$: C, 64.8; H, 10.3; N, 7.6.
Found: C, 64.8; H, 10.1; N, 7.4.

When this reduction was scaled up (4 to 20 times the above quantities), it was impossible to obtain only the ester. Apparently, when larger amounts of ester are distilled (bath temperature of 150°), lactamization partially occurs. A first fraction of the ester (about 10–20%) was followed by the lactam (IV) (20–30%), b.p. 170–190°/37 mm. The compound solidified spontaneously and was recrystallized from anhydrous ether. M.p. 167–168.5°. Cronyn (1) reports m.p. 163.5–165.5°.

Anal. Calc'd for $C_8H_{13}NO$: C, 69.0; H, 9.4; N, 10.1.
Found: C, 69.4; H, 9.4; N, 10.1.

A higher-boiling fraction (over 200°/37 mm.) was also observed, which according to analysis may consist of diethyl 3-imino-bis(cyclohexylacetate).

Anal. Calc'd for $C_{20}H_{35}NO_4$: N, 4.0. Found: N, 4.25.

When 2.0 g. of ethyl *cis*-(3-aminocyclohexyl)acetate, m.p. 112°, was heated *in vacuo* (bath temperature 140–150°) for 3 hours and then distilled, 1.32 g. of the lactam (IV) was obtained, m.p. 167–168° from anhydrous ether.

Morphan (I). A solution of 3.5 g. of the lactam (IV) in 50 ml. of anhydrous dioxane was added, with stirring, to a boiling suspension of 2 g. (excess) of lithium aluminum hydride in 100 ml. of dioxane. The mixture was refluxed for four hours after the addition was complete. It was then cooled and cautiously decomposed by the addition of excess sodium hydroxide solution, extracted with dioxane, and the extract thoroughly dried with solid potassium hydroxide. Upon distillation, 2.9 g. of an oil was obtained, consisting of unchanged starting material and an amine. It was taken up in 20% hydrochloric acid and the solution thoroughly extracted with ether. The acid phase was then made alkaline and

[2] All melting and boiling points are uncorrected.

the oil which separated (1.6 g.) taken up in ether and converted into the hydrochloride (1.2 g.). It melted at 288° (dec.). Cronyn (1) reports for material which was sublimed, m.p. 300–302° (dec.).

Anal. Calc'd for $C_8H_{16}ClN$: Cl, 22.0. Found: Cl, 22.3 (Volhard titration).

To a cold aqueous solution of the hydrochloride, dilute alkali was added with vigorous stirring. Upon seeding, the oily base was induced to crystallize; it showed m.p. 131–132° and had all properties of a secondary amine. Cronyn (1) reports m.p. 135–137° for material which was sublimed.

cis-(3-Aminocyclohexyl)acetic acid. A mixture of 1.8 g. of *m*-nitrophenylacetic acid, 0.2 g. of Adams' catalyst, and 50 ml. of glacial acetic acid was shaken with hydrogen at 25 p.s.i. and room temperature until six moles of hydrogen had been absorbed. Catalyst and solvent were removed and the oily residue triturated with acetone. Recrystallization from aqueous ethanol gave 1.2 g. of *cis*-(3-aminocyclohexyl)acetic acid, m.p. 269° (dec.). Cronyn (1) reports m.p. 272–273° (dec.).

Anal. Calc'd for $C_8H_{15}NO_2$: C, 61.1; H, 9.5; N, 8.9.
Found: C, 61.6; H, 9.5; N, 9.15.

A sample (0.5 g.) of the acid was heated in a sealed tube at 200° for three hours. On trituration with ether, the product gave 0.25 g. of the lactam (IV), m.p. 165°. The melting point was not depressed by admixture of a sample obtained from the ester (III).

SUMMARY

1. Reduction of ethyl *m*-nitrophenylacetate in glacial acetic acid yielded ethyl *cis*-(3-aminocyclohexyl)acetate (III) and—through cyclization in the course of the treatment—the lactam (IV) of *cis*-(3-aminocyclohexyl)acetic acid.

2. Reduction of the lactam (IV) with lithium aluminum hydride yielded morphan, 2-azabicyclo[3.3.1]nonane (I).

REHOVOTH, ISRAEL

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF OREGON]

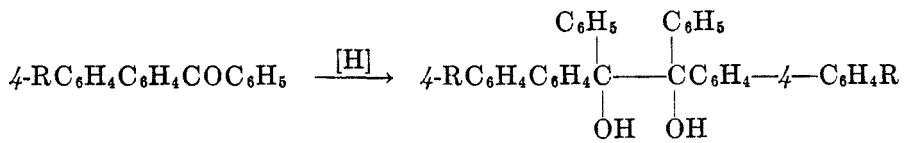
THE REDUCTION OF DIARYL KETONES TO STEREOISOMERIC BENZOPINACOLS

RUSSELL GAERTNER

Received March 13, 1950

In this report we wish to describe the isolation of a pair of stereoisomeric benzopinacols from each of two diaryl ketones, *p*-phenylbenzophenone (I) and 4-(*p*-anisyl)benzophenone (II), by the action of phenylmagnesium bromide containing unchanged magnesium. Some reactions of the products are considered.

p-Phenylbenzophenone (I) was added to a phenyl Grignard reagent which contained some unconverted metal, and two isomeric benzopinacols were easily isolated from the hydrolyzed reaction mixture. The more insoluble compound (IIIb), identified by analysis and thermal dismutation to the starting ketone, melted in thirty seconds at 206–207° (dec.) when placed in the bath at 205°. It should be mentioned that melting points of these compounds may vary considerably depending on the rate of heating and the temperature at which they are placed in the bath.



I. R = H
II. R = *p*-CH_3O

III. R = H. *a.* m.p. 190°; *b.* m.p. 207°
IV. R = *p*-CH_3O. *a.* m.p. 177°; *b.* m.p. 206°.

The second isomer (IIIa), when heated slowly from room temperature, appeared to sinter slightly over a wide temperature range, finally melting at 188.5–190° (dec.). It is completely soluble in cold acetone and may be separated by virtue of this fact. If a sample is placed in the bath at 172°, liquefaction occurs (presumably with loss of benzene of solvation), the sample resolidifies, and then remelts at 188.5–190° as before, *p*-phenylbenzophenone being one of the products of decomposition.

Reduction of diaryl ketones or their precursors with a number of reagents has led to the isolation of presumably stereoisomeric benzopinacols. Among these are: sodium with 2,2′-dibenzoylbiphenyl (1) and *o*-phenylbenzophenone (2); the magnesium iodide-magnesium couple with the former ketone and *o*-chlorobenzophenone (3); the zinc-acetic acid couple with the latter compound (3) and *o*-phenylbenzophenone (2); and Grignard reagents (containing unchanged magnesium) with methyl *o*-phenylbenzoate (2) and ethyl *o*-chlorobenzoate (3).

There are many reports of the isolation of a single benzopinacol from the reaction of Grignard reagents with ketones (4–8); in some of these cases a pair of stereoisomers was theoretically possible. Besides the esters listed above, a single pinacol has been obtained in several instances by treatment of compounds of this class with Grignard reagents (9, 10).

The literature concerning the reduction of I is confusing. A single benzo-

pinacol melting at 198° has been reported to be the product of the reaction of magnesium iodide and magnesium (7, 2) or with sodium (1). A form melting at 212° was obtained by Bergmann and Fujise (11), using *bis*-(*p*-dimethylaminophenyl)methane as the reducing agent. Later, Bergmann and Wolff (12) isolated still another substance, m.p. 181°, suggested as a possible stereoisomer, by subjecting α,β-epoxy-β,*p*-diphenylpropiophenone to the action of phenylmagnesium bromide. This work was repeated by Bachmann and Wiselogle (13) with entirely different results. From the epoxide, in the absence of magnesium, these authors were able to isolate either *p*-phenylbenzophenone in 60% yield or, with an excess of the reagent, *p*-phenyltriphenylcarbinol in 51% yield. In the presence of magnesium and magnesium bromide, there was obtained a 45% yield of the benzopinacol (m.p. 198°) previously reported from their laboratory. It should be pointed out that Bergmann and Wolff used one of a pair of stereoisomeric epoxides in their work while Bachmann and Wiselogle were able to obtain only a single product following the former authors' directions for the epoxidation of the corresponding chalcone. We believe that our high-melting pinacol (IIIb) is undoubtedly the 198° compound of Bachmann and Wiselogle (13) and probably is identical with the 212° isomer of Bergmann and Fujise (11). Furthermore, it seems likely that IIIa is the 181° compound of Bergmann and Wolff (12). These suppositions are strongly supported by the equilibration experiments to be described presently.

Details of the reduction of 4-(*p*-anisyl)benzophenone (II) to pinacols, a reaction which appears not to be recorded elsewhere, were quite analogous to those relating to the work with I. In this case, the less soluble isomer (IVb), m.p. 205–206°, was also characterized by analysis and by isolation of the starting ketone among its decomposition products, as was the lower-melting compound (IVa), m.p. 176–177.5°.

In view of the conflicting reports concerning the first pair of isomers, it seemed of interest to study the reduction of both ketones by the magnesium bromide-magnesium couple, both alone and followed by treatment of the mixture with phenyl Grignard reagent. The isomerization of a pinacol obtained by reduction of α-benzoylnaphthalene to a lower-melting isomer by ethylmagnesium bromide (14) and similar results with *sym*-di-*o*-chlorobenzopinacol by the action of phenyl Grignard reagent (3) have been reported.

Reduction of I with magnesium bromide and magnesium gave only the high-melting pinacol (IIIb), previously reported to be the sole product of reduction with the iodide reagent (7). However, on similar treatment, the anisyl compound (II) yielded a mixture of the two pinacols (IVb and IVa) in a weight ratio of 5.4:1. When phenylmagnesium bromide was formed in the reaction mixture after the ketone had been reduced, IIIa was obtained in greater amount than IIIb (2.4:1). Conversely, II formed largely IVb (6:1 of IVa).

Finally, each of the high-melting pinacols was equilibrated using phenylmagnesium bromide. IIIb was partially isomerized to give about an equal amount of IIIa. IVb was incompletely converted to IVa (2.4 IVb recovered to 1 IVa isolated). Although it appears that these data indicate that equilibration was not consistently complete, they explain qualitatively the mode of formation of

stereoisomers, and appear to offer a means of reconciling the previously-discussed disagreement in the literature on this subject. It was early recognized that pinacolates dissociate to ketyls (7); it seems but a step to suppose that this radical may invert and reassociate.

In the course of characterization of these two pairs of isomeric compounds, the ultraviolet absorption spectra were determined. They are presented in

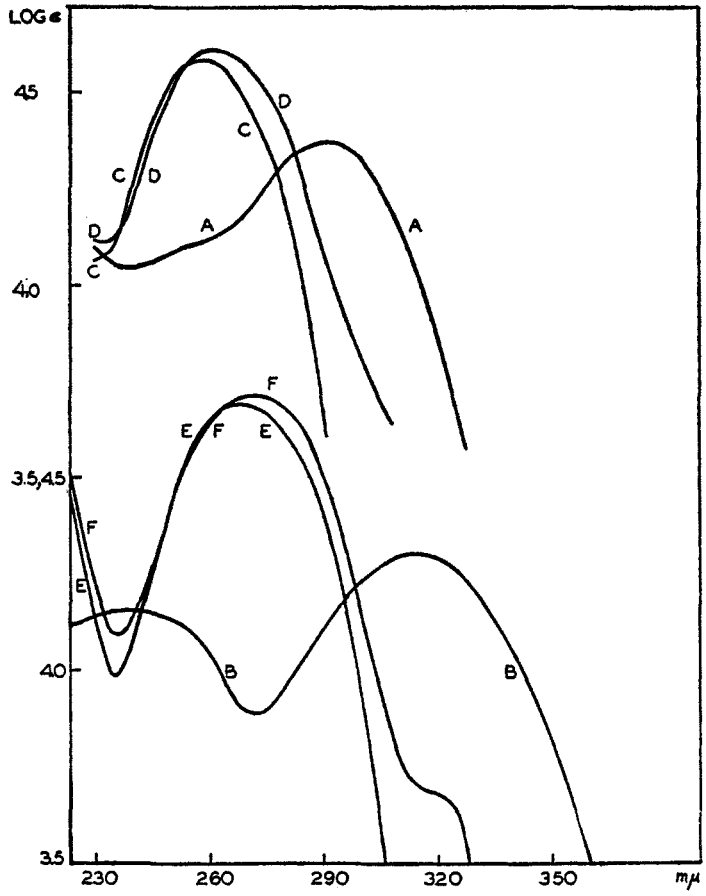


FIGURE 1. ULTRAVIOLET ABSORPTION SPECTRA OF KETONES AND BENZOPINACOLS

Curve A—I; curve B—II; curve C—IIIa; curve D—IIIb; curve E—IVa; curve F—IVb.

Figure 1. It is to be noted that in both cases there is a consistent bathochromic shift in passing from the lower- to the higher-melting isomer, obscured in the low wave-length region by a similar shift in the maxima and a slightly greater general absorption by the latter. This is additional evidence that these compounds are indeed stereoisomeric in nature. Although *d*, *l*, and *dl* modifications of the same compound exhibit identical spectra, such differences between the spectra of *dl* and *meso* forms have been reported previously with tartaric acid (15), various tartrates (16), and a series of several arylated compounds similar to

benzopinacols (17), the *meso* forms possessing the higher general absorptions. Spectra of the original ketones, of which that of *p*-phenylbenzophenone had been determined by Anderson and Gooding (18), are included for comparison.

In view of the shifts observed in the absorption maxima for the two series of pinacols, suggesting considerable interaction of the methoxyl substituent with the biphenyl nucleus, it seemed that this effect might be manifested in the 'migration aptitude' of these groups. Differences due to stereoisomerism would also be of interest. The rearrangement of each of the four pinacols by acetyl chloride in benzene-acetic acid (completed with iodine), followed by cleavage of the pinacolones with alkali, has been carried out by methods somewhat similar to those of Bachmann and Moser (19), and the mixtures of acids so obtained analyzed by

TABLE I

REARRANGEMENT OF THE BENZOPINACOLS

PINACOL	SAMPLE, G.	METHANES, G. (%)	ARYLBENZOIC ACID, G.[f]	MIGRATION APTITUDE, ARYLPHENYL[g]
IIIa	1.19	—[c]	0.108	3.2
IIIb	2.00	1.49 (105)	.161	3.6
IVa	1.82[a]	1.21 (98)[d]	.069	8.2
IVb	2.00[b]	1.31 (99)[e]	.108	5.3

[a] Contains one mole of benzene of solvation. [b] Contains two moles of ethanol of solvation. [c] Loss of methanes by sublimation. [d] Includes 0.051 g. of phenolic methanes. [e] Includes 0.016 g. of phenolic methanes. [f] These values were calculated from solubilities of the acids under the conditions of the isolations: *p*-phenylbenzoic acid, 0.02 g./100 ml. of water; *p*-anisylbenzoic acid, 0.033 g./100 ml. of water. The latter is a composite value inasmuch as it was determined on the actual acid mixture produced; this undoubtedly contains phenolic acid produced in both acid-rearrangement and alkaline-cleavage steps. [g] Relative to phenyl as unity.

isolation of *p*-phenylbenzoic or *p*-anisylbenzoic acid, respectively. The results are summarized in Table I.

The value of 3.6 agrees well with that (3.75) of Hatt, Pilgrim, and Stephenson (2) for the migration aptitude of the biphenylyl group in the same compound. However, these authors reported this value using perchloric acid for the rearrangement, and stated that the use of acetyl chloride-benzene-acetic acid mixtures led to a value of 1.87. They have criticized the use of this reagent on the apparently valid grounds that the long heating might cause dismutation to ketones and incomplete rearrangement was their experience. They showed that the presence of ketones during cleavages led to invalid equivalent weights for the acids obtained. They were also unable to duplicate the original value (11.5) of Gomberg and Bachmann (7).

It is of interest then that the acetyl chloride method was brought into agreement with the perchloric acid results by completing the rearrangement with iodine and the cleavage of pinacolones by fusion with sodium and potassium hydroxides (2), at least in this example. It also seemed desirable to have migration aptitudes which were at least somewhat comparable to those of Bachmann and his coworkers (20).

Migration aptitudes for the 4-(*p*-anisyl)phenyl group in the low-melting (IVa, 8.2) and high-melting isomers (IVb, 5.3) seem to indicate a genuinely higher tendency for this group to wander, compared to the unsubstituted group. However, in view of the possibilities for cleavage of the methoxyl group, etc., these values are less certain. Since heating solutions of the low-melting isomer for some hours resulted in formation of some of the high-melting form with loss of pinacol presumably due to pyrolysis, the lower value of 5.3 is regarded as the most reliable for the migration aptitude of the 4-(*p*-anisyl)phenyl group, having been obtained with the more stable high-melting form. The differences in the values obtained for stereoisomers in both cases are thought to be insufficient, in view of the difficulties involved, to support a claim that stereoisomerism is an important factor in the rearrangement of benzopinacols. It is interesting to compare these values with that which has been reported for *p*-anisyl [70 or more (19)].

Acknowledgment: We wish to express our indebtedness to the Graduate School for a research grant made in support of this work.

EXPERIMENTAL PART[1,2]

Isolation of the pinacols. The Grignard reagents were prepared in the usual way and always contained some unchanged metal. Since one experiment carried out under an atmosphere of nitrogen gave similar results to those obtained without this precaution, it was not used routinely.

From 4-(p-anisyl)benzophenone. To the reagent prepared from 39 g. of bromobenzene and 6.07 g. of magnesium in 200 ml. of ether was added the solid ketone (12 g.) in 3–4-g. portions over a period of 30 minutes. A vigorous reaction occurred; the solution became purple and then yellow during a two-hour heating period. The mixture was poured into ice and saturated ammonium chloride solution. The high-melting insoluble pinacol was removed by filtration, washed, and dried. The crude product weighed 2.85 g.; m. p. 197–200° (placed in the bath at 195°). After recrystallization by solution in hot dioxane followed by the addition of several volumes of ethanol, it melted at 205–206° (204°) with evolution of a gas. Drying *in vacuo* for 17 hours at 56° did not remove two moles of ethanol of crystallization.

Anal. Calc'd for $C_{44}H_{46}O_6$: C, 78.76; H, 6.92.
Found: C, 78.76; H, 6.16.

Concentration of the above solvent layer, addition of benzene, distillation to a residue of about 50 ml., and addition of three volumes of Skellysolve B (60–70°) gave 1.6 g. of white crystals of the lower-melting isomer of the pinacol. From the mother liquors 6.3 g. (m.p. 95–98°) of crude 4-(*p*-anisyl)triphenylcarbinol was isolated (21). This form was completely soluble in cold acetone (the high-melting pinacol is quite insoluble) and was recrystallized by addition of benzene to this solution, followed by distillation to remove most of the acetone. A sample melted at 160–165° (160°), resolidified, and remelted at 181–183° (dec.). Drying *in vacuo* at 56° for 16 hours gave crystals containing one mole of benzene of crystallization.

Anal. Calc'd for $C_{45}H_{40}O_4$: C, 84.12; H, 6.13.
Found: C, 83.84, 84.25; H, 6.00, 5.92.

The isomeric pinacols were also characterized by thermal dismutation to the original

[1] Microanalyses were carried out by the Clark Microanalytical Laboratory, Urbana, Illinois.

[2] All melting points are corrected. The temperature in parentheses is that at which the sample was placed in the bath, at least 30 seconds being allowed for the attainment of thermal equilibrium.

ketone, among other products. Thus from the pyrolysis at 160–240° of 0.55 g. of lower-melting isomer was isolated 0.31 g. of 4-(*p*-anisyl)benzophenone; m.p. 166–168° alone or mixed with the authentic material. Similar results were obtained using the high-melting pinacol.

From p-phenylbenzophenone. The procedure and course of the reaction of this ketone with phenylmagnesium bromide were quite similar to those described for 4-(*p*-anisyl) benzophenone. From 10 g. of the ketone were obtained by identical methods 1.15 g. of the high-melting pinacol and 1.62 g. of its low-melting isomer. The former, purified by recrystallization from dioxane-ethanol, melted at 206–207° (205°). It is undoubtedly the 198° compound of Bachmann and Wiselogle (13) and probably the 212° compound of Bergmann and Fujise (11).

Anal. Calc'd for $C_{38}H_{30}O_2$: C, 88.01; H, 5.82.
Found: C, 87.59; H, 5.92.

After being purified by recrystallization from acetone-benzene, the low-melting isomer melted, before drying, at 170° (170°) (dec.) almost completely, resolidified rapidly and then melted at 188.5–190° (dec.). The last value refers to the unsolvated crystals.

Anal. Calc'd for $C_{38}H_{30}O_2$: C, 88.01; H, 5.82.
Found: C, 88.30, 88.41; H, 5.93, 6.15.

The latter isomer is believed to be that (m.p. 181°) reported by Bergmann and Wolff (12). Both forms were pyrolyzed to *p*-phenylbenzophenone. The high-melting form (0.25 g.) yielded 0.11 g.; m.p. 98.5–100.5°, when heated briefly at 220–230°. From 0.20 g. of the low-melting isomer was obtained by similar treatment 0.09 g.; m.p. 100.5–102°. Neither product depressed the melting point (100.5–102°) of an authentic sample of the ketone.

No attempt was made to isolate the *p*-phenyltriphenylcarbinol formed in this Grignard reaction. The use of ethylmagnesium bromide in place of the phenyl reagent gave only traces of the impure pinacols; again the carbinol was not isolated.

Reduction of the ketones by magnesium bromide and magnesium. Magnesium bromide in ether-benzene over amalgamated magnesium was prepared by reaction of magnesium powder with anhydrous mercuric bromide according to the method of Gomberg and Bachmann (7). From 1.9 g. of magnesium, 4.27 g. of anhydrous mercuric bromide, and 3 g. of *p*-phenylbenzophenone, after heating in ether-benzene for 14 hours, was obtained 2.75 g. (92%) of the high-melting pinacol; none of the low-melting isomer could be detected.

However, reduction of 3 g. of the *p*-anisyl compound in the same manner gave a mixture of both the high- and low-melting compounds described previously. The former (2.55 g.) predominated over the latter (0.47 g.).

These reductions were repeated with the formation of phenylmagnesium bromide in the reaction mixture after the reduction of the ketone was complete. Thus, 5.2 g. of *p*-phenylbenzophenone, reduced as above, followed by the addition of 0.5 g. of magnesium and 6.6 g. of bromobenzene in that order, after a further heating period of 12 hours, gave 1.15 g. of the high-melting form and 2.75 g. of the low-melting isomer. Similarly, 6 g. of the anisyl ketone yielded 0.80 g. of low-melting pinacol and 4.78 g. of the high-melting form.

Equilibration of the pinacols by phenylmagnesium bromide. Finally the two high-melting pinacols were added to a five- to ten-fold excess of the Grignard reagent. From 1 g. of *sym*-di-*p*-phenylbenzopinacol (IIIb) were obtained 0.45 g. of unchanged material and 0.50 g. of the low-melting isomer. Of three grams of the methoxypinacol, 1.55 g. was recovered and 0.65 g. was isomerized.

Ultraviolet absorption spectra. The spectra of the two pinacols in each series and the parent ketone were determined in direct comparison with one another and with the solvent using a Beckman Model DU Spectrophotometer. Ethanol was a satisfactory solvent for the two low-melting isomers but it was found that the high-melting isomers were quite insoluble in this medium. *n*-Butanol proved more useful for these compounds; therefore all of the curves reported here were obtained with solutions in a solvent mixture consisting of 12.5 parts by volume of ethanol (95%) and one part of *n*-butanol and were compared to a mixture of the same composition. These curves did not differ noticeably from those obtained in ethanol or in dioxane-ethanol mixtures which were also investigated in prelim-

inary runs. The concentrations of the anisyl pinacols are corrected for the solvents of crystallization.

Rearrangement of the pinacols. In preliminary experiments, the two isomeric pinacols from *p*-phenylbenzophenone, when recrystallized from acetic acid containing a crystal of iodine, gave as the only isolated product the pinacolone (m.p. 198°) shown by Gomberg and Bachmann (7) to be that resulting from migration of a biphenylyl group. The methoxy pinacols gave mixtures of pinacolones, which were not resolved.

The results of the quantitative analyses of the pinacolones obtained on rearrangement of the isomeric pinacols have been summarized above in the table. The procedures for rearrangement, cleavage, and analysis were similar to those of Bachmann and Moser (19). Our methods differ from theirs in that the residue from the rearrangement, after distillation of the acetyl chloride and benzene, was routinely heated with 0.05 g. of iodine in acetic acid to complete the reaction. Furthermore, it was found that heating the neutral fraction (triarylmethanes) from the alkaline cleavage (in methanol) of the pinacolones with a mixture of 3 g. each of potassium and sodium hydroxides and a few drops of methanol and water at 200–250° for a short time gave a small additional amount of arylbenzoic acid (2), production of which was taken as the principal basis for the calculations. This procedure was therefore also included routinely.

SUMMARY

Using methods involving essentially reduction with magnesium bromide, magnesium, and phenylmagnesium bromide, both *p*-phenylbenzophenone and 4-(*p*-anisyl)benzophenone have been converted to separable mixtures of stereoisomeric benzopinacols. Isomerization of the pinacols by the phenyl Grignard reagent has been studied.

Ultraviolet absorption spectra for both ketones and the four pinacols have been determined.

A value of 5.3 has been found for the migration aptitude of the 4-(*p*-anisyl)-phenyl group.

EUGENE, OREGON

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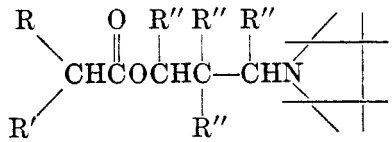
[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UPJOHN COMPANY]

ANTISPASMODICS. IV. TERTIARYAMINO ALKYL ESTERS OF DISUBSTITUTED ACETIC ACID

ROBERT BRUCE MOFFETT, JAMES H. HUNTER, AND E. H. WOODRUFF

Received March 13, 1950

In previous work (1, 2) it was found that pyrrolidylethyl esters have higher antispasmodic activity than the pyrrolidylpropyl esters. To test further this generalization and to determine whether it would extend to branched chain compounds, we have now prepared a series of pyrrolidylpropyl esters in which methyl groups are substituted on the propyl link (Formula I).

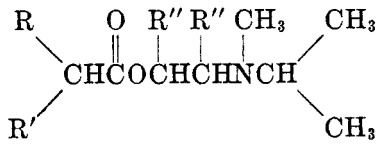


I R″ = H or CH_3

The low activity of these compounds (Table II) has confirmed this generalization.

Included in this paper are a few pyrrolidylbutyl and pyrrolidylethoxyethyl esters. These also have low activity.

A number of N-isopropyl-N-methylaminoalkyl esters (Formula II) have been prepared.



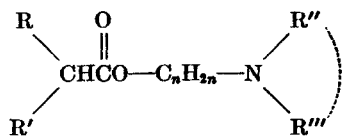
II R = H or CH_3

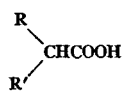
Their activity (Table II) seems to be in general a little greater than that of the isomeric diethylaminoalkyl esters.

These esters were prepared from the corresponding acid chlorides and tertiary-amino alcohols by the method previously described (1, 2). The preparation of the requisite pyrrolidyl alcohols (3) and N-isopropyl-N-methylamino-ethanol and -isopropanol (4) have been recently reported. 2-(N-Isopropyl-N-methyl-amino)propanol was prepared[1] by the reductive alkylation of 2-aminopropanol with acetone in the presence of platinum and hydrogen, followed by methylation with formaldehyde and formic acid.

[1] Prepared by Mr. Gordon F. Kurtz in these laboratories.

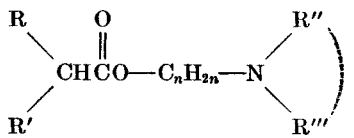
TABLE I

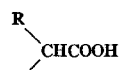
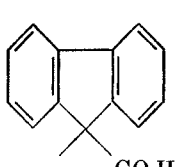
FREE BASES 

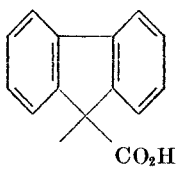
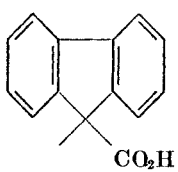
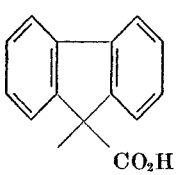
NO.	ACID USED 	AMINO ALCOHOL USED HOC_nN_{2n}—N	YIELD, %[a]	B.P. °C.	B.P. mm.	n_D^{25}	EMPIRICAL FORMULA	NITROGEN, % Calc'd	NITROGEN, % Found[b]
1	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH(CH_3)CH_2CH_2$—$NCH_2CH_2CH_2CH_2$	83.8	140	0.016	1.5205	$C_{22}H_{31}NO_2$	4.10	4.19
2	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH(CH_3)CH_2CH_2$—$NCH_2CH_2CH_2CH_2$	81.3	135	.22	1.4671	$C_{18}H_{33}NO_2$	4.74	4.82
3	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3)CH_2$—$NCH_2CH_2CH_2CH_2$	97.0	128	.01	1.5223	$C_{22}H_{31}NO_2$	4.10	4.08
4	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH(CH_3)CH_2$—$NCH_2CH_2CH_2CH_2$	96.1	100	.013	1.4681	$C_{18}H_{33}NO_2$	4.74	4.72
5	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH(CH_3)$—$NCH_2CH_2CH_2CH_2$	92.3	146	.024	1.5213	$C_{21}H_{29}NO_2$	4.28	4.38
6	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2CH(CH_3)$—$NCH_2CH_2CH_2CH_2$	96.2	115	.027	1.4717	$C_{18}H_{33}NO_2$	4.74	4.75
7	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2C(CH_3)_2CH_2$—$NCH_2CH_2CH_2CH_2$[c,d]	85.5	130	.007	1.5187	$C_{23}H_{33}NO_2$	3.94	3.92
8	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2C(CH_3)_2CH_2$—$NCH_2CH_2CH_2CH_2$	90.6	131	.11	1.4677	$C_{19}H_{35}NO_2$	4.53	4.57

9	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	86.0	138	.17	1.5192	$C_{21}H_{29}NO_2$	4.28	4.26
10	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	87.7	162	.38	1.5241	$C_{22}H_{31}NO_2$	4.10	4.21
11	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	95.4	130	.07	1.4698	$C_{18}H_{33}NO_2$	4.74	4.83
12	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}O{-}CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	87.2	152	.03	1.5188	$C_{21}H_{29}NO_3$	4.08	4.07
13	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2{-}O{-}CH_2CH_2{-}NCH_2CH_2CH_2CH_2$	75.1	130	.04	1.4691	$C_{18}H_{33}NO_3$	4.49	4.50
14	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.2	112	.015	1.5091	$C_{19}H_{27}NO_2$	4.65	4.69
15	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.2	145	.15	1.5017	$C_{19}H_{29}NO_2$	4.62	4.84
16	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	79.4	123	.01	1.5140	$C_{20}H_{29}NO_2$	4.44	4.46
17	$CH_2CH_2CH_2CH{=}CHCHCH(CH_2CH_2CH{=}CHCH)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	51.1	125	.03	1.4918	$C_{19}H_{31}NO_2$	4.59	4.58
18	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH_2{-}N(CH_3)CH(CH_3)_2$	77.2	98	.03	1.4547	$C_{16}H_{31}NO_2$	5.20	5.26
19	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH(CH_3)CH_2{-}N(CH_3)CH(CH_3)_2$[c, e]	63.8	122	.01	1.5080	$C_{21}H_{31}NO_2$	4.25	4.52
20	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3){-}N(CH_3)CH(CH_3)_2$	85.6	116	.01	1.5082	$C_{20}H_{29}NO_2$	4.44	4.47

TABLE I—*Continued*

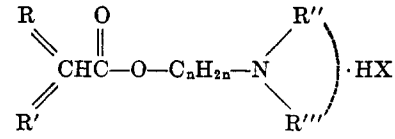
FREE BASES 

NO.	ACID USED 	AMINO ALCOHOL USED HOC_nN_{2n}—N 	YIELD, %[a]	B.P. °C.	B.P. mm.	n_D^{25}	EMPIRICAL FORMULA	NITROGEN, % Calc'd	NITROGEN, % Found[b]
21	$CH_2CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH(CH_3)—N(CH_3)CH(CH_3)_2$	78.4	129	.02	1.5131	$C_{21}H_{31}NO_2$	4.25	4.17
22	$CH_2CH_2CH_2CH_2CHCH(CH_3CH_2CH_2)COOH$	$HOCH_2CH(CH_3)—N(CH_3)CH(CH_3)_2$	79.2	85	.01	1.4578	$C_{17}H_{33}NO_2$	4.94	4.99
23	$CH_2CH_2CH{=}CHCHCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	55.0[f]	130	.04	—	$C_{19}H_{27}NO_2$	—	—
24	$CH_2CH_2CH_2CH_2CHCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	75.9[f]	130	.04	—	$C_{19}H_{29}NO_2$	—	—
25	$C_6H_5OCH(C_6H_5)COOH$	$HOCH_2CH_2—N(CH_2CH_3)_2$	52.0[f]	175	.07	—	$C_{20}H_{25}NO_3$	—	—
26		$HOCH_2CH_2—NCH_2CH_2CH_2CH_2$[g]	—	—	—	—	—	—	—

27		$HOCH_2CH_2CH_2-N(CH_2CH_2CH_2CH_2)$[a]	—	—	—	—	—	—	—	
28		$HOCH(CH_3)CH_2-N(CH_2CH_2CH_2CH_2)$[a]	—	—	—	—	—	—	—	
29		$HOCH_2CH(CH_3)-N(CH_2CH_2CH_2CH_2)$[a]	—	—	—	—	—	—	—	

[a] Yield based on acid chloride. [b] Analyses by Mr. Harold Emerson and staff of our Microanalytical Laboratory. [c] No crystalline salt was obtained from this free base, but it was dissolved in dilute hydrochloric acid and tested pharmacologically (Table II, footnote [e]). [d] Antispasmodic activity, 0.05. [e] Antispasmodic activity, 0.013. [f] Yield based on acid used. The acid chloride was not isolated in this run. [g] The free base was not isolated. See Table II for salt.

TABLE II

SALTS  ·HX

NO.[a]	SALT FORMING ACID	YIELD, %[b]	M.P., °C.[c]	CRYSTALLIZING SOLVENT	EMPIRICAL FORMULA	ANALYSES, %		ANTISPASMODIC ACTIVITY[e]
						Calc'd	Found[d]	
1	HCl	74.0	153–154.5	MeEtCO	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.23	0.01
2	HCl	87.5	125–127	EtOAc	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.78	.01
3	HCl	71.8	119–123	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.31	.01
4	HCl	78.2	88–89	EtOAc + Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.72	.01
5	HCl	83.8	133–136	MeEtCO	$C_{21}H_{30}ClNO_2$	Cl, 9.74	9.73	.03
6	HCl	68.4	78–80	EtOAc + Et_2O	$C_{18}H_{34}ClNO_2$	Cl, 10.68	10.64	.01
8	HCl	90.2	134–135.5	EtOAc	$C_{19}H_{36}ClNO_2$	Cl, 10.02	10.00	.01
9	HCl	84.6	101–103	EtOAc	$C_{21}H_{30}ClNO_2$	Cl, 9.74	9.52	.01
10	HCl	65.4	97–99	EtOAc	$C_{22}H_{32}ClNO_2$	Cl, 9.38	9.47	.01
11	Citric acid	92.0	93.5–94.5	EtOH + EtOAc	$C_{24}H_{41}NO_9$	N, 2.87	2.89	.01
12	Citric acid	79.3	87–90	MeEtCO	$C_{27}H_{37}NO_{10}$	N, 2.62	2.65	.01
13	Citric acid	92.2	77–79	EtOAc	$C_{24}H_{41}NO_{10}$	N, 2.78	2.85	.01
14	HCl	64.0	93–98	EtOAc + Et_2O	$C_{19}H_{28}ClNO_2$	Cl, 10.49	10.44	.15
15	HCl	75.3	105–106.5	EtOAc + EtO_2	$C_{19}H_{30}ClNO_2$	Cl, 10.43	10.48	.33
16	HCl	65.3	121–124	EtOAc	$C_{20}H_{30}ClNO_2$	Cl, 10.08	10.21	.33
17	HCl	66.5	90–97	EtOAc + Et_2O	$C_{19}H_{32}ClNO_2$	Cl, 10.37	10.32	.12
18	HCl	77.6	74–80	EtOAc + Et_2O	$C_{16}H_{32}ClNO_2$	Cl, 11.59	11.70	.10
20	Citric acid	76.9	83–90	EtOH + EtOAc + Et_2O	$C_{16}H_{37}NO_9$	N, 2.76	2.92	.17
21	Citric acid	71.3	85–95	EtOH + EtOAc + Et_2O	$C_{27}H_{39}NO_9$	N, 2.69	2.84	.30
22	Citric acid	87.4	81–84	EtOH + EtOAc + Et_2O	$C_{23}H_{41}NO_9$	N, 2.95	2.91	.10
23	HCl	94.5	146–147	EtOAc + Et_2O	$C_{19}H_{28}ClNO_2$	Cl, 10.49	10.58[f]	.14
24	HCl	78.6	128–129	EtOAc	$C_{19}H_{30}ClNO_2$	Cl, 10.43	10.61[g]	.12
25	HCl	72.8	114–115	EtOAc	$C_{20}H_{26}ClNO_3$	Cl, 9.74	9.88[h]	.01
26	HCl	62.9[i]	109–114[j]	Me_2CO	$C_{20}H_{22}ClNO_2$	N, 4.07 Cl, 10.31	4.05 10.38	.02

TABLE II (*Continued*)

NO.[a]	SALT FORMING ACID	YIELD %[b]	M.P., °C.[c]	CRYSTALLIZING SOLVENT	EMPIRICAL FORMULA	ANALYSES, %		ANTISPASMODIC ACTIVITY
						Calc'd	Found[d]	
27	Citric acid	27.2[i]	108–112[k]	EtOH	$C_{27}H_{31}NO_9$	N, 2.73	2.77	.01
28	HCl	58.1[i]	217–220	EtOH	$C_{21}H_{24}ClNO_2$	N, 3.92 Cl, 9.91	3.92 9.82	.01
29	HCl	45.3[i]	157–162	Me_2CO	$C_{21}H_{24}ClNO_2$	N, 3.92 Cl, 9.91	4.11 9.81	.01

[a] Numbers correspond to the numbers of the free bases in Table I. [b] The yield is based on the distilled free base and would in most cases be essentially quantitative except that the filtrates from the crystallizations were usually not reworked. [c] Melting points are uncorrected. [d] Table I footnote [b]. [e] Preliminary testing was done by Dr. Milton J. Vander Brook of our Department of Pharmacology by the method of Magnus [Arch. ges. Physiol. (Pflügers), **102**, 123 (1904); Arch. ges. Physiol. (Pflügers), **103**, 515 (1904)] and the results are expressed as a fraction of the activity of atropine sulfate when tested on muscle stimulated with acetylcholine chloride. [f] Calc'd: C, 67.54; H, 8.35; N, 4.14. Found: C, 67.46; H, 8.21; N, 4.07. [g] Calc'd: C, 67.14; H, 8.90. Found: C, 67.20; H, 8.68. [h] Calc'd: C, 66.01; H, 7.20; N, 3.88. Found: C, 65.12; H, 7.28; N, 4.01. [i] Yield based on the acid chloride used in the preparation. [j] A sample of this hydrochloride heated at 100° under a vacuum of 0.01 mm., sintered and then again crystallized, m.p. 131–136°. *Anal.* Found: N, 4.35; Cl, 10.30. [k] After sintering at about 93–96°.

EXPERIMENTAL

2-(N-Isopropylamino)propanol.[1] This was prepared in 85% yield from acetone and 2-aminopropanol by the procedure described by Hancock and Cope (5) for 2-isopropylaminoethanol. B.p. 71° (15 mm.).

2-(N-Isopropyl-N-methylamino)propanol.[1] This was prepared in 65% yield from the above amine by the procedure described by Icke, Wisegarner, and Alles (6) for β-phenylethyldimethylamine. B.p. 81° (35 mm.), n_D^{25} 1.4371.

Anal. Calc'd for $C_7H_{17}NO$: N, 10.68. Found: N, 10.71.

SUMMARY

Twenty-nine new tertiary amino alkyl esters of disubstituted acetic acids have been prepared and their antispasmodic activity is reported.

KALAMAZOO 99, MICHIGAN

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[CONTRIBUTION FROM ABBOTT LABORATORIES]

THE ACTION OF LITHIUM ALUMINUM HYDRIDE ON 3-METHYL-5-PHENYLHYDANTOIN AND 5-PHENYLHYDANTOIN

I. J. WILK AND W. J. CLOSE

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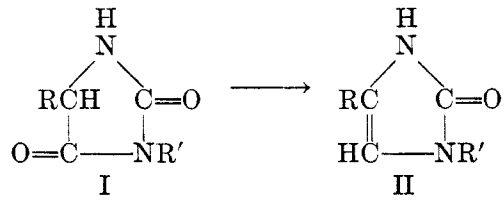
During investigations on the properties of hydantoins in these laboratories the reduction of these compounds with lithium aluminum hydride (1) was studied. The hydantoin nucleus (I) possesses two amide-type linkages, each of which is subject to reduction. Partial reduction may lead to an imidazolone (II) or an imidazole (III).[1] Complete reduction of both carbonyls leads to an imidazolidine (IV).[2]

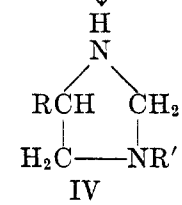


I

Ia. R = C_6H_5, R′ = CH_3
Ib. R = C_6H_5, R′ = H

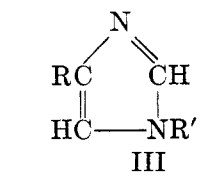
II

IIa. R = C_6H_5, R′ = CH_3
IIb. R = C_6H_5, R′ = H



IV

IVa. R = C_6H_5, R′ = CH_3



III

IIIa. R = C_6H_5, R′ = CH_3

We have found it possible to reduce selectively the carbonyl groups of certain hydantoins to type II compounds. Thus, when 3-methyl-5-phenylhydantoin (Ia) was treated dropwise with an ether solution of lithium aluminum hydride and allowed to stand overnight, it was converted to the 2(3H)-imidazolone (IIa) in good yield.

It was difficult to cause the 2-carbonyl group to undergo reaction. However, by prolonged refluxing of IIa with the reagent, a small amount of the imidazole (IIIa) could be obtained. The melting point of this product was in agreement with that reported by Hazeldine (5).

The completely reduced imidazolidine could be obtained from the methyl-phenylhydantoin by altering the conditions of reaction. On treating Ia with an excess of lithium aluminum hydride under Soxhlet conditions, IVa was obtained in fair yield.

[1] Compare the reduction of oxindoles by Julian and Printy (2).

[2] Compare the reduction of 2-pyrrolidone derivatives (3, 4).

When 5-phenylhydantoin (Ib) was subjected to the same conditions used to prepare IIa, the corresponding 4-phenyl-2(3H)-imidazolone (IIb) was obtained.

Assignment of the 2(3H)-imidazolone structure to the compounds described was made primarily on the basis of the following data: IIa was reduced catalytically with platinum oxide (6) to a compound whose analytical values agreed with those calculated for 4-cyclohexyl-1-methyl-2-imidazolidone. Furthermore, reduction with palladium black yielded a compound corresponding to 1-methyl-4-phenyl-2-imidazolidone. Reduction of IIb with palladium black in a similar manner gave 4-phenyl-2-imidazolidone, the melting point of which agreed with that reported by Kanewskaja (7) as well as by Cook (8). When this known compound was methylated, the 1-methyl-4-phenyl-2-imidazolidone obtained was shown to be identical with the product obtained from IIa.

The structure of the imidazolidine (IVa) was demonstrated by benzoylation, which resulted in ring rupture and formation of N^1,N^2-dibenzoyl-N^2-methyl-1-phenylethylenediamine.

EXPERIMENTAL[3]

1-Methyl-4-phenyl-2(3H)-imidazolone (IIa). To a stirred suspension of 19 g. (0.1 mole) of 3-methyl-5-phenylhydantoin in 300 cc. of anhydrous ether was added a solution of 3.8 g. (0.1 mole) of lithium aluminum hydride in 400 cc. of anhydrous ether so that a constant reflux rate was maintained. This addition required about three hours. Stirring was continued at room temperature for 16 hours; the complex was then decomposed by adding dilute hydrochloric acid followed by concentrated acid. The remaining precipitate was separated and recrystallized from ethyl alcohol. The yield was 11.5 g. (66%); m.p. 275–278°. Five grams of unreacted hydantoin could be isolated from the ether layer. No basic material was recovered from the acid layer.

Anal. Calc'd for $C_{10}H_{10}N_2O$: C, 69.0; H, 5.8; N, 16.1.
Found: C, 69.2; H, 5.7; N, 15.9.

1-Methyl-4-phenylimidazole (IIIa). A solution of 1.9 g. (0.051 mole) of lithium aluminum hydride was placed in a round-bottom flask and 3.0 g. (0.017 mole) of IIa was placed in a Soxhlet. Refluxing was continued for three weeks, but even after this extended period of time some of the imidazolone was still in the Soxhlet. The complex was decomposed in the usual manner, and the unreacted IIa removed by filtration. The acidic layer was made alkaline with sodium hydroxide and extracted with ether. The ether was removed, and the residue (0.5 g.) recrystallized from Skellysolve C; the product melted at 109.0–109.5° (5).

Anal. Calc'd for $C_{10}H_{10}N_2$: C, 75.9; H, 6.4; N, 17.7.
Found: C, 76.2; H, 6.5; N, 17.9.

4-Cyclohexyl-1-methyl-2-imidazolidone. Reduction of IIa with Adams' catalyst in glacial acetic acid under a hydrogen pressure of 30 pounds and recrystallization of the product from water gave material melting at 126°.

Anal. Calc'd for $C_{10}H_{18}N_2O$: C, 65.9; H, 10.0; N, 15.4.
Found: C, 65.9; H, 9.7; N, 15.3.

1-Methyl-4-phenyl-2-imidazolidone. Reduction of IIa as above except with palladium black catalyst gave a product melting at 131–133° (recrystallized from water).

Anal. Calc'd for $C_{10}H_{12}N_2O$: C, 68.2; H, 6.9; N, 15.9.
Found: C, 68.4; H, 6.7; N, 15.6.

1-Methyl-4-phenylimidazolidine (IVa). In a 3-neck flask equipped with a condenser, Soxhlet extractor, stirrer, and calcium-chloride tube were placed 100 cc. of anhydrous

[3] Microanalyses by E. F. Shelberg and staff. Catalytic hydrogenations by M. Freifelder and G. R. Stone.

ether and 11.4 g. (0.3 mole) of lithium aluminum hydride. Nineteen grams (0.1 mole) of 3-methyl-5-phenylhydantoin was placed in the Soxhlet, and refluxing was carried out for 11 hours. The complex was decomposed as before. The layers were separated, and the acid layer made alkaline by adding sodium hydroxide. This was extracted several times with ether, and the ether solution dried over sodium sulfate. The ether residue was distilled at 88.5° (2 mm.). The yield was 7.0 g. (43%); n_D^{23} 1.5200.

Anal. Calc'd for $C_{10}H_{15}N_2$: C, 73.6; H, 9.3; N, 17.2.
Found: C, 73.3; H, 9.4; N, 16.9.

Benzoylation of IVa. Two grams of the imidazolidine was treated with benzoyl chloride under Schotten-Baumann conditions. The precipitate of N^1,N^2-dibenzoyl-N^2-methyl-1-phenylethylenediamine was recrystallized from 50% ethanol. The product melted at 122–123°.

Anal. Calc'd for $C_{23}H_{22}N_2O_2$: C, 77.1; H, 6.2; N, 7.8.
Found: C, 77.0; H, 6.0; N, 7.5.

4-Phenyl-2(3H)-imidazolone (IIb). The procedure described for IIa was used with 17.6 g. (0.1 mole) of 5-phenylhydantoin and 5.7 g. (0.15 mole) of lithium aluminum hydride. The product melted at 340–343° after recrystallization from alcohol.

Anal. Calc'd for $C_9H_8N_2O$: C, 67.5; H, 5.0; N, 17.5.
Found: C, 67.4; H, 4.9; N, 17.5.

4-Phenyl-2-imidazolidone. The catalytic reduction of IIb was carried out in the manner described for IIa, yielding material melting at 158–159° after recrystallization from water (7, 8).

Anal. Calc'd for $C_9H_{10}N_2O$: C, 66.6; H, 6.2; N, 17.3.
Found: C, 66.8; H, 6.3; N, 17.4.

Methylation of 4-phenyl-2-imidazolidone. 4-Phenyl-2-imidazolidone (0.13 g.) was methylated with methyl sulfate in alkaline 50% methanol in the usual manner. The product melted at 133–134°. The mixed melting point with 1-methyl-4-phenyl-2-imidazolidone prepared from IIa was 132–133°.

SUMMARY

Selective reduction of 5-phenylhydantoin and its 3-methyl derivative with lithium aluminum hydride yields the corresponding 2(3H)-imidazolones. Under different conditions the 3-methyl-5-phenylhydantoin was converted also to an imidazole and to an imidazolidine. Several new imidazole derivatives are described.

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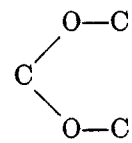
[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

OBSERVATIONS ON 2-(*p*-BIPHENYLOYL)BENZOIC ACID

ERNST D. BERGMANN AND S. PINCHAS[1]

Received March 16, 1950

Scholl and Neovius (1) have shown that 4-phenylbenzophenone-2′-carboxylic acid (I) is reduced to the corresponding diphenylmethane derivative by very prolonged treatment with copper-activated zinc dust and ammonia. In an investigation of the reducibility of certain *o*-aroylbenzoic acids, I was subjected to the usual procedures of the Wolff-Kishner and the Clemmensen reduction, respectively. In the former case, in which the method of Huang-Minlon (2) was applied, the reaction proceeded only to the stage of 3-keto-4,5-benzo-6-(*p*-biphenylyl)-2,3-dihydropyridazine (II) which was not further reducible, and in the latter, the reduction stopped at the stage of the secondary carbinol which was withdrawn from the further influence of the reducing agent by ring-closure to the lactone (III). Both heterocyclic systems showed remarkable stability. These observations are in accord with the fact that I—like many other *o*-acylbenzoic acids (3)—reacts with phenylmagnesium bromide to give the lactone (IV) corresponding to the normal triarylcarbinol expected (4). The "methyl ester" of I did not react at all with phenylmagnesium bromide; with benzylmagnesium chloride, however, reaction in the ratio of 1:1 took place, and the reaction product lost spontaneously 1 mole of water. The "normal" formula (V) of α-phenyl-β-(*o*-carbomethoxyphenyl)-β-(*p*-biphenylyl)ethylene is excluded by the resistance of the product to boiling alcoholic potash solution; one will assume following Fieser (3), that the methyl ester does not correspond in structure to the acid (I), but has the lactol form (VI) from which by interaction with benzylmagnesium chloride and dehydration, 2-benzylidene-5-methoxy-5-(*p*-biphenylyl)-2,5-dihydro-3,4-benzisofuran (VII) is formed. Formula VI explains also the observation, that the methyl ester does not respond to the Reformatsky reaction with zinc and ethyl bromoacetate: only true carbonyl groups undergo this reaction. Formula VII was established by the results of the investigation of the infrared spectrum. This (Fig. 1) showed three bands, at 1071, 1109, and 1160 cm^{-1}, respectively. It has been observed in this laboratory (4) that all acetals and ketals exhibit a triplet of bands with the wave lengths given, *i.e.*, this triplet is characteristic for the group



which, indeed is present in VII. This evidence supplements the spectrochemical work carried out by von Auwers and Heinze (5), and the ultraviolet absorption study undertaken by Hantzsch and Schwiete (6) on the esters of acids of type I.

[1] Part of a thesis presented by S. Pinchas to the Hebrew University in partial fulfilment of the requirements for the degree of Ph.D.

No systematic work appears to have been done on the Wolff-Kishner reduction of *o*-aroylbenzoic acids; Martin, in a recent review (7), indicates, without any references, that for this reaction the usual reduction by means of zinc dust and alkali appears preferable. The formation of a carbinol (as III) in the Clemmensen reduction is definitely in contradiction with current ideas on the mechanism of this reaction—although the formation of ("dimolecular") pinacols (8) or

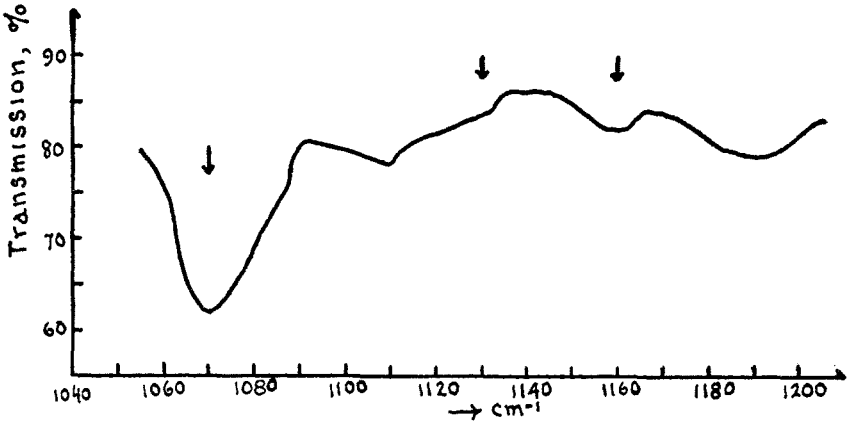
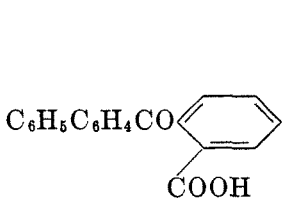
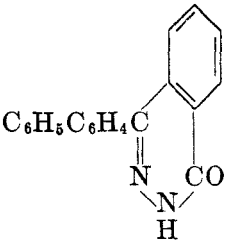


FIGURE 1. INFRARED SPECTRUM OF 2-BENZYLIDENE-5-METHOXY-5-(*p*-BIPHENYLYL)-2,5-DIHYDRO-3,4-BENZISOFURAN (VII) IN CARBON TETRACHLORIDE (0.060 g. per cc.; 0.1 mm.)

their lactones (9, 10) has been observed in specific cases. However, *o*-benzoylbenzoic acid was known to be reducible to the corresponding benzyl compound.



I



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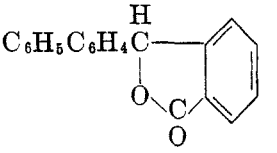
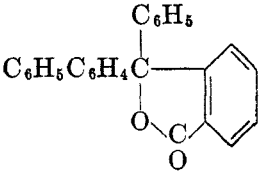


III



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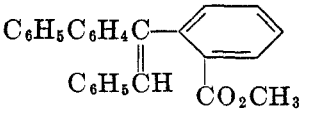

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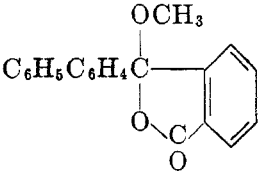
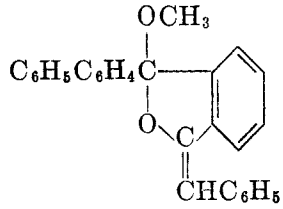


VI



VII

EXPERIMENTAL

3-Keto-6-(p-biphenylyl)-4,5-benzo-2,3-dihydropyridazine (II). A mixture of the acid (I) (1) (3.0 g.), sodium hydroxide (0.8 g.), diethylene glycol (20 cc.), and hydrazine hydrate (1.5 cc.) was treated according to the procedure of Huang-Minlon (2). Dilute (5%) sulfuric acid gave a precipitate which was recrystallized repeatedly from alcohol (200 vols.) and formed white needles of m.p. 278°, insoluble in aqueous alkali and unchanged, when subjected anew to the same reduction process. Yield, almost quantitative.

Anal. Calc'd for $C_{20}H_{14}N_2O$: C, 80.5; H, 4.7.

Found: C, 80.6; H, 4.8.

3-(p-Biphenylyl)phthalide (III). A solution of the acid (I) (2 g.) in glacial acetic acid (200 cc.) was reduced in the usual manner with activated zinc wool (5 g.) and repeated additions of concentrated hydrochloric acid. When the metal had dissolved, the solution was diluted with water and the solid product recrystallized from alcohol or benzene (250 vols.). Colorless prisms, m.p. 210°; yield, 1.6 g. The substance was insoluble in aqueous alkali, but dissolved in boiling alcoholic alkali (hydrolysis); acidification gave III again.

Anal. Calc'd for $C_{20}H_{14}O_2$: C, 83.9; H, 4.9.

Found: C, 83.9; H, 4.8.

The substance has been prepared before by Elbs (11) using zinc dust and aqueous ammonia as reducing agent.

Lactone (IV) of 4-phenyl-triphenylcarbinol-2'-carboxylic acid. A suspension of the acid (I) (3 g.) in benzene (150 cc.) was treated (two hours at room temperature, 30 minutes reflux) with a Grignard solution, prepared from magnesium (0.8 g.) and bromobenzene (5.0 g.) in ether (20 cc.). The reaction product was decomposed with 5% hydrochloric acid and the unchanged starting material (2 g.) removed from the benzene layer with sodium carbonate solution. After evaporation of the solvent, there remained an oil which crystallized upon trituration with warm methanol. From methanol, microcrystalline powder, m.p. 86°. Yield, 0.5 g.

Anal. Calc'd for $C_{26}H_{18}O_2$: C, 86.2; H, 5.0.

Found: C, 85.6; H, 5.5.

From the mother-liquors, small quantities of a substance of m.p. 171° (leaflets from alcohol) were obtained; it was not further investigated.

pseudo-Methyl 4-phenylbenzophenone-2'-carboxylate (VI). A mixture of the acid (I) (57 g.), methanol (300 cc.), and concentrated sulfuric acid (7 cc.) was refluxed for four hours. Upon cooling, the ester crystallized in practically quantitative yield. After recrystallization from methyl alcohol, it had m.p. 103°[2].

2-Benzylidene-5-methoxy-5-(p-biphenylyl)-2,5-dihydro-3,4-benzisofuran (VII). In small portions, the pseudo-methyl ester (VI) of I (12.5 g.) was added to the Grignard solution prepared from benzyl chloride (5 g.) and magnesium turnings (1 g.) in ether (25 cc.). When the spontaneous reaction subsided, the solution was stirred vigorously for three hours and decomposed with dilute sulfuric acid (150 cc.). The ethereal solution left, after drying and

[2] Kaiser (12) gives m.p. 85–90° for this substance; this corresponds to an impure preparation.

evaporation, an oil which was triturated at 0° with a mixture of isopropanol and acetone. From this solvent mixture, the product formed colorless crystals of m.p. 143°, easily soluble in most organic solvents. The yield was only about 1 g.

Anal. Calc'd for $C_{28}H_{22}O_2$: C, 86.1; H, 5.6.
Found: C, 85.9; H, 5.9.

REHOVOTH, ISRAEL

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[FROM THE WEIZMANN INSTITUTE OF SCIENCE]

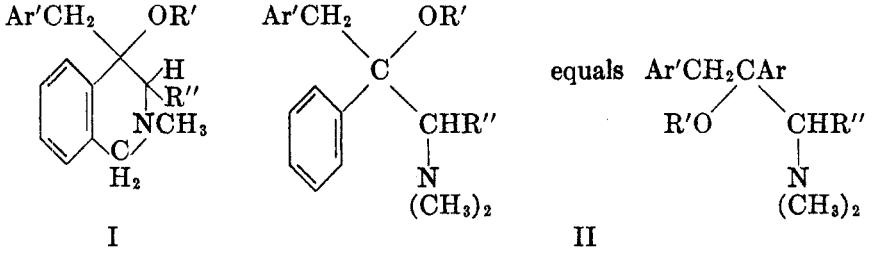
BENZYLISOQUINOLINE STUDIES. PART I. OPEN-RING MODELS OF 4-BENZYLISOQUINOLINES

DAVID SHAPIRO

Received March 20, 1950

The natural alkaloids of the benzylisoquinoline group, among them morphine, contain the benzyl group in the 1-position. It appeared of interest to investigate whether the 3- and 4-benzylisoquinoline systems, respectively, have biological properties similar to these alkaloids. One derivative of 3-benzylisoquinoline, *viz.* 6,7-dimethoxy-3-(3′,4′-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinoline has been described by Sugasawa, Kakemi, and Kazumi (1), and some other 3- and 4-substituted isoquinolines by Whaley and Hartung (2).

In the course of this research, to which forthcoming papers will be devoted, the system (II) was studied which can be considered as a 4-benzyltetrahydroisoquinoline (I) with an opened pyridine ring (3).[1]



I II

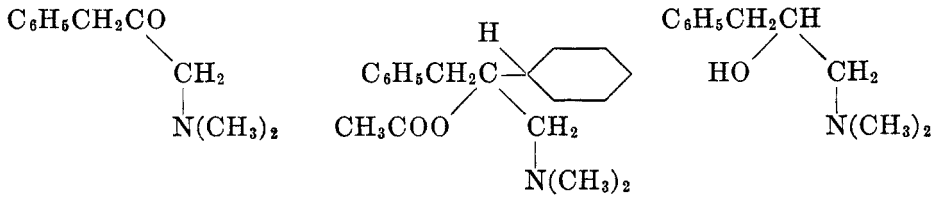
A similar trend of thought prompted the work of Kuelz, *et al.* (5), who found in the bis(phenylethyl)amines powerful analgesics; these bases are derived from the morphine molecule by opening both the nitrogen-containing heterocyclic ring and the furan system (2).

Three approaches to the synthesis of II were explored: (*a*) For R″ = H, dimethylaminoacetonitrile was a suitable starting material. It reacted with benzylmagnesium chloride (6), to give 1-phenyl-3-dimethylamino-2-propanone (III) which yielded II (Ar′ = Ar = C_6H_5, R′ = R″ = H, and Ar′ = C_6H_5, Ar = *p*-methoxyphenyl, R′ = R″ = H) upon reaction with phenyl- and *p*-methoxyphenyl-magnesium bromide, and subsequent hydrolysis, respectively. If the product of the last Grignard reaction was not hydrolyzed, but treated with acetic anhydride (7), the acetyl derivatives of the tertiary carbinols were obtained (II, R′ = CH_3CO, R″ = H).

For the purpose of comparison, III was also treated with cyclohexylmagnesium bromide, and the acetyl derivative (IV) was isolated. III could be hydrogenated catalytically to 1-phenyl-3-dimethylamino-2-propanol (V), which was also converted into the corresponding acetate. These compounds are derived

[1] Morrison and Rinderknecht (4) have prepared homologs of II, in which another methylene group is interposed between the "CHR" group of II and the nitrogen atom.

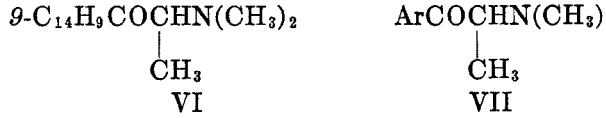
from the general formula (II), if Ar′ = C_6H_5, R″ = H, and Ar is replaced by cyclohexyl and hydrogen, respectively.



III IV V

(*b*) As Thomson and Stevens (6) have pointed out, the above reaction of dimethylaminoacetonitrile with benzylmagnesium chloride or arylmagnesium halides cannot be extended to α-dimethylaminopropionitrile or its higher homologs. Only in one case, an exception from the rule has been observed: α-dimethylaminopropionitrile gives, with 9-phenanthrylmagnesium bromide, the expected 9-(α-dimethylaminopropionyl)phenanthrene (VI), but this could not be induced to react further with benzylmagnesium chloride to II (Ar′ = phenyl, Ar = 9-phenanthryl, R′ = H, R″ = CH_3). It is interesting that also an attempt to prepare from VI the corresponding secondary alcohol, failed; 9-propylphenanthrene was obtained instead. Similar hydrogenolytic reactions have recently been described by Metayer (8).

For the synthesis of the substances of type II with R″ = CH_3, the reaction of benzylmagnesium chloride with α-dimethylaminopropiophenones (VII) proved suitable. Through the corresponding α-bromoketones, α-dimethylaminopropiophenone and its 4-methoxy-, 3,4-dimethoxy-, and 3,4-methylenedioxy derivatives were prepared; reaction with benzylmagnesium chloride afforded the following alcohols II: Ar′ = C_6H_5, R′ = H, R″ = CH_3, and Ar = phenyl, 4-methoxyphenyl, 3,4-dimethoxyphenyl or 3,4-methylenedioxyphenyl. The corresponding acetyl derivatives were prepared either by direct acetylation of the Grignard product or by acetylation of the carbinols with acetic anhydride.



VI VII

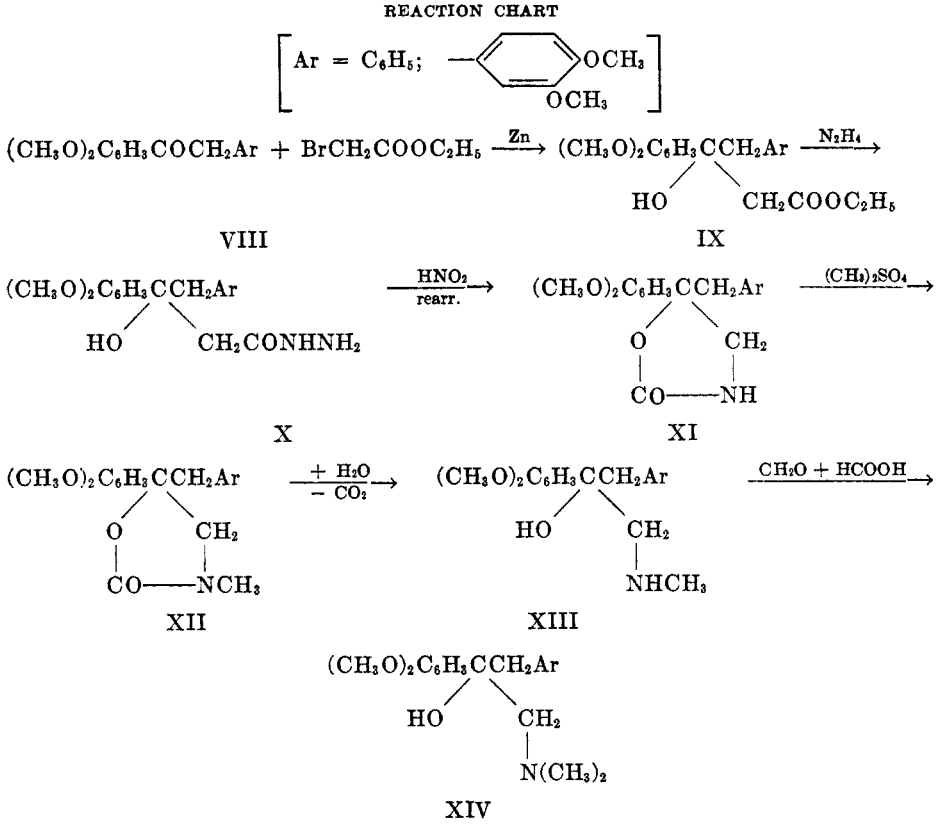
(*c*) The usefulness of this method is limited by the difficult availability of alkoxy-substituted benzylmagnesium chlorides (9–12). For the preparation of II (Ar′ = Ar = 3,4-dimethoxyphenyl, R′ = R″ = H) and—as a model experiment—for that of II (Ar = 3,4-dimethoxyphenyl, Ar′ = phenyl, R′ = R″ = H), a different method was adopted, outlined in the following Chart.

1-Phenylacetyl-3,4-dimethoxybenzene [in the second sequence: 3,4, 3′,4′-tetramethoxydesoxybenzoin (VIII)] reacted with ethyl bromoacetate to give ethyl β-hydroxy-β-(3,4-dimethoxyphenyl)-γ-phenylbutyrate (IX). When the corresponding hydrazide (X) was treated with nitrous acid and the azide decomposed in absence of water, the Curtius rearrangement was accompanied by isomerization to 5-benzyl-5-(3,4-dimethoxyphenyl)-2-oxazolidone (XI) which

was the methylated in the 3-position (XII). Hydrolysis of the ring system with liberation of carbon dioxide led to 1-phenyl-2-(3,4-dimethoxyphenyl)-3-methylamino-2-propanol (XIII), in which the nitrogen atom could be further methylated to (XIV) by formaldehyde and formic acid (13–19).

The Curtius rearrangement of β-hydroxyacid azides has been described first by Schroeter (20) and has been employed recently by Baltzly and Buck (21) and Ide and Blatzly (22). This reaction recalls another method of producing oxaxole derivatives, *viz.* the transformation of the azides of α-benzamidocinnamic and -β,β-dimethylacrylic acids, into 2-phenyl-4-benzylidene- and -4-isopropylidene-5-oxazolone (23).

REACTION CHART



In the second sequence (Ar = 3,4-dimethoxyphenyl), the last step (methylation by formic acid and formaldehyde), unexpectedly, did not give (XIV), but its dehydration product, probably α-dimethylaminomethyl-3,4,3′,4′-tetramethoxy stilbene.

Pharmacological properties. Through the courtesy of Dr. A. Krebser, a number of substances prepared in the course of the investigation were tested in the laboratories of Messrs. J. R. Geigy, Basle (Switzerland) for their analgesic and pressor activity, and were also compared with papaverine. The analgesic activity

was tested on mice; the pressor activity on cats in Numal narcosis. The comparison with papaverine was carried out using the method of Krawkow and Pissemski (rabbit's ear) (Table VI).

EXPERIMENTAL

1-Phenyl-3-dimethylamino-2-propanone (III) was prepared according to Thomson and Stevens (6) with slight modifications: to a Grignard solution, prepared from 8.7 g. of magnesium, 47.5 g. of benzyl chloride, and 200 cc. of ether, was added in an atmosphere of nitrogen and with stirring, a mixture of 17 g. of dimethylaminoacetonitrile (24) and 75 cc. of ether at −10 to 0°. Stirring was continued until the mixture reached room temperature. After 12 hours, ammonium sulfate and ice were added, the ether layer extracted with 100 cc. of 25% sulfuric acid, and the acid solution heated at 95° for one hour. It was then cooled, made alkaline with 33% sodium hydroxide solution, and after addition of an excess of potassium carbonate, extracted with ether. The ether solution was dried with potassium carbonate and distilled. B.p. 141°/26 mm.; yield, 19 g.

Picrate: crystallized from ethanol, m.p. 126–127°.

Anal. Calc'd for $C_{17}H_{18}N_4O_8$: N, 13.8. Found: N, 13.8.

1-Phenyl-3-dimethylamino-2-propanol (V). The ketone was hydrogenated in presence of Raney nickel at room temperature and atmospheric pressure. The theoretical quantity of hydrogen was absorbed in 12 hours. The product boiled at 140°/26 mm. and was characterized by its *picrate*; crystallized from ethanol, m.p. 134–135°.

Hydrochloride of the acetyl derivative of (V) (*"Substance A"*). From 1.7 g. of V with 10 cc. of benzene and 0.8 g. of acetyl chloride at 40° for 3 hours. The crystals which separated (2.1 g.), were filtered and washed with benzene. After recrystallization from acetone with some ethanol, the hydrochloride melted at 177–179°.

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: C, 60.7; H, 7.8; N, 5.4.
Found: C, 60.5; H, 8.2; N, 5.4.

The reaction of 1-phenyl-3-dimethylamino-2-propanone (III) (in benzene solution) with Grignard compounds (3 mole) was carried out in a nitrogen atmosphere and at 5–10°; the reaction product was decomposed with cold ammonium sulfate solution, extracted with dilute sulfuric acid, precipitated with alkali, and taken up with ether (Table I). For the preparation of the acetyl derivatives, the product of the Grignard reaction was treated with acetic anhydride at 25° before the addition of ammonium sulfate; in this case, it was preferable to extract the base with acetic acid and to precipitate it with ammonia (method *a*). Alternatively, the aminoalcohol was acetylated with acetyl chloride in benzene solution at 40°; thus, the hydrochloride of the acetyl derivative was obtained (method *b*) (Table II).

9-(α-Dimethylaminopropionyl)phenanthrene (VI). To a Grignard reagent, prepared from 25.7 g. of 9-bromophenanthrene, 2.4 g. of magnesium, 75 cc. of ether, and 50 cc. of benzene (25), 5 g. of α-dimethylaminopropionitrile (24) in 50 cc. of benzene was added. After refluxing for 10 hours and decomposition with ammonium chloride, the filtered benzene-ether layer was heated for one hour at 95–100° with 100 cc. of 25% sulfuric acid, the solvents being distilled off simultaneously. The acid solution was then washed twice with benzene, made alkaline with 30% sodium hydroxide solution, and extracted with fresh benzene. B.p 156–160°/0.1 mm.; yield, 7.5 g.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.3; H, 6.9.
Found: C, 82.6; H, 6.7.

Hydrochloride, from butyl acetate-methanol (5:1), m.p. 233–235°.

Anal. Calc'd for $C_{19}H_{20}ClNO$: C, 72.8; H, 6.4.
Found: C, 73.4; H, 7.1.

When an alcoholic solution of VI was shaken with hydrogen in the presence of Raney nickel until absorption ceased, and the filtrate was evaporated, there remained an oil which contained no basic substance. In the distillate, however, a volatile amine was present. The oil crystallized spontaneously and formed needles; from an ethanol-acetone mixture,

m.p. 63°. The m.p. and the analytical data show that the substance is 9-propylphenanthrene (26).

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Found: C, 92.4; H, 7.3.

The starting materials for the *preparation of the substances* (II), in which R'' = CH_3, the α-dimethylaminopropiophenones (VII), were the corresponding propiophenones, which were brominated in acetic acid at 10–20°; *p*-methoxypropiophenone (27), 3,4-di-

TABLE I

2-SUBSTITUTED 1-PHENYL-3-DIMETHYLAMINO-2-PROPANOLS, $C_6H_5CH_2C(HO)(Ar)CH_2N(CH_3)_2$

Ar	B.P., °C./mm.	Yield, %	Picrate	M.P., °C.	Analysis					
					Calc'd			Found		
					C	H	N	C	H	N
C_6H_5	135–140/0.3	35.3	$C_{23}H_{24}N_4O_8$	175–177[a]	57.0	5.0	11.6	57.4	5.3	11.6
p-$CH_3OC_6H_4$	155/0.3[b]	15.4	$C_{24}H_{26}N_4O_9$	184–186[a]	56.0	5.0	10.9	56.1	5.4	11.0

[a] Recrystallized from alcohol. [b] Also obtained (in 85% yield) from 4-methoxy-ω-dimethylaminoacetophenone and benzylmagnesium chloride.

TABLE II

2-SUBSTITUTED 1-PHENYL-3-DIMETHYLAMINO-2-ACETOXYPROPANES, $C_6H_5CH_2C(CH_3COO)(R)CH_2N(CH_3)_2$

R	Method	B.P., (°C./mm.)	Yield, %	Picrate	M.P., °C.	Analysis						Code No.
						Calc'd			Found			
						C	H	N	C	H	N	
C_6H_5	*a*	135–140/0.3[a]	30.0	$C_{25}H_{26}N_4O_9$	155–156[b]	57.0	4.9	10.6	57.4	5.2	10.9	B
p-$CH_3OC_6H_4$	*b*	—	Quant.	$C_{26}H_{28}N_4O_{10}$	160[c]	56.0	5.0	10.9	56.1	5.4	11.0	
Cyclohexyl	*a*	135–136/0.1	18.0	$C_{25}H_{32}N_4O_9$	134–35[c]	56.4	6.0	10.5	56.5	6.0	10.7	C

[a] Hydrochloride, from ethanol-methyl ethyl ketone, m.p. 181–183°. *Anal.* Calc'd. for $C_{19}H_{24}ClNO_2$: C, 68.5; H, 7.2; N, 4.2. Found: C, 68.6; H, 7.3; N, 4.0. [b] Recrystallized from ethanol. [c] Recrystallized from ethanol-acetone.

methoxypropiophenone (28, 29), and 3,4-methylenedioxypropiophenone (30). 3,4-Methylenedioxy-α-bromopropiophenone was obtained in 60% yield; it crystallized from methanol and melted at 52–53°.

Anal. Calc'd for $C_{10}H_9BrO_3$: C, 46.6; H, 3.5; Br, 31.1.
Found: C, 46.6; H, 3.4; Br, 31.0.

The bromine was replaced by the methylamino group when the bromoketone (0.15 mole) in benzene solution was added, at 5° and with stirring, to an ethereal solution of dimethylamine (0.3 mole) over a period of 40 minutes. Stirring was continued as the temperature rose gradually to 30°. After three hours, the mixture was filtered, washed once with water, and extracted with 15% hydrochloric acid. After alkalinization, the base was extracted with ether [Table III; α-dimethylaminopropiophenone (VII, Ar = C_6H_5): (31)].

The interaction of the aminoketones listed in Table III with benzylmagnesium chloride led to the 1-phenyl-2-aryl-3-dimethylamino-2-butanols (II, R′ = H, R″ = CH_3) (Table IV). When the product of the Grignard reaction was treated with acetic anhydride (method *a*), or the isolated carbinols were acetylated with acetyl chloride (method *b*), the acetyl derivatives of these alcohols (II, R′ = CH_3CO, R″ = CH_3) were obtained, in the latter case as hydrochlorides (Table V).

TABLE III

α-DIMETHYLAMINOPROPIOPHENONES $ArCOCH(CH_3)N(CH_3)_2$

CODE NO.	Ar	B.P. (°C./MM.)	YIELD, %	HYDROCHLORIDE, M.P.	PICRATE	M.P., °C.	ANALYSIS					
							Calc'd			Found		
							C	H	N	C	H	N
D	*p*-Methoxyphenyl	135/3	81	176–178[a]	$C_{18}H_{20}N_4O_9$[b]	163	49.5	4.6	12.8	49.5	4.5	12.8
E	3,4-Dimethoxyphenyl	131/0.2	83	145–148[c, d]	$C_{19}H_{22}N_4O_{10}$[e]	156	48.9	4.7	12.0	48.9	4.5	12.4
F	3,4-Methylenedioxyphenyl	110–112/0.2	85	252–254 (decomp.)[f]	$C_{18}H_{18}N_4O_{10}$[b]	156–157	48.0	4.0	12.4	48.2	4.1	12.0

[a] After softening between 90–100°. [b] Recrystallized from ethanol. [c] Recrystallized from isopropanol. [d] Ref. 12. [e] Recrystallized from ethanol-acetone. [f] Recrystallized from ethanol-methanol.

TABLE IV

1-PHENYL-2-ARYL-3-DIMETHYLAMINO-2-BUTANOLS, $C_6H_5CH_2C(HO)(Ar)CHN(CH_3)_2$

Ar	YIELD, %	PICRATE	RECRYSTALLIZED FROM	M.P., °C.	ANALYSIS					
					Calc'd			Found		
					C	H	N	C	H	N
p-Methoxyphenyl	73	$C_{25}H_{28}N_4O_9$	Ethanol	173	56.8	5.3	10.6	56.4	5.0	10.2
3,4-Dimethoxyphenyl	85	$C_{26}H_{30}N_4O_{10}$	Ethanol-acetone	199–200	55.9	5.4	10.0	55.9	5.2	9.7
3,4-Methylenedioxyphenyl	80	$C_{25}H_{26}N_4O_{10}$	Ethanol-acetone	201	55.4	4.8	10.3	55.4	4.5	10.0

Ethyl β-hydroxy-β,γ-bis(3,4-dimethoxyphenyl)butyrate (IX, *Ar = 3,4-dimethoxyphenyl*). To 4 g. of freshly activated powdered zinc (32), there was added a little iodine and 15 cc. of a 40°-solution of 14.8 g. of 3,4,3′,4′-tetramethoxydesoxybenzoin (VIII) and 4.6 cc. of ethyl bromoacetate in 50 cc. of benzene and 10 cc. of ether. The mixture was heated with stirring until reaction set in, and the remainder of the solution added during 45 minutes. After refluxing for two hours, the reaction mixture was cooled to 5° and decomposed with 10% sulfuric acid. The ether-benzene layer was washed successively with 5% sulfuric acid, 10% sodium carbonate solution, and water, dried and evaporated *in vacuo*. The resulting thick, yellowish oil was dissolved in two parts of ether and left overnight at low temperature. The crystals (3 g.) which separated were identified as unchanged starting material. The filtrate, upon evaporation, left 14 g. (= 74%) of a thick oil which was pure enough for the next step.

TABLE V

1-PHENYL-2-ARYL-3-DIMETHYLAMINO-2-ACETOXYBUTANES, $C_6H_5CH_2\underset{\displaystyle CH_3COO \quad Ar \quad CH_3}{\overset{\displaystyle \diagup \; | \; \diagdown}{C}}CHN(CH_3)_2$

CODE NO.	Ar	B.P., °C./MM.	YIELD, %	HYDROCHLORIDE	M.P., °C.	ANALYSIS						PICRATE	M.P., °C.	ANALYSIS					
						Calc'd			Found					Calc'd			Found		
						C	H	N	C	H	N			C	H	N	C	H	N
G	Phenyl	154/0.35	60[a]	$C_{20}H_{26}ClNO_2$[b]	204–205	69.2	7.5	4.0	69.4	7.0	4.3	$C_{26}H_{28}N_4O_9$[c]	182–184	57.8	5.2	10.4	58.0	5.5	10.7
H	*p*-Methoxyphenyl	152/0.3	80[d]	$C_{21}H_{28}ClNO_3$[b]	187	66.8	7.5	3.7	67.1	7.5	3.3	$C_{27}H_{30}N_4O_{10}$[f]	170	56.8	5.3	9.8	56.9	5.2	9.8
J	3,4-Dimethoxyphenyl	165/0.3	43[a] 80[d]	[g]	218–219							$C_{28}H_{32}N_4O_{11}$[f]	210	56.0	5.3	9.3	56.3	5.4	9.6
K	3,4-methylenedioxyphenyl	160–165/0.3	42[a]	[g]	218–219							$C_{27}H_{28}N_4O_{11}$[c]	181–182	55.5	4.8	9.6	55.4	5.2	9.6

[a] Method (*a*). [b] Recrystallized from ethanol-butyl acetate or acetone-methanol. [c] Recrystallized from ethanol. [d] Method (*b*). [e] Recrystallized from acetone-methanol. [f] Recrystallized from acetone-ethanol. [g] From isopropanol-methanol.

For further purification the crude ester was treated with Girard T reagent, and recrystallized from ether. M.p. 72°.

Anal. Calc'd for $C_{22}H_{28}O_7$: C, 65.3; H, 6.9.

Found: C, 65.0; H, 7.0.

The 3,4,3′,4′-tetramethoxydesoxybenzoin (VIII) was prepared either by reduction of veratroin (33) with stannous chloride (34) or from veratrole and homoveratroyl chloride (35) with aluminum chloride according to Allen and Buck (36).

β-Hydroxy-β,γ-bis(3,4-dimethoxyphenyl)butyrhydrazide (X, *Ar = 3,4-dimethoxyphenyl*). A mixture of 10.8 of the foregoing ester, 3 cc. of hydrazine hydrate and 6 cc. of methanol was refluxed for 3½ hours. To the clear solution, two parts of ether were added and the mixture was cooled for two hours. The hydrazide was collected, washed with ether-methanol (1:1) (8 g., 77%) and recrystallized from methanol. M.p. 154–155°.

Anal. Calc'd for $C_{20}H_{26}N_2O_6$: C, 61.5; H, 6.6; N, 7.2.

Found: C, 61.7; H, 6.5; N, 6.9.

5-(3,4-Dimethoxyphenyl)-5-(3,4-dimethoxybenzyl)-2-oxazolidone. (XI, *Ar = 3,4-dimethoxyphenyl*). The hydrazide (3.6 g.) was suspended in a mixture of 40 cc. of ice water and 1.5 cc. of acetic acid and an aqueous solution of 1.5 g. of sodium nitrite was added with vigorous stirring. Benzene was then added and stirring continued until the gummy mass which formed had dissolved completely. The benzene solution was filtered from a little unchanged hydrazide, dried carefully and distilled (evolution of nitrogen). The oily residue was triturated with cold benzene, containing a little petroleum ether, and filtered. Yield, 3.2 g. Needles from methanol, m.p. 161°.

Anal. Calc'd for $C_{20}H_{23}NO_6$: C, 64.4; H, 6.2; N, 3.8.

Found: C, 64.5; H, 6.2; N, 4.1.

5-(3,4-Dimethoxyphenyl)-5-(3,4-dimethoxybenzyl)-3-methyl-2-oxazolidone. (XII, *Ar = 3,4-dimethoxyphenyl*). For the methylation, 2.7 g. of the oxazolidone was added to a solution of 0.4 g. of sodium methoxide in 10 cc. of methanol. The mixture was evaporated *in vacuo* to dryness, the residue taken up with 15 cc. of toluene and the mass evaporated again. To the resulting cake, 15 cc. of toluene and 0.8 cc. of methyl sulfate was added and the mixture heated for one hour on the water-bath, after which period the reaction was neutral. The toluene solution was washed with water, dried, and evaporated *in vacuo*. The residue (2.7 g.) was triturated with ether, containing a few drops of methanol, and recrystallized from a mixture of ether and methanol. M.p. 118–120°.

Anal. Calc'd for $C_{21}H_{25}NO_6$: C, 65.1; H, 6.5; N, 3.6.

Found: C, 64.7; H, 6.1; N, 3.7.

1,2-Bis(3,4-dimethoxyphenyl)-3-methylamino-2-propanol (XIII, *Ar = 3,4-dimethoxyphenyl*). The foregoing derivative (1.5 g.) was heated at 55–60° with 4 cc. of concentrated hydrochloric acid until the evolution of carbon dioxide ceased. After addition of 25 cc. of methanol, the reaction product was concentrated *in vacuo* at 50°, and the operation was repeated. Then, the resulting syrup was successively triturated with ether and acetone and gave a crystalline powder (0.4 g.) of m.p. 220–222°. The *free base* had m.p. 105° and is characterized by a well-defined *picrate*, from acetone-alcohol mixture, m.p. 184°.

Anal. Calc'd for $C_{26}H_{30}N_4O_{12}$: C, 52.9; H, 5.1; N, 9.5.

Found: C, 52.5; H, 5.2; N, 9.8.

α-Dimethylaminomethyl-3,4,3′,4′-tetramethoxystilbene (?). When 0.5 g. of the above base, m.p. 105°, was added to a mixture of 0.3 cc. of formalin solution and 0.2 cc. of formic acid, effervescence set in at once. The reaction was completed by heating at 80° for thirty minutes. The product was converted into its *picrate*, by treatment with alcoholic picric acid solution. From alcohol-acetone mixture, m.p. 188–189°.

Anal. Calc'd for $C_{27}H_{30}N_4O_{11}$: C, 55.3; H, 5.1; N, 9.5.

Found: C, 55.5; H, 5.3; N, 9.3.

β-Hydroxy-β-(3,4-dimethoxyphenyl)-γ-phenylbutyrhydrazide (X, *Ar = C_6H_5*). From 1-phenylacetyl-3,4-dimethoxybenzene (VIII, Ar = C_6H_5) (37), the ester (IX, Ar = C_6H_5) was prepared, as described above, in 76% yield, and the crude oily compound converted into the hydrazide. Yield, 70%. It crystallized from methanol, m.p. 88°.

Anal. Calc'd for $C_{18}H_{22}N_2O_4$: C, 65.5; H, 6.6; N, 8.5.
Found: C, 65.4; H, 6.7; N, 8.7.

The hydrazide is easily soluble in acetone, but after a few minutes, the *isopropylidene-hydrazide* crystallized; such reactions of hydrazides with ketones have been described before by Curtius and co-workers (38). After recrystallization from methanol, the product melted at 137–139°.

Anal. Calc'd for $C_{21}H_{26}N_2O_4$: C, 68.0; H, 7.0; N, 7.5.
Found: C, 68.1; H, 7.2; N, 7.1.

TABLE VI

PHARMACOLOGICAL PROPERTIES OF SUBSTANCES PREPARED

CODE NUMBER OF SUBSTANCE	ANALGESIC ACTION ON THE MOUSE, MG./KG.		COMPARISON WITH PAPAVERINE(= 1)	PRESSOR ACTIVITY, MG./KG.	
A	50	0	1:117	5	0
				10	positive
B	50	0	1:80		
C	50	0	1:200		
D	50	0	1:55.5	3	0
				10	positive
E	50	0	1:23		
	100	0			
F	50	0	1:122	5	0
	100	0			
G	50	0		3	positive
H	50	0		1	0
				>3	positive
J	50	0	1:204	3	0
K	50	0	1:172		
	100				

1-Phenyl-2-(3,4-dimethoxyphenyl)-3-dimethylamino-2-propanol (XIV, $Ar = C_6H_5$). The above described sequence of reactions was carried out with the foregoing hydrazide (3 g.). The *oxazolidone* which was formed by rearrangement of the azide, crystallized from methanol and had m.p. 148°.

Anal. Calc'd for $C_{18}H_{19}NO_4$: C, 69.0; H, 6.1; N, 4.5.
Found: C, 69.0; H, 6.3; N, 4.8.

The eventually resulting tertiary amine gave a *picrate* of m.p. 219–220°, after recrystallization from ethanol-acetone mixture.

Anal. Calc'd for $C_{25}H_{23}N_4O_{10}$: C, 55.2; H, 5.2; N, 10.3.
Found: C, 55.7; H, 5.2; N, 10.6.

SUMMARY

1. 1-Phenyl-3-dimethylamino-2-propanone (III), available from dimethylaminoacetonitrile and benzylmagnesium chloride, was converted into alcohols of type II by reaction with phenyl-, *p*-methoxyphenyl-, and cyclohexyl-magnesium bromide, and by catalytic hydrogenation.

2. In accordance with previous observations, α-dimethylaminopropionitrile does not react normally with aryl- and aralkyl-magnesium halides. Only 9-phenathrylmagnesium bromide was found to give the corresponding ketone (VI).

3. From α-dimethylaminopropiophenone, its 4-methoxy-, 3,4-dimethoxy-, and

3,4-methylenedioxy-derivatives, tertiary carbinols of type II were synthesized by means of benzylmagnesium chloride.

4. A third method leading to II consists in the Curtius rearrangement of the azides of the β-hydroxyacids, which are available by reaction of ethyl bromoacetate and zinc with suitably substituted dexsoxybenzoins. This arrangement leads to oxazolidones (XI) which can be N-methylated and which are hydrolyzed (with loss of carbon dioxide) to N-methylamines of the desired type II.

5. The pharmacological properties of the substances prepared are reported.

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[CONTRIBUTION FROM THE LABORATORY OF RADIOCHEMISTRY, DEPARTMENT OF CHEMISTRY, AND THE GASTRIC LABORATORY, DEPARTMENT OF INTERNAL MEDICINE, COLLEGE OF MEDICINE, UNIVERSITY OF CINCINNATI]

COMPOUNDS FOR CANCER RESEARCH. V. RADIOACTIVE SULFONAMIDES[1]

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This paper describes the syntheses of a series of sulfonamides prepared in a continuation of the search by this laboratory for a substance which will localize selectively in tumor tissue (1, 2). Were such a material found and made radioactive it would have diagnostic and therapeutic potentialities.

The selection of the sulfonamide linkage as a fundamental structure was made for the following reasons: (a) the function is apparently not attacked by enzymes; (b) sulfonamides have been shown to reduce the effective vitamin intake of animals by suppressing the intestinal flora, and this reduction of essential vitamins in the diet of tumor-bearing mice is known to inhibit the growth of tumors (3); and (c) sulfonamides have been reported to localize in certain tissues (4).

Although no localization of a chemical material in malignant tissue is known to be involved, the following experiments are suggestive. Boyland (3) administered large and repeated doses of certain aromatic amines containing sulfur such as 4,4′-diaminophenyl sulfoxide and sulfamyl sulfanilic acid, and reported the inhibition of tumors in mice. With further investigation complete inhibition of growth of spontaneous tumors in 4 of 4 mice was obtained by methylene blue, 4,4′-diaminophenyl sulfoxide, and 4,4′-diaminophenyl ether, the last being generally most effective (5). In general the inhibition of tumor growth continued only for the period of dosing.

It has been shown in rats that tumor (hepatoma) glycolysis lowers the *p*H of the tumor from 7.0 to 6.4, primarily because of the formation of lactic acid (6). Therefore, an injection of glucose a short time prior to the ingestion of a sulfonamide might very conceivably, by lowering the *p*H in the tumor, suppress the ionization of an acidic sulfonamide, thus reducing its solubility and forcing its deposition in the cancer tissue.

A desirable compound would require that its solubility at *p*H 6.4 should be perhaps one half the solubility at the *p*H of blood serum, 7.4. Schmitt and colleagues (7) examined six sulfonamides and found for four of these that the ratio of the solubility at *p*H 7.2 to that at *p*H 6.4 was two or greater. With *p*H 7.4 as the upper limit these ratios were even more pronounced.

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For dibasic acids Michaelis (8) has derived the following relationship between solubility and pH.

$$\Lambda = \lambda\left(1 + \frac{K_I}{[H^+]} + \frac{K_I K_{II}}{[H^+]^2}\right)$$

Λ = total solubility = concentration of all the material present, whether as the undissociated molecule or ion.
λ = partial solubility = concentration of the undissociated molecule in the saturated solution.
K_I = primary ionization constant.
K_{II} = secondary ionization constant.
$[H^+]$ = concentration of hydrogen ion.

We may now set up two equations for the solubility–pH relationship at the two pH values in question, 7.4 and 6.4. We may neglect the $\frac{K_I K_{II}}{[H^+]^2}$ term since it will be a very small number. Eliminating λ from the two equations by setting $\Lambda_{7.4} = 2\,\Lambda_{6.4}$, we obtain

$$2\left(1 + \frac{K_I}{[H^+]_{6.4}}\right) = 1 + \frac{K_I}{[H^+]_{7.4}}$$

Solving for K_I:

$$K_I = \frac{[H^+]_{7.4}[H^+]_{6.4}}{[H^+]_{6.4} - 2[H^+]_{7.4}} = \frac{(3.98 \times 10^{-8})(3.98 \times 10^{-7})}{(3.98 \times 10^{-7}) - 2(3.98 \times 10^{-8})}$$
$$= 4.98 \times 10^{-8}.$$

This is the minimum value of the ionization constant for our sulfonamide.

Work recently carried out in this laboratory has indicated that tumor mice show a considerably different uptake picture of radioactive iodosulfapyridine than normal mice (9). If this can be extended to man, it would be a possible means for the diagnosis of malignancy.

DISCUSSION AND PROCEDURE

It is proposed that the radioactivity be introduced as S^{35} in p-toluenesulfonyl chloride prepared from toluene and sulfuric-S^{35} acid.[4] It was obviously essential to prepare the p-toluene-S^{35}-sulfonyl chloride in the highest possible yield and purity. By the use of a water-removing apparatus, stirring, and excess toluene, the yield of sodium p-toluene sulfonate based on sulfuric-S^{35} acid was raised from 38% (10) to 60%. p-Toluenesulfonyl chloride could then be obtained in satisfactory yield and purity by heating sodium p-toluene-S^{35}-sulfonate with a mixture of phosphorus pentachloride and phosphorus oxychloride.

The mono- and di-tosylated derivatives and certain intermediates of the following aromatic amines were prepared: benzidine, 4,4′-diaminophenyl sulfide, 4,4′-diaminodiphenylmethane, and 4,4′-diaminophenyl ether.

[4] Obtained from the U. S. Atomic Energy Commission, Oak Ridge, Tennessee.

Monotosyl derivatives of benzidine and 4,4′-diaminodiphenylmethane were prepared by masking one amino group by acetylation. The monotosyl derivative of 4,4′-diaminophenyl sulfide was best obtained by the tosylation of 4-nitro-4′-aminophenyl sulfide, followed by reduction of the nitro group to the amine. The monotosyl derivative of 4,4′-diaminophenyl ether was prepared by condensing *p*-hydroxyacetanilide with *p*-bromonitrobenzene and sodium hydride in Methyl Carbitol solution.

EXPERIMENTAL

Sodium p-toluene-S^{35}-sulfonate. A three-necked, standard-taper flask equipped with a thermometer, a mercury-sealed stirrer, and a side-arm water trap attached to a condenser sealed against moisture, was assembled. The water trap was packed with calcium chloride-glass beads to 0.5 of an inch below the side arm. The trap was filled with purified toluene (11) until the liquid level was slightly below the level of calcium chloride. A mixture of 10 ml. (0.18 mole) of H_2SO_4 containing 4 mc. of $H_2S^{35}O_4$ and 20 ml. (0.19 mole) of toluene (11) was heated with stirring at such a rate that the temperature rose to 195° in one hour. The flame was removed, the solution cooled to 100°, and 3–4 ml. of toluene was added with thorough mixing. Heating was resumed. This process was repeated through four or five additions, with simultaneous removal of wet toluene from the bottom of the trap, until no more water (cloudiness) was seen on heating. The side arm was emptied partly and the flask heated to 150° to remove excess toluene. The total time required was five hours.

The hot reaction mixture was washed into 100 ml. of water. The solution was neutralized by the careful addition of sodium hydroxide, followed by 30 g. of sodium chloride. The mixture was heated to boiling, and water was added, if necessary, to dissolve the salt. Filtration removed 2–3 g. of yellow, waxy *p*-tolyl sulfone ($CH_3C_6H_4SO_2C_6H_4CH_3$). On cooling in an ice bath sodium *p*-toluene sulfonate separated and was collected. The cake was washed with 25 ml. of saturated sodium chloride solution and pressed dry.

After dissolving the cake in 50 ml. of water, 10 g. of sodium chloride was added, a further 20–25 ml. of water being required to bring the latter into solution. The solution was stirred a few minutes with 0.5 g. of charcoal, filtered hot, and concentrated to 70–75 ml. Crystallization was permitted to take place without disturbance in the cold. The yield of colorless material was 19.7–22 g. (56.6–63.2%) (Fieser reports 37.8%). The sulfonate was identified and its purity confirmed by preparation of the *p*-toluidine salt (m.p. 197°) (10). An attempt to increase the yield only led to increased sulfone formation.

p-Toluenesulfonyl-S^{35} chloride. A mixture of 10 g. (0.051 mole) of sodium *p*-toluene-S^{35}-sulfonate (dried at 140°), 5 g. (0.024 mole) of phosphorus pentachloride, and 10 ml. (0.109 mole) of phosphorus oxychloride was refluxed with frequent shaking at 160° for 1.5 hours. Excess phosphorus oxychloride was removed at the pump and the mass washed into 400 ml. of ice-water. The nearly white solid was washed with a little cold water and dried over phosphorus pentoxide. The material weighed 8.6 g. (89.6%) and melted at 69°. This is the literature value (19).

N,N′-Di-p-tosyl-S^{35}-benzidine was prepared from 6.1 g. of purified benzidine (13), 14.5 g. of *p*-toluene-S^{35}-sulfonyl chloride, and 20 ml. of dry pyridine. The dried material melted at 236–239° and weighed 9.4 g. Successive recrystallizations from aqueous acetone and charcoal gave a colorless product weighing 7.6 g. (40.6%). The large crystalline plates melted at 248°. Willstätter (12) reports 243°.

The radioactivity was measured using a Geiger counter 4 mg./sq. cm. and a Higginbotham scaler circuit. Comparison was made with a sample of the original $H_2S^{35}O_4$. A sample of two ml. containing 0.00107 g. gave 115 c./m. or a total of 813,960 c./m. The original sample of $H_2S^{35}O_4$ measured at the same time gave an equivalent of 2,550,000 c./m. The yield was therefore 31.9%. A less pure sample weighing 1.644 g. was obtained from the mother liquors which gave an equivalent of 188,000 c./m. or 7.39%. The mother liquors were examined and a total recovery in all steps was 79% based on the original $H_2S^{35}O_4$. Further

investigation will be necessary to determine the sources of error but it was probably due to the different forms in which the S^{35} was measured.

The following experiments were carried out with non-radioactive material but the methods were exactly those suitable for employment with our radioactive *p*-toluene-S^{35}-sulfonyl chloride.

N-Acetylbenzidine was prepared by the procedure of Cain (14). Recrystallization from 50% alcohol and charcoal yielded a colorless material melting at 199–200°. Cain (14) reports m.p. 199°.

N-Acetyl-N'-p-tosylbenzidine was prepared by stirring for one hour on the water-bath a solution of 2.26 g. (0.01 mole) of N-acetylbenzidine, 1.91 g. (0.01 mole) of *p*-toluenesulfonyl chloride, and 10 ml. of pyridine. The color quickly changed from purple-red to orange. The solution was added slowly and with stirring to 125 ml. of ice-water, made acidic with concentrated hydrochloric acid, and left for several hours. The lightly colored solid when filtered weighed 3.1 g.; m.p. 218–221°. Recrystallization from aqueous alcohol and charcoal, followed by drying at 120–130°, yielded 2.8 g. (73.8%) of colorless microcrystalline needles melting at 227.5°.

Anal. Calc'd for $C_{21}H_{20}N_2O_3S$: S, 8.43. Found: S, 8.37, 8.25.

N-p-Tosylbenzidine. To a hot solution of 1.0 g. (0.0026 mole) of N-acetyl-N'-*p*-tosylbenzidine in 25 ml. alcohol was added 25 ml. of 20% hydrochloric acid. The mixture was heated at reflux for 40 minutes. The solution was concentrated at the pump with warming to remove alcohol, cooled, and neutralized with concentrated ammonia with stirring. The yield was 0.9 g. of lightly-colored material melting at 158–164°. Recrystallization from aqueous alcohol and charcoal afforded 0.8 g. (91%) of near-colorless crystalline material, m.p. 164–165°. It was previously prepared from *p*-tosylhydrazobenzene or azobenzene and *p*-toluenesulfinic acid (20).

Anal. Calc'd for $C_{19}H_{18}N_2O_2S$: S, 9.47. Found: S, 9.0, 8.95.

N-N'-bis(p-Tosylaminophenyl) sulfide. A solution of 2.16 g. (0.01 mole) of *bis*(*p*-aminophenyl) sulfide (15), 3.82 g. (0.02 mole) of *p*-toluenesulfonyl chloride, and 15 ml. of dry pyridine was treated as previously described. The crude material melted at 184–189°. Several recrystallizations from absolute alcohol (charcoal) yielded 4.3 g. (82%) of colorless crystalline material melting sharply at 195°.

Anal. Calc'd for $C_{26}H_{24}N_2O_4S_3$: S, 18.33. Found: S, 18.40.

N-p-Tosylamino-p'-nitrophenyl sulfide. After this paper was prepared for publication an account of the preparation of this compound by Baker, Querry, and Kadish appeared (21). They reported m.p. 154–155°. Our material, after several recrystallizations from benzene-petroleum ether mixture, melted at 157.5–158.5° and weighed 3.2 g. (80%).

Anal. Calc'd for $C_{19}H_{16}N_2O_4S_2$: S, 16.01. Found: S, 15.9, 15.85.

N-p-Tosylamino-p'-aminophenyl sulfide. To a hot solution of 2.0 g. (0.005 mole) of N-p-tosylamino-p'-nitrophenyl sulfide in 20 ml. of glacial acetic acid was added, during one minute, 4.5 g. (0.02 mole) of stannous chloride dihydrate dissolved in 8 ml. of hot concentrated hydrochloric acid. After warming at 60° for 30 minutes the solution was cooled, an equal volume of benzene added, and the solution was neutralized by carefully adding concentrated ammonia with vigorous shaking. The benzene layer was removed, fresh benzene added, and the extraction repeated. The extract was dried over calcium sulfate, filtered through glass wool, and the benzene removed. The light-yellow solid was dissolved in 30% alcohol and permitted to stand overnight (seeding was at times necessary for crystallization to occur). Yield, 1.5 g. of material melting at 140–143°. Recrystallization from 30% alcohol (charcoal) gave 1.3 g. (70.4%) of colorless glistening microcrystals, m.p. 142–143°.

Anal. Calc'd for $C_{19}H_{18}N_2O_2S_2$: S, 17.30. Found: S, 17.12.

N,N'-di-p-Tosylaminodiphenylmethane. A solution of 3.96 g. (0.02 mole) of *p,p'*-diaminodiphenylmethane, 7.64 g. (0.04 mole) of *p*-toluenesulfonyl chloride, and 30 ml. of pyridine was warmed on the water-bath for one hour and poured with stirring into 300 ml. of cold water. Kuhn, Jacob, and Furter (22) using sodium hydroxide instead of pyridine reported m.p. 164°. Two recrystallizations of our material with aqueous alcohol (charcoal), followed by drying at 120°, gave 6.2 g. (61%) of colorless crystals, m.p. 186–187.5°.

Anal. Calc'd for $C_{27}H_{26}N_2O_4S_2$: S, 12.65. Found: S, 12.31.

N-p-Acetylamino-p'-aminodiphenylmethane. This compound was prepared according to the method of Kaslow and Stayner (23) who reported m.p. 135.5–136°. We obtained m.p. 133–134°.

Anal. Calc'd for $C_{15}H_{16}N_2O$: N, 11.66. Found: N, 11.38, 11.59.

N-p-Tosylamino-N'-p-acetylaminodiphenylmethane. A solution of 2.40 g. (0.01 mole) of N-*p*-acetylamino-*p'*-aminodiphenylmethane and 1.90 g. (0.01 mole) of *p*-toluenesulfonyl chloride in 10 ml. of pyridine was warmed for one hour on the water-bath and the solvent removed at the pump. The reddish oil remaining was taken up in aqueous alcohol and permitted to stand overnight. A sample of the dried material melted at 167–168°. Recrystallization from aqueous alcohol (charcoal) yielded 3.25 g. of micro needles, m.p. 167.9–169.2°. Yield, 82.5%.

Anal. Calc'd for $C_{22}H_{22}N_2O_3S$: N, 7.10. Found N, 7.15.

On two occasions in the preparation of this compound a material was obtained which melted at 136–137°. A mixed melting point determination showed no depression but instead, a sharply defined transformation at 137° with no further visible change until 169°, at which point there was complete melting. Possibly these were polymorphic forms; however, there was evidence, though apocryphal, of both quantitative and qualitative nature that the lower-melting substance was a pyridine adduct—that is, two molecules of pyridine had combined with one of the normal product. A lack of material prevented a complete elucidation of the matter.

N-p-Tosylamino-p'-aminodiphenylmethane. To a hot solution of 1.97 g. (0.005 mole) of N-*p*-tosylamino-N'-*p*-acetylaminodiphenylmethane in 20 ml. of alcohol was added 25 ml. of 20% hydrochloric acid and the mixture refluxed for 30 minutes. The solution was concentrated at the pump to remove alcohol and concentrated ammonia was added dropwise with stirring until the mixture was alkaline. After standing overnight the white precipitate was filtered, washed with water, and dried. The crude material melted at 137–140°. Recrystallization from aqueous alcohol (charcoal) yielded 1.4 g. (79%) of a near-white crystalline material, m.p. 156–158°.

Anal. Calc'd for $C_{20}H_{20}N_2O_2S$: S, 9.11. Found: S, 9.0, 9.1.

N,N'-di-p-Tosylaminophenyl ether. Ditosylation was carried out as previously described using 2 g. of *p,p'*-diaminophenyl ether and 3.82 g. of *p*-toluenesulfonyl chloride. Several recrystallizations from aqueous alcohol (charcoal) yielded a white crystalline substance weighing 3.6 g.; m.p. 179–180°. Yield, 71%.

Anal. Calc'd for $C_{26}H_{24}N_2S_2O_5$: S, 12.61. Found: S, 12.22, 12.41.

N-p-Acetylamino-p'-nitrophenyl ether. This compound has been prepared by Ravrick, Brewster, and Dains (24) from *p*-nitrofluorobenzene and *p*-hydroxyacetanilide. They reported m.p. 153°. We used *p*-hydroxyacetanilide, *p*-bromonitrobenzene, sodium hydride, copper powder, and Methyl Carbitol. The melting point was the same but the yield was somewhat less (28–32%).

Anal. Calc'd for $C_{14}H_{12}N_2O_4$: N, 10.3. Found: N, 10.0, 10.3.

p-Nitro-p'-aminophenyl ether. To a hot solution of 1.36 g. (0.005 mole) of N-*p*-acetylamino-*p'*-nitrophenyl ether in 15 ml. of alcohol was added 25 ml. of 20% hydrochloric acid and reflux maintained for 45 minutes. On standing the amine hydrochloride separated in light-yellow, feathery needles. These were washed with a small amount of cold water and dried at 120°; m.p. 215–217°, weight, 0.75 g.

Concentrated ammonia was added slowly with stirring to the filtrate and the yellow precipitate permitted to settle. After filtering, washing, and drying, the free base weighed 0.28 g., m.p. 128–129°. The total crude yield on the basis of the free amine was 87%. Recrystallization of the free base from aqueous alcohol (charcoal) afforded a yellow, finely crystalline material, m.p. 134–135°.

Anal. Calc'd for $C_{12}H_{10}N_2O_3$: N, 12.18. Found: N, 12.2, 12.1.

N-p-Tosylamino-p'-nitrophenylether. A solution of 1.33 g. (0.005 mole) of *p*-nitro-*p'*-aminophenyl ether hydrochloride and 0.95 g. (0.005 mole) of *p*-toluenesulfonyl chloride in 5 ml. of pyridine was warmed for one hour on the water-bath and poured into 200 ml. of

cold water. Concentrated hydrochloric acid was added with stirring until the mixture was definitely acidic. Recrystallization of the gray-yellow solid from alcohol (charcoal) yielded 1.45 g. (75.5%) of fine crystals, m.p. 154–155°.

Anal. Calc'd for $C_{19}H_{16}N_2O_5S$: N, 7.29. Found: N, 7.32.

N-Tosylamino-p'-aminodiphenyl ether. To a hot solution of 1.92 g. (0.005 mole) of N-*p*-tosylamino-*p'*-nitrophenyl ether in 20 ml. of glacial acetic acid was added, during one minute, 4.5 g. (0.02 mole) of stannous chloride dihydrate dissolved in 8 ml. of hot, concentrated hydrochloric acid. After warming at 60° for 30 minutes the solution was cooled and transferred to a separatory funnel. An equal volume of benzene was added and the solution neutralized by carefully adding concentrated ammonia with vigorous shaking. The benzene layer was removed, fresh benzene added, and the extraction repeated. After drying over calcium sulfate, the extract was filtered through glass wool and the benzene removed. Recrystallization of the red solid from aqueous alcohol (charcoal) yielded 1.1 g. (77.5%) of white microcrystalline needles, m.p. 141–142°.

Anal. Calc'd for $C_{19}H_{18}N_2O_3S$: N, 7.91. Found: N, 7.91, 7.84.

An alternate preparation of this material, but in poor yield, was obtained from *p,p'*-diaminophenyl ether dihydrochloride, *p*-toluenesulfonyl chloride, and pyridine.

SUMMARY

In continuation of the search for substances that will localize in tumor tissue the preparation of a series of sulfonamides and certain intermediates is described, together with the proposed scheme for making these materials radioactive. As an example, the preparation of N,N'-di-*p*-tosyl-S^{35}-benzidine is given in detail.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY, UNIVERSITY OF WISCONSIN AND THE METCALF CHEMICAL LABORATORY, BROWN UNIVERSITY]

PROPERTIES OF DINITROÖLEFINS: REACTIONS WITH BASES, CHLORINE, AND HYDROGEN

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Preparation of two dinitroölefins, 2,3-dinitro-2-butene and 3,4-dinitro-3-hexene, from available 1-chloro-1-nitroparaffins by the action of aqueous alkali has been reported in a patent (1a). In reactions with ammonia and some organic bases these dinitroölefins exhibit evidences of aromatic character. Their reactions with various bases, chlorine, and some catalytic reductions are here reported.

Ammonia displaced one nitro group from each of these dinitroölefins to yield a nitroimine, a reaction analogous to the preparation of *o*-nitroaniline by ammonolysis of *o*-dinitrobenzene, assuming a tautomeric shift in the aliphatic case. (The authors recognize the possibility of a tautomeric equilibrium between the nitroimine and an olefinic nitroamine but prefer the former structure.) The imino group was rapidly hydrolyzed by acid at room temperature and alkali liberated ammonia from the nitroimine in the cold, whereas *o*-nitroaniline must be heated with the base. Aniline formed N-substituted nitroimines with the dinitroölefins in an analogous manner (Table I).

The structure of the nitroimines was established by hydrogenating one of them, 2-nitro-3-iminobutane, to 2,3-diaminobutane, a known compound, with a platinum catalyst in 60% yield. Determination of the ammonia liberated at the same time accounted for the other 40% of the starting material. The dinitroölefins were also reduced to the corresponding diamines with platinum or nickel catalysts in low yields (25–33%). The catalytic reduction of 2-nitro-3-(N-phenyl)iminobutane resulted only in hydrogenolysis, from which aniline was recovered in essentially quantitative yield.

A molecular compound resembling in character the picrates of tertiary amines was formed from 2,3-dinitro-2-butene and quinoline. Similar molecular compounds are known in which the nitro moiety may be a polynitroparaffin such as tetranitromethane (1b) but the present case is the first example in which the polynitro component is a dinitroölefin. Nitroparaffins may also act as oxidizing agents for organic bases, yielding salts from which the base may be regenerated (1c). Whether such an oxidation-reduction took place in this instance cannot be said with certainty from the evidence. The analytical data, however, indicates that the molecular compound does not contain a simple ratio of components. Quinoline could still be regenerated from the adduct as was shown by precipitating it as the picrate from an alcohol solution of the molecular compound with a saturated solution of picric acid. The 2,3-dinitro-2-butene was not recovered as such but an alcohol solution of the molecular compound was converted to 2-nitro-3-iminobutane by treatment with aqueous ammonia.

Other tertiary amines such as pyridine, dimethylaniline, isoquinoline, quinal-

dine, and α-picoline gave deep colors with 2,3-dinitro-2-butene in carbon tetrachloride, 95% ethanol, and absolute ethanol, an evidence (2a) of molecular-compound formation but no solid products were isolated. In the case of the stronger bases, pyridine and α-picoline, the color deepening was followed by profound decomposition and evolution of heat.

Secondary amines (diethylamine, morpholine, piperidine, di-*n*-butylamine, methylaniline) likewise gave deep colors with both dinitroölefins but no crystalline substances were isolated.

Whereas the base, ammonia, will displace one nitro group in a dinitroölefin, warm aqueous alkali has no apparent effect on these compounds. In fact, during their purification, the unreacted 1-chloro-1-nitroparaffin may be removed from

TABLE I

NITROIMINES OF FORMULA $RCHNO_2C(=NR')R$

R	R'	M.P. °C.[a]	CARBON, %		HYDROGEN, %		NITROGEN, %	
			Calc'd	Found	Calc'd	Found	Calc'd	Found
CH_3	H	159–160					24.13	24.2
C_2H_5	H	83–83.5					19.45	19.5[b]
CH_3	C_6H_5	97–98	62.50	62.72	6.25	6.23	14.58	14.66
C_2H_5	C_6H_5	62.5–63	65.47	65.62	7.27	7.59	12.72	12.58
C_2H_5	$C_6H_4NH_2(p)$	175.5–177	61.25	61.46	7.28	7.29		

[a] All melting points reported in this paper are corrected. [b] Imino nitrogen: Calc'd, 9.72. Found, 10.4.

the desired product by washing with warm alkali. When alcoholic potassium hydroxide was added to a dinitroölefin, however, a vigorous reaction ensued, potassium nitrite precipitated, and a deep red solution of a polymer remained. When the order of addition was reversed, for example, by adding a methanol solution of 3,4-dinitro-3-hexene to a methanol solution of potassium hydroxide, a white salt formed, to which we have assigned the structure of the potassium salt of 1-nitro-1-methoxypropane. The yield is quantitative according to the following equation:

$$CH_3CH_2C(NO_2)=C(NO_2)-CH_2CH_3 + KOH + CH_3OH \rightarrow CH_3CH_2C(OCH_3)=NO_2K + CH_3CH_2COOH + \tfrac{1}{2}H_2N_2O_2$$

The formation of potassium hyponitrite was suggested by the following observations. Immediately after running the reaction, no nitrite was present in the alkaline filtrate but after standing overnight, nitrite was present. If the filtrate was acidified with acetic acid, it did not show the presence of nitrite upon standing. The filtrate gave the Rao test (2b) for hyponitrous acid.

Potassium acetate was identified in the filtrate from the preparation of the potassium salt of 1-nitro-1-ethoxyethane by an analogous reaction.

The dinitroölefins reduce alkaline permanganate solution rapidly giving nitric acid and the corresponding carboxylic acid. The compounds are slightly soluble in concentrated sulfuric acid but may be recovered unchanged upon pouring into water. Bromine and chlorine do not add to the olefinic bond under ordinary conditions but liquid chlorine in a closed tube added to the double bond and also substituted in the side chain of 2,3-dinitro-2-butene during the course of a week's exposure to sunlight.

EXPERIMENTAL

3-Nitro-4-iminohexane. Five grams of 3,4-dinitro-3-hexene (1a) was shaken with 25 ml. of 28% ammonium hydroxide solution at room temperature for several minutes whereupon the imine separated, m.p. 81–84°, yield 3.4 g., 83%. The nitroiminohexane was recrystallized from 95% ethanol (yellow rhombs) or water (white plates), to the pure compound, m.p. 83–83.5°. The reaction takes the same path in liquid ammonia at a slower rate.

For preparing the N-substituted iminonitro compounds, the dinitroölefin was dissolved in cold 95% ethanol and an alcohol solution of the amine was added slowly. Upon cooling in an acetone-Dry Ice bath, the nitroimines separated and were recrystallized from 95% ethanol. Yields, 50–70%.

When the alcohol filtrate from the preparation of 3-nitro-4-(N-phenyl)iminohexane was poured into water, a yellow brown crystalline substance was obtained. After recrystallization from absolute ethanol, it gave m.p. 97–98° and was identified as diazoaminobenzene.

3,4-Diaminohexane. A solution of 1.65 g. of pure 3-nitro-4-iminohexane in 100 ml. of absolute ethanol was reduced in 9 minutes at room temperature in the presence of 0.6 g. of platinum oxide catalyst using a mechanical shaker at a pressure of 40–30 p.s.i. of hydrogen. After decanting the alcohol solution, distillation gave 1.2 g. of an oil, b.p. 165–180°. Conversion of this oil to the *bis*-benzamide indicated a yield of 63% of pure diamine in the reduction. From the alcohol distillate, ammonia was recovered as 0.038 g. of ammonium chloride, indicating hydrogenolysis had taken place to the extent of 6.2% during the reduction.

Reduction of 14.4 g. (0.1 mole) of the 3-nitro-4-iminohexane gave 5.3 g. (46%) of 3,4-diaminohexane (b.p. 168–175°) from which a pure fraction, b.p. 175–176°, was obtained, n_D^{25} 1.4499. The compound has the characteristic odor of the aliphatic diamines, is hygroscopic, colorless, and absorbs carbon dioxide rapidly. The following derivatives were prepared by methods described in the literature (3):

Bis-benzamide: m.p. (closed tube) 332–333°, from a large volume of 95% ethanol.

Anal. Calc'd for $C_{20}H_{24}N_2O_2$: N, 8.64. Found: N, 8.36, 8.59.

Bis-phenylthiourea: m.p. 193–194°, from absolute methanol.

Anal. Calc'd for $C_{20}H_{26}N_4S_2$: C, 62.13; H, 6.78.
Found: C, 62.30; H, 6.89.

Bis-acetamide: m.p. 297–298°, from 95% ethanol.

Anal. Calc'd for $C_{10}H_{20}N_2O_2$: N, 14.00; Found: N, 13.70.

Oxalate: m.p. 199–200°, after softening at 195°; recrystallized from water, followed by two sublimations at 0.2 mm. The oxalate was found to be unreliable as a means of estimating the diamine when ammonia was present. The two oxalates were difficult to separate by recrystallization and ammonium oxalate sublimed with the diamine oxalate. Melting points with two to three degree ranges between 195° and 224° were obtained from various preparations of the diamine where ammonia was not first removed.

Anal. Calc'd for $C_8H_{18}N_2O_4$: C, 46.59; H, 8.80.
Found: C, 46.15; H, 8.63.

With a W-6 Raney nickel catalyst (4) at an initial pressure of 3000 p.s.i. of hydrogen at 35°, yields of 62–70% of 3,4-diaminohexane were obtained in reducing 0.03 mole of 3-nitro-4-iminohexane. The loss of nitrogen as ammonia was 15%.

The catalytic reduction of 3,4-dinitro-3-hexene gave unsatisfactory results with both W-6 Raney nickel and platinum oxide catalysts. The reduction with W-6 catalyst was run as before, except that an initial temperature of 50° was required to start the reduction; yield of diamine, 25%; loss of nitrogen *via* ammonia, 15%. The reduction method of Kindler (5) with platinum oxide in glacial acetic acid to which concentrated sulfuric acid was added gave 23% yield of the diamine.

Reduction of 0.04 mole of 3-nitro-4-(N-phenyl)iminohexane with a platinum oxide catalyst at 45 p.s.i. of hydrogen resulted in complete hydrogenolysis as aniline was recovered in quantitative yield. Other products were not identified.

2,3-Diaminobutane. By reducing 0.05 mole of 2-nitro-3-iminobutane in the presence of 1 g. of platinum oxide in the same way as described for the higher homolog, 2,3-diaminobutane was obtained, b.p. 130–150° (6, 7). Yield, 60%; loss of nitrogen *via* ammonia, 40%. The compound was identified as the oxalate, m.p. 237–238° (8), and as the dibenzamide, m.p. 296–297°. Morgan and Hickinbottom (6) report the dibenzamide, m.p. 236–238°.

Anal. Calc'd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45.

Found: C, 72.79; H, 6.59; N, 9.76.

The reduction of 2,3-dinitro-2-butene with W-6 Raney nickel catalyst under identical conditions described for the higher homolog gave a 33% yield of 2,3-diaminobutane.

Chlorination of 2,3-dinitro-2-butene. Two grams of 2,3-dinitro-2-butene, sealed with 5 ml. of carbon tetrachloride and 5 ml. of liquid chlorine in a Carius tube, was exposed to sunlight for one week. Fractionation of the reaction product gave 0.4 g. of colorless liquid, b.p. 170–176°, which did not reduce permanganate solution. A chlorine analysis indicated that substitution had taken place as well as addition to the double bond. The product was not further identified.

Anal. Calc'd for $C_4H_5Cl_3N_2O_4$: Cl, 42.30. Found: Cl, 42.74.

Attempts to chlorinate the dinitroölefin with chlorine gas and sulfuryl chloride were not successful.

Potassium salt of 1-nitro-1-methoxypropane. An ice-cold solution of 1.0 g. of 3,4-dinitro-3-hexene in 10 ml. of absolute methanol was added dropwise to a stirred solution of 5 g. of potassium hydroxide in 25 ml. of absolute methanol in an ice-bath. A slight yellow color appeared at the surface as the two solutions met but rapid stirring resulted in a white precipitate of the salt in a colorless solution. The potassium salt was filtered, after adding 15 ml. of dry acetone, and washed with methanol and dry ether. Yield, 0.85 g.; 96%. A sample was recrystallized twice from methanol to which a few drops of water were added. The compound remained white for a week over potassium hydroxide in a desiccator but slowly turned yellow.

Anal. Calc'd for $C_4H_8KNO_3$: K, 24.87; N, 8.92.

Found: K, 25.05; N, 9.39.

Using absolute ethanol as solvent, the potassium salts of 1-nitro-1-ethoxypropane and 1-nitro-1-ethoxyethane were prepared in an analogous manner. A quantitative yield of the first salt was obtained but the latter was more soluble and less stable. A sample of the potassium salt of 1-nitro-1-ethoxypropane was recrystallized from ethanol containing a few drops of water.

Anal. Calc'd for $C_5H_{10}KNO_3$: N, 8.18. Found: N, 8.2.

Molecular compound of 2,3-dinitro-2-butene and quinoline. Three grams of 2,3-dinitro-2-butene dissolved in 20 ml. of absolute ethanol was cooled to 10°. After adding 5 ml. of colorless quinoline[1] dropwise, the solution darkened and when it reached a red color it was cooled rapidly. A yellow-green solid separated which was recrystallized from 95% ethanol or chloroform and petroleum ether (b.p. 60–68°) to yield 3.0 g. of bright yellow crystals, m.p. 104–104.5°.

Anal. Calc'd for $C_{15}H_{15}N_3O_3$: C, 62.48; H, 6.29; N, 14.57.

Found: C, 62.67, 62.41; H, 6.22, 6.32; N, 14.36, 14.50.

[1] From the Skraup synthesis. Freshly distilled commercial quinoline failed to give a crystalline product.

The product was obtained only in absolute ethanol as solvent but showed a negligible amount of ethoxyl to be present by a quantitative determination. One gram of the complex was converted to 0.17 g. of 2-nitro-3-iminobutane by shaking an alcohol solution of the complex with aqueous ammonia. A few milligrams of quinoline picrate were precipitated from an alcohol solution of 0.1 g. of the complex by adding an excess of a saturated alcoholic solution of picric acid.

Acknowledgment. Part of the work described here was done at the University of Wisconsin while one of us (L. B. C.) was on leave of absence. Six of the analyses were performed there by Messrs. Bennett G. Buell and Edward A. Shiner. Mr. J. F. Jones prepared the W-6 catalyst for the reductions. I wish to acknowledge the kindness of the Organic Chemistry Department at Wisconsin in extending the facilities of the laboratory to me for this work.

SUMMARY

1. Nitroölefins exhibit aromatic character in reactions with ammonia and various amines, resembling *o*-dinitrobenzene in behavior.

2. The olefinic double bond in these compounds is inert to halogen addition.

3. With alcoholic solutions of strong alkalis, the nitroölefins give a new class of compounds, salts of nitro ethers.

4. Some catalytic reductions of nitroölefins and nitroketimines are described.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

THE METHOXYMERCURATION OF N-ALLYLPHTHALIMIDE

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It is generally accepted that the products obtained in the methoxymercuration of an unsaturated compound can be predicted from knowledge of the dipole direction of the unsaturated grouping, the entering mercury group being considered the positive fragment (1). However, no proof of the structure of the methoxymercurial derived from an N-allylamide compound has ever been reported. Since the basic organic structure of almost all the mercurial diuretics (Mercuhydrin, Salyrgan, etc.), employed in the clinical therapy of congestive heart failure, is of the N-allylamide type, it is important that this proof be sought. The purpose of the work was to seek the proof using some simple structure (N-allylphthalimide) which would yield readily crystallized derivatives and then to apply the experience and knowledge gained to a study of the structure of Mercuhydrin.[2] For that matter, the methoxymercurial derived from N-allylphthalamic acid is employed in Italy as a diuretic (2).

Carrara and Mori (3) apparently were the first to study the addition of mercuric acetate in methanol to N-allylphthalimide. They reported a yield of 60% and arbitrarily assigned structure II, N-(2-acetoxymercuri-3-methoxypropyl)phthalimide, to the compound. The isomeric structure (I) was reported by Tabern (4) in the patent literature for the addition compound of mercuric acetate in methanol to N-allylphthalamic acid. No proof of structure was offered in either reference, though general considerations would favor the orientation proposed by Tabern.

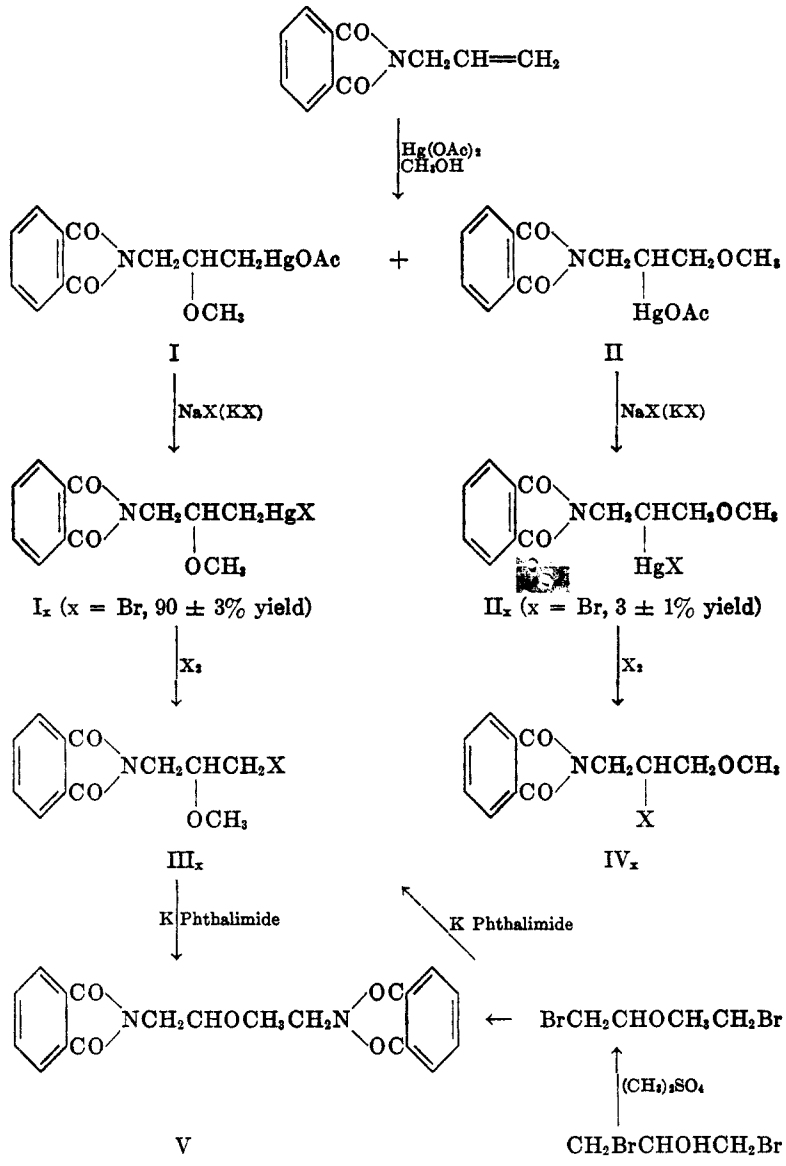
In more precise work of this laboratory, it was found that the addition of mercuric acetate in methanol to N-allylphthalimide actually gave *both* isomers —the predominant one in yields of 90 ± 3%, the minor one in yields of 3 ± 1%.[3] This is the first conclusive example of the isolation of both isomers from a methoxymercuration reaction. It is true that Connor and Wright (5) have indicated the formation of such a mixture in the methoxymercuration of oleic acid, but the properties of the mercurials were such as not to warrant separation and identification.

[1] Lakeside Laboratories Fellow, 1947–1948 and 1948–1949. Abstracted from a thesis by Max V. Sigal, Jr., in partial fulfillment of the requirements for the degree Doctor of Philosophy, Vanderbilt University.

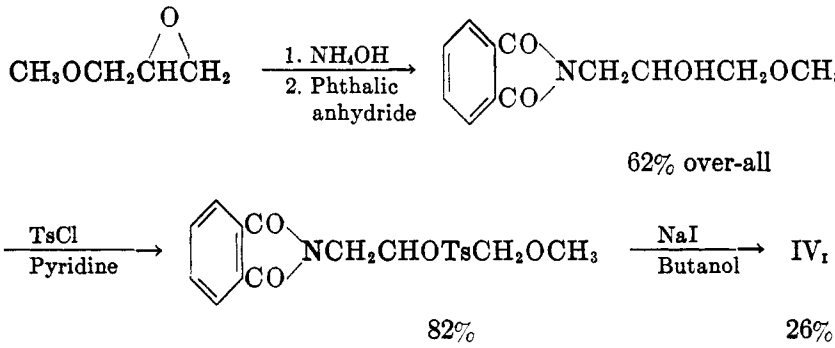
[2] The authors acknowledge the financial support of Lakeside Laboratories, Inc., who suggested the work on Mercuhydrin and have given their fullest cooperation on all phases of the problem.

[3] Since the acetates were too soluble in most solvents for semi-quantitative isolation work, the yields were actually based on the mercuric bromides obtained from the acetates by treatment with potassium bromide.

FLOW CHART



The structure of I, the predominant isomer, was proved to be N-(2-methoxy-3-acetoxymercuripropyl)phthalimide by the series of reactions given in the Flow Chart and described in the Experimental. The structure of II, the less predominant isomer, was proved to be N-(2-acetoxymercuri-3-methoxypropyl)phthalimide by its degradation to IV_I, which was identical with the synthetic compound made as follows:



EXPERIMENTAL

A. *The methoxymercuration of N-allylphthalimide.* To a hot solution of mercuric acetate (127.2 g., 0.40 mole) in 1100 cc. of absolute methanol, a solution of N-allylphthalimide (75.5 g., 0.403 mole, m.p. 69–70°[4]) in 500 cc. of hot methanol was added all at once. The resulting solution was refluxed for three hours, filtered hot, and allowed to crystallize. The methoxyacetoxymercurial (I) thus formed was washed with 200 cc. of cold methanol and air-dried (149 g., 78%, m.p. 138–139.5°).

Anal. Calc'd for $C_{14}H_{15}HgNO_5$: Hg, 41.97. Found: Hg, 41.58, 41.72, 41.83.[5]

The mother-liquor was concentrated to about 700 cc. and then treated with a hot solution of aqueous potassium bromide (10.6 g., 0.09 mole) in 75 cc. of water. The methoxybromomercurial (I_{Br}) crystallized slowly. After standing for 24 hours, the crystals were collected and air-dried (24.1 g., 12%, m.p. 165–171°).[6] The filtrate, on standing for another day, deposited the isomeric methoxybromomercurial (II_{Br}), which, when dried, weighed 8.6 g. (4.3%, m.p. 122–124.5°; recrystallized from methanol, m.p. 124–125.5°).

Anal. Calc'd for $C_{12}H_{13}BrHgNO_3$: Hg, 40.23; Br, 16.03.
Found: Hg, 39.91, 40.07; Br, 15.96, 15.95.

This procedure was repeated several times and the yields duplicated, *i.e.*, I and/or I_{Br}, 90±3%; II_{Br}, 3±1%.

B. *Halides of the predominant isomer (I_x, x = Cl, Br, and I).* To a hot solution of I (108 g., 0.226 mole) in 1200 cc. of methanol, a hot solution of potassium halide (0.24 mole) in 250 cc. of water was added. I_x began to crystallize immediately and, on cooling, filtering, and air-drying, gave the following results:

METHOXYHALOMERCURIAL	M.P., °C.	YIELD, %	Hg		HALOGEN	
			Calc'd	Found	Calc'd	Found
I_{Br}	173 –174	93	40.23	40.09 (Avg.)	16.03	15.9 (Avg.)
I_{Cl}	171.2–172	96	44.16	43.91	7.81	7.7
I_I	159 –160.2	97	36.76	36.75	23.25	23.4

[4] All melting points were taken with a partial immersion thermometer, 0–300°, corrected by comparison with U.S.P. reference standards.

[5] The mercury and halogen determinations of the methoxymercurials were done in this laboratory by the method of Rauscher (6). All other determinations were done by Clark Microanalytical Laboratory, Urbana, Ill.

[6] The wide melting point range of this I_{Br} crop indicated contamination with some II_{Br}, to be described.

The halides were so insoluble in methanol and other solvents (except acetic acid), that recrystallization of large batches was not practical. The analytical results were obtained with original crops. The halides were quite stable but darkened over a period of months, if they were not protected from light.

C. *The halogenation of the methoxyhalomercurials.* 1. *Iodination of the predominant isomer, N-(2-methoxy-3-bromomercuripropyl)phthalimide* (I_{Br}). A well-stirred suspension of I_{Br} (5 g., 0.01 mole) in 100 cc. of methanol containing iodine (2.6 g., 0.01 mole) was refluxed until the color of iodine had practically disappeared (20 min.). The solution was then concentrated at water-pump vacuum to about 20 cc. and diluted with 50 g. of 20% aqueous potassium iodide solution. The demercurated product separated as an oil, but solidified on standing in the refrigerator. It was filtered, washed with more aqueous iodide solution, with water, and then air-dried (3.6 g., more than quantitative). Recrystallization from 50 cc. of methanol gave a first crop (2.75 g., m.p. 107.5–108.5°) and a second crop (0.3 g., m.p. 106–107.5°), representing a total yield of 88% N-(2-methoxy-3-iodopropyl)phthalimide (III_I).

A similar iodination of I_I, using carbon tetrachloride in place of methanol, gave a yield of 87% of III_I, m.p. 103–105°; recrystallization from methanol m.p. 108–109°; identical with first iodination compound.

Anal. Calc'd for $C_{12}H_{12}INO_3$: I, 36.77; C, 41.76; H, 3.51.

Found: I, 37.23; C, 42.15; H, 3.48.

The two experiments showed that iodine replacement was independent of solvent effect, and either the bromomercurial or iodomercurial could be converted to the demercurated iodo compound (III_I).

2. *Iodination of the less predominant isomer, N-(2-Bromomercuri-3-methoxypropyl)phthalimide* (II_{Br}). The iodination of II_{Br} (1.35 g., 0.0027 mole) gave 0.80 g. (86%, m.p. 70–71°) of N-(2-iodo-3-methoxypropyl)phthalimide (IV_I). IV_I had unusual properties. When recrystallized from petroleum ether (b.p. 69–70°), the m.p. was 71–72°. When heated above its m.p., allowed to resolidify, and then recrystallized from petroleum ether, the m.p. was 79.5–80°. When the low-melting form was dissolved in petroleum ether and seeded with the high-melting form, the resultant recrystallized product melted at 78.7–80°.

Anal. Calc'd for $C_{12}H_{12}INO_3$: I, 36.77; C, 41.76; H, 3.51.

Found: I, 37.22; C, 42.22; H, 3.78.

3. *Bromination of* I_{Br}. The bromination of I_{Br} in ethyl acetate, catalyzed by bright sunlight, was erratic and yielded an inferior demercurated product (III_{Br}, average yield 55%; m.p. 101–102.5° after recrystallization from methanol). The bromine analysis was slightly high, indicative of some uncontrolled bromination which is apparently inherent in this process (7); however, the mixed melting point showed no depression with the authentic sample to be described. III_{Br} was obtained in a better state of purity *via* the phthalamic acid route. I_{Br} (121 g., 0.243 mole) was dissolved in 500 cc. of a warm 5% aqueous solution of sodium hydroxide. The solution was diluted to 1 liter, mixed with several grams of Supercel and filtered. The filtrate was acidified with acetic acid and the white solid, N-(2-methoxy-3-bromomercuripropyl)phthalamic acid (VI_{Br}), washed with water and air-dried (116 g., 92.5%, m.p. 135–136° with dec.; recrystallization of 3 g. of VI_{Br} from 65 cc. of methanol, m.p. 136° sharply with dec.). Crude VI_{Br} (108 g., 0.21 mole) was redissolved in 500 cc. of water containing sodium hydroxide (8.5 g., 0.215 mole). After filtration of the solution to remove an insoluble residue (5.6 g.), potassium bromide (38.5 g.) was added. To this stirred solution, cooled in an ice-bath and exposed to bright sunlight, a solution of bromine (33.5 g., 0.21 mole) in 250 cc. of water containing 38.5 g. of potassium bromide was added over a period of 45 minutes. The solution was acidified with hydrobromic acid (litmus), allowed to stand in the refrigerator for one hour, filtered to remove a small amount of foreprecipitation, and refrigerated overnight. N-(2-Methoxy-3-bromopropyl)phthalamic acid (VII_{Br}) formed (29.7 g., 45%, m.p. 113–115.5°). The filtrate, on continued refrigeration, deposited a further amount of VII_{Br} (10 g., 15.3%, m.p. 118–120°). Recrystallization of the

first crop from 350 cc. of chloroform yielded pure VII_{Br} (18.5 g., m.p. 118–119°, Neutral equivalent, calc'd: 316. Found: 317.8, 315.5). VII_{Br} was converted to the phthalimide (III_{Br}) by refluxing for one hour in glacial acetic acid. After recrystallization from methanol, III_{Br} was obtained in a good state of purity (m.p. 102.5–103.5°).

Anal. Calc'd for $C_{12}H_{12}BrNO_3$: Br, 26.81; C, 48.34; H, 4.04.
Found: Br, 26.73; C, 48.79; H, 4.06.

D. *The synthesis of reference compounds and comparison with the degradation products of the mercurials.* 1. *1,3-Dibromo-2-methoxypropane.* Glycerol-1,3-dibromohydrin (8) was converted to 1,3-dibromo-2-methoxypropane by the method of Krantz and Foreman (9). In a 1-liter, round-bottomed flask, glycerol-1,3-dibromohydrin (408 g., 1.87 moles) and freshly distilled methyl sulfate (276 g., 2.2 moles) were heated by means of a water-bath for 12 hours. The reaction mixture was then cooled and neutralized with sodium bicarbonate solution (180 g. in 2 liters of water). The oily layer was separated, washed consecutively with *cold*, 50% aqueous sodium hydroxide, cold concentrated ammonium hydroxide, diluted with chloroform, washed further with water, and dried. The crude product (143 g.) distilled at 82–94° at 17 mm. Redistillation yielded pure 1,3-dibromo-2-methoxypropane (b.p. 89.5–92.5° at 22 mm., n_D^{25} 1.5100; 124 g.; 28.5%.)

2. *The Gabriel reaction with 1,3-dibromo-2-methoxypropane.* A mixture of potassium phthalimide (37 g., 0.2 mole), 1,3-dibromo-2-methoxypropane (60 g., 0.26 mole), xylene (75 cc.), and sodium iodide (0.5 g.) was refluxed for 10 hours with considerable darkening. After steam-distilling to remove the excess 1,3-dibromo-2-methoxypropane, the diphthalimido compound was separated by reason of its insolubility in petroleum ether (b.p. 69–70°). To remove phthalic acid, it was suspended in 2% sodium hydroxide and washed with water (6.2 g., 17%, m.p. 200–205°). Two recrystallizations of 3.2 g. of crude V from 150-cc. portions of ethyl acetate yielded pure 1,3-diphthalimido-2-methoxypropane (V, 1.2 g., m.p. 208.5–209°).

Anal. Calc'd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43.
Found: C, 65.79; H, 4.27.

A mixed melting point of V with the diphthalimido compound obtained from III_I by the Gabriel reaction (62% yield) showed no depression.

Anal. Calc'd for $C_{20}H_{16}N_2O_5$: C, 65.93; H, 4.43.
Found: C, 66.20; H, 4.34.

The petroleum ether extract yielded 14 grams of crude N-(2-methoxy-3-bromopropyl)-phthalimide (23%, m.p. 95–100°). Two recrystallizations from methanol (1 g. per 10 cc.) raised the melting point to 102.5–103.5° (9.2 g.). Further recrystallization gave the pure compound (m.p. 103.2–104°).

Anal. Calc'd for $C_{12}H_{12}BrNO_3$: Br, 26.81; C, 48.34; H, 4.04.
Found: Br, 27.01; C, 48.57; H, 4.04.

A mixed melting point of synthetic N-(2-methoxy-3-bromopropyl)phthalimide with III_{Br}, derived from the mercurial, showed no depression, thus establishing the structure of III_{Br}.

3. *The synthesis of N-(2-iodo-3-methoxypropyl)phthalimide* (IV_I). (a). *1-Chloro-3-methoxy-2-propanol.* The general procedure of Koelsch (10) was used, and the properties of the compound compared well with that of Flores-Gallardo and Pollard (11), (b.p. 170–171° at 748 mm., n_D^{25} 1.4422, 72% yield).

(b). *1,2-Epoxy-3-methoxypropane (Methyl glycidyl).* The basic procedure of Clark and Hartman (12) was used, and the properties of the methyl glycidyl obtained compared well with those of Flores-Gallardo and Pollard (11). (b.p. 112–117° at 750 mm., 71% yield.)

(c). *2-Hydroxy-3-methoxypropylamine.* The method of Knorr and Knorr (13) was used to make this new compound [62% yield; b.p. 90–91° at 10 mm., n_D^{25} 1.4536–38, d_{25}^{25} 1.0591; Neutral equiv. Calc'd: 109; Found, 105; *urea derivative* (14), m.p. 92.5–94° after recrystallization from ethylene chloride].

(d). *N-(2-Hydroxy-3-methoxypropyl)phthalimide.* The method of Cope, *et al.* (15) was used to make this new compound. The yield of crude product was quantitative (m.p. 57–61°).

Crystallization of a small amount from petroleum ether (b.p. 69–70°; 0.5 g. from 100 cc.) gave the pure compound, m.p. 61.5–62.5°.

Anal. Calc'd for $C_{12}H_{13}NO_4$: C, 61.27; H, 5.7.

Found: C, 61.24; H, 5.54.

(e). *The tosyl ester of N-(2-Hydroxy-3-methoxypropyl)phthalimide and other less successful derivatizations.* Attempts were first made to convert the hydroxy compound directly to the corresponding halogen derivative. Treatment of N-(2-hydroxy-3-methoxypropyl)phthalimide with phosphorus triiodide gave an unknown iodo derivative which did not give the correct analysis; 15% yield; m.p. 118–120°.

Anal. Calc'd for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.51.

Found: C, 42.7; H, 3.17.

Treatment of the hydroxy compound with thionyl chloride gave a poor yield of the *sulfite ester*, m.p. 139–139.5°;

Anal. Calc'd for $C_{24}H_{24}N_2O_9S$: C, 55.80; H, 4.68.

Found: C, 55.87; H, 4.73.

Treatment of N-(2-hydroxy-3-methoxypropyl)phthalamic acid (prepared as an oil from the amine and phthalic anhydride) with excess thionyl chloride yielded N-(2-chloro-3-methoxypropyl)phthalimide (20%, m.p. 71–72.5° from methanol and water).

Anal. Calc'd for $C_{12}H_{12}ClNO_3$: Cl, 14.0. Found: Cl, 13.5.

The tosylation of N-(2-hydroxy-3-methoxypropyl)phthalimide was accomplished as follows: the phthalimide (14 g., 0.06 mole) and *p*-toluenesulfonyl chloride (11.3 g., 0.06 mole) were mixed in 25 cc. of dry pyridine and allowed to stand overnight. The tosyl ester which crystallized was washed with 50% methanol-water. The filtrate on dilution with water deposited a further amount of the tosyl ester. The combined crude yield was 19 g., 82%, m.p. 150–156°. Recrystallization from ethanol gave 15 g. of tosyl ester m.p. 157–157.6°. The analytical sample melted at 157.2–157.8°.

Anal. Calc'd for $C_{19}H_{19}NO_6S$: S, 8.23. Found: S, 8.44.

(f). *N-(2-Iodo-3-methoxypropyl)phthalimide.* Attempts to replace the chlorine group of N-(2-chloro-3-methoxypropyl)phthalimide by sodium iodide in acetone at 110° (sealed tube) and by sodium iodide in refluxing butanol failed. On the other hand, the replacement of the tosyl ester by iodine using sodium iodide and refluxing butanol was successful as described (16): the tosyl ester (6 g., 0.015 mole) and sodium iodide (6.75 g., 0.04 mole) were dissolved in 90 cc. of dry *n*-butanol and refluxed for several hours. By this time, the sodium-*p*-toluenesulfonate, which had separated out, caused considerable bumping. It was removed and the filtrate refluxed for four more hours. After a second filtration, the butanol was removed by distillation at reduced pressure (water aspirator). The residue was extracted with two 50-cc. portions of petroleum ether (b.p. 69–70°) and the remaining product dissolved in hot methanol. On cooling the methanol, some unreacted tosyl ester crystallized which was removed by filtration. The methanol filtrate was diluted with water, whereupon the iodo derivative crystallized. The iodo compound from the petroleum ether extract and from the methanol-water weighed 1.3 g. (26%). Recrystallization from petroleum ether gave pure N-(2-iodo-3-methoxypropyl)phthalimide, m.p. 79–80°; repeated recrystallizations, m.p. 80–80.2°.

Anal. Calc'd for $C_{12}H_{12}INO_3$: C, 41.76; H, 3.5; I, 36.77.

Found: C, 41.54; H, 3.46; I, 36.23.

A mixed melting point of the synthetic sample and of IV$_I$, the iodo derivative of the methoxymercuration product, showed no depression. Furthermore, when the low-melting form of IV$_I$ (m.p. 70–71°) was seeded in petroleum ether with the synthetic sample, the melting point was raised to 79–80°. When the synthetic sample (m.p. 79–80°) was recrystallized from methanol-water, the melting point was again lowered (m.p. 70–80°).

E. *An alternate procedure for the methoxymercuration of N-allylphthalimide* (17). A mixture of mercuric chloride (10.3 g., 0.0375 mole) and mercuric acetate (12 g., 0.0375 mole) in hot methanol was added to N-allylphthalimide (14.2 g., 0.075 mole) dissolved in 100 cc. of hot methanol. After refluxing for three hours, it was allowed to cool overnight, and the

crystals obtained were washed with 50 cc. of methanol, and air-dried (29.7 g., 87%, m.p. 169–170.5°). The identity of this product was established as N-(2-methoxy-3-chloromercuripropyl)phthalimide (Ic_l) by iodination to III_I (81%, m.p. 107–108°; mixed m.p. with III_I showed no depression). By concentration of the filtrate, the isomeric chloromercurial was obtained in an impure state (2 g., m.p. 110–120°). Repeated recrystallization from methanol gave 0.3 g., m.p. 128–129°. The identity of this product was established as N-(2-chloromercuri-3-methoxypropyl)phthalimide by iodination to IV_I (quantitative yield, m.p. 79.5–80°, mixed m.p. with IV_I showed no depression).

SUMMARY

The methoxymercuration of N-allylphthalimide yielded two position isomers whose structures were proved to be N-(2-methoxy-3-acetoxymercuripropyl)-phthalimide, the predominant isomer, and N-(2-acetoxymercuri-3-methoxypropyl)phthalimide, the less predominant isomer.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, VANDERBILT UNIVERSITY]

STUDIES CONCERNING THE STRUCTURE OF MERCUHYDRIN[1]

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Mercuhydrin is a widely used diuretic, composed of a complex of theophylline and the methoxymercuration product of β-carboxypropionylallylurea (1, 2). Most of the work of this problem was concerned only with the structure of the methoxymercuration product which will be called M. When this work was begun, little was known of the precise structure of M or other methoxymercurials of a similar nature. It had been demonstrated that Salyrgan, another diuretic, contained a methoxyl grouping (3). The mercury atom had usually been assigned the 3-position in the allylamide fragment, although no proof of this orientation was recorded in the literature (4). In fact, it was not even certain whether M was a homogeneous substance. With this background and with the results of the work described in the preceding paper, the following studies on the structure of M were made.

It was not certain whether the starting material possessed structure (I) or (II):

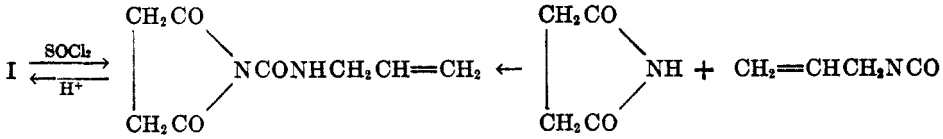
$$HOOCCH_2CH_2CONHCONHCH_2CH{=}CH_2$$

I

$$HOOCCH_2CH_2CON(CH_2CH{=}CH_2)CONH_2$$

II

though structure I was favored by analogy to the amide obtained by the acetylation of methylurea (5). The problem was solved by smooth conversion of I to N-succinyl-N′-allylurea:



Mild hydrolysis regenerated I. Since I was also synthesized from the reaction product of succinimide and allyl isocyanate, there could be no doubt that the structure of the starting material was N-(β-carboxypropionyl)-N′-allylurea (I).

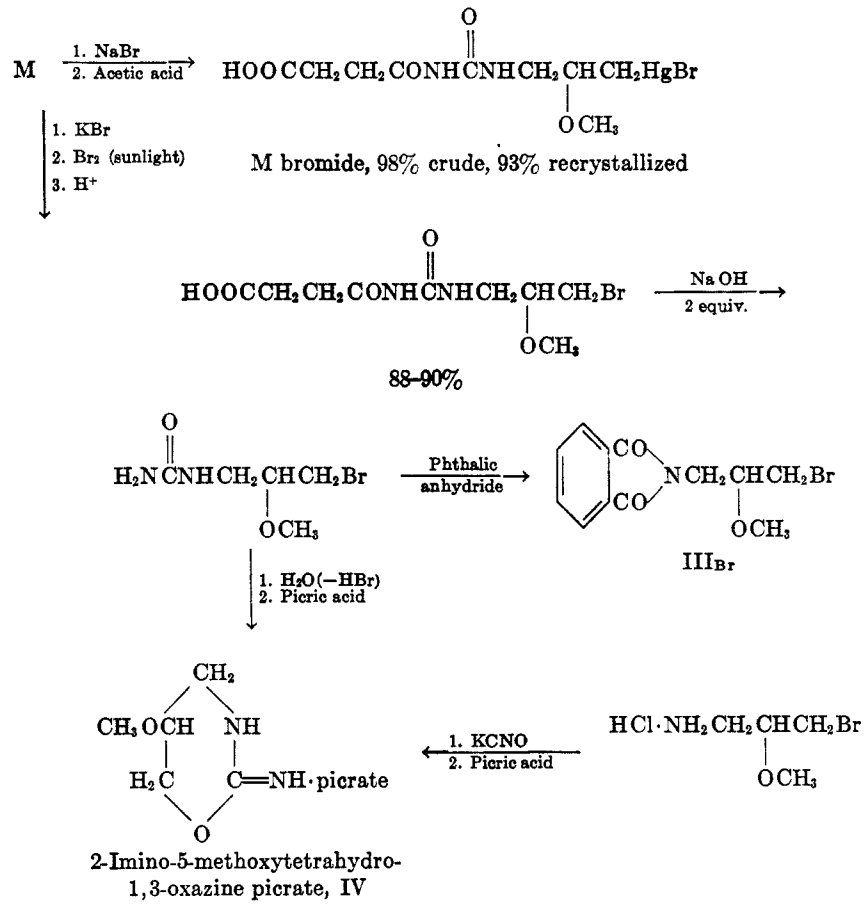
The methoxymercuration of I gave M in good yield. As agreed with other observers, the structure of this product (or others with free carboxyl groups or complexing groups) was uncertain and perhaps variable (6). Analyses and chemical behavior of M indicated the general structure:

[1] This laboratory is indebted to Lakeside Laboratories, Inc., Milwaukee, Wis., for suggesting and financing this problem and for permission to publish the results.

[2] Lakeside Laboratory Fellow. Abstracted from a thesis by Max V. Sigal, Jr., in partial fulfillment of the degree, Doctor of Philosophy, Vanderbilt University.

$H(OOCCH_2CH_2CONHCONHCH_2CHOCH_3CH_2Hg)_xOOCCH_3$. Van Loon and Carter (7) have encountered similar compounds. Analyses of M purified by solution in sodium bicarbonate and reprecipitation with acetic acid indicated the structure: $HOOCCH_2CH_2CONHCONHCH_2CHOCH_3CH_2HgOH$. The recalcitrant nature of M, as ascertained by its insolubility in water and other solvents and by its non-crystalline characteristics, was overcome by converting it to the crystalline M halides, using the appropriate potassium or sodium halide, thus facilitating the investigation of the homogeneity of M, itself. Intensive investigation of the M halides prepared from M both of this laboratory and of plant batches indicated that, within the limits of detection, the M halides were perfectly homogeneous substances (8).

The structure of M bromide was proved by the following series of reactions:



2-Imino-5-methoxytetrahydro-1,3-oxazine picrate, IV

N-(2-Methoxy-3-bromopropyl)urea was unstable, decomposing in hot aqueous solutions or on standing to the tetrahydroöxazine (IV). A similar tetrahydrooxazine has been prepared by Gabriel and Lauer (9) from 3-bromopropylamine

and potassium cyanate.[3] The identical compound was prepared from potassium cyanate and 2-methoxy-3-bromopropylamine hydrochloride, the latter having been obtained from the acid hydrolysis of the N-(2-methoxy-3-bromopropyl)-phthalamic acid. Further confirmation of the identity of the urea was obtained by its conversion to the corresponding phthalimide by the method of Smith and Emerson (10).

Thus, it has been shown that the methoxymercuration of the N-allylamide type structure, which is possessed by the starting material of most diuretics, leads predominantly (in the case of N-allylphthalimide) or apparently exclusively (in the case of N-(β-carboxypropionyl)-N′-allylurea) to 2-methoxy-3-acetoxy (or hydroxy)-mercuripropyl derivatives.

EXPERIMENTAL

A. *The structure of β-(carboxypropionyl)allylurea* (I or II). I (or II) (m.p. 143.5–145°, 25 g., 0.125 mole) was suspended in a solution of thionyl chloride (9.2 cc., 0.125 mole) in benzene (150 cc.). Evolution of gas began at 40° and continued for four hours while the mixture was brought gradually to 78°. During this period, I (or II) had dissolved, and on cooling a solid product crystallized; this was washed with 40 cc. of benzene and air-dried (19 g., 83%, m.p. 87.5–89°). Pure succinylallylurea was obtained by recrystallization from isopropyl alcohol (m.p. 90–92°, hydrolysis equiv. Calc'd: 182; Found: 180). It (1 g.) was reconverted by dilute sulfuric acid (0.5 g. in 12 cc. of water) to β-carboxypropionylallylurea (74%, m.p. 142–144°; mixed m.p. the same).

Attempted synthesis of succinylallylurea from allyl isocyanate (11) and succinimide by the method of Menschutkin (12) yielded the impure compound which could not be separated from succinimide. However, hydrolysis of this impure compound with dilute sulfuric acid yielded a small amount of β-carboxypropionylallylurea (m.p. 142–144°; mixed m.p. with authentic sample 143–145°). This series of reactions is compatible only if the original urea structure is considered to be N-(β-carboxypropionyl)-N′-allylurea (I).

B. *M—The methoxymercuration product of* I. To a hot solution of mercuric acetate (15 g., 0.048 mole) in 200 cc. of methanol, a hot solution of I (10 g., 0.05 mole) in 150 cc. of methanol was added all at once. A white solid separated immediately, and the resulting suspension was refluxed for three hours, cooled to room temperature overnight, filtered, and the solid obtained washed with 100 cc. of methanol (20 g., 91%, m.p. 177–178.5° dec.). The mercury analysis was considerably higher than that calculated for an acetoxy derivative (Hg found: 44.3; Hg calc'd for acetoxy derivative: 40.9).

The purification of M, as prepared here or from plant batches, was carried out by slow solution in aqueous sodium bicarbonate and reprecipitation with acetic acid (average yield 90%, m.p. 188.5–190.5° dec.). The mercury analyses corresponded to the hydroxy compound N-(β-carboxypropionyl)-N′-(2-methoxy-3-hydroxymercuripropyl)urea.

Anal. Calc'd for (M) $C_9H_{16}HgN_2O_6$: Hg, 44.8. Found: Hg, 44.7, 44.9, 44.75.

Purification by solution in aqueous sodium hydroxide gave smaller yields due to the hydrolysis of the succinyl grouping.

C. *The M halides.* The halides were prepared from M (crude or purified; 0.05 mole) by slow solution in 50 cc. of water containing 0.052 mole of sodium or potassium halide. A slight amount of fore-precipitate was removed by filtration, and the filtrate acidified with three cc. of acetic acid. The M halide which precipitated was washed with water and

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[3] IV is isomeric with 5-methoxyhexahydro-2-pyrimidone. The burden of proof of the correct structure rests on the work of Gabriel and Lauer (9). However, this does not affect the proof of structure of M.

M HALIDE	M.P., °C. (dec.)	Hg		N (Kjeldahl)	
		Calc'd	Found	Calc'd	Found
Chloride	161 -162.5	42.93	43.13	6.0	5.96
Bromide	163 -164	39.20	39.21	5.47	5.43
Iodide	144.8-145.5	Unstable			

recrystallized from methanol (1 g. per 50 cc. for I and Cl; 1 g. per 80 cc. for Br). The yields were 98% (crude) and 92-93% (recrystallized from methanol).

Intensive investigation of the mother liquors of M bromide or fractional acetic acid precipitation of the sodium salt solution failed to disclose the presence of any isomeric M bromide (8).

D. *The degradation of M bromide.* Crude M (43 g., 0.096 mole) was dissolved in 150 cc. of water containing 18 g. of potassium bromide. To the filtered solution, cooled in an ice-bath and exposed to strong sunlight, a solution of bromine (16 g., 0.1 mole) in 85 cc. of water containing 20 g. of potassium bromide was added with stirring as rapidly as the color of bromide disappeared. The mixture was filtered and acidified with hydrobromic acid. The solid was washed with water (26.2 g., 88%, m.p. 134-136.5°). Recrystallization of 22 g. from 100 cc. of methanol gave pure N-(β-carboxypropionyl)-N′-(2-methoxy-3-bromopropyl)urea; m.p. 135.5-137°.

Anal. Calc'd for $C_9H_{15}BrN_2O_5$: Neutral equiv., 311; N, 9.01; Br, 25.69; CH_3O, 9.97.
Found: Neutral equiv., 310.5; N, 8.83; Br, 25.56; CH_3O, 10.28.

The above compound (15 g., 0.048 mole) was hydrolyzed overnight in the refrigerator by aqueous sodium hydroxide (3.9 g., 0.1 mole in 40 cc. of water) to N-(2-methoxy-3-bromopropyl)urea (5.1 g., 50%, m.p. 94-95°). Wasteful crystallization from water gave the pure compound, m.p. 98-98.8°.

Anal. Calc'd for $C_5H_{11}BrN_2O_2$: Br, 37.86. Found: Br, 37.7.

The pure compound, on standing or preferably on boiling with water, cyclized to 2-imino-5-methoxytetrahydro-1,3-oxazine (IV, 87% yield as the picrate; picrate m.p. 196-197° after recrystallization from water).

Anal. Calc'd for $C_5H_{10}N_2O_2 + C_6H_3N_3O_7$: N, 19.5; C, 36.78; H, 3.65.
Found: N, 19.96; C, 36.85; H, 3.55.

N-(2-Methoxy-3-bromopropyl)urea was further characterized by its conversion to N-(2-methoxy-3-bromopropyl)phthalimide using the procedure of Smith and Emerson (10) [25% crude yield; m.p. after crystallization from petroleum ether (b.p. 69-70°) and then from methanol, 102.5-103.5°].

E. *The synthesis of reference compounds and comparison with M degradation products.* N-(2-Methoxy-3-bromopropyl)phthalamic acid (4.4 g., 0.014 mole), whose structure had been proved in the preceding paper, was refluxed with 100 cc. of 2.4 *N* hydrochloric acid for four hours. The mixture was cooled, the phthalic acid which crystallized removed by filtration, and the filtrate evaporated to dryness at water-aspirator pressure. The crude 2-methoxy-3-bromopropylamine hydrochloride remaining was dissolved in 10 cc. of water, filtered, and mixed with potassium cyanate (1.0 g.). After standing briefly, the mixture was filtered, evaporated almost to dryness, redissolved in 5 cc. of water and treated with a saturated aqueous picric acid solution. IV was obtained (28% yield, m.p. 194-195°; recrystallized from water m.p. 196-197°).

Anal. Calc'd for $C_{11}H_{13}N_5O_9$: N, 19.5; C, 36.78; H, 3.65.
Found: N, 19.7; C, 37.0; H, 3.79.

A mixed melting point of this picrate and the picrate of the cyclized product obtained from M by bromination and hydrolysis showed no depression.

Furthermore, the mixed melting point of N-(2-methoxy-3-bromopropyl)phthalimide, whose structure was proved in the first paper, and of the phthalimide prepared from M by bromination, hydrolysis, and phthalation was undepressed.

F. *The preparation of M bromide from Mercuhydrin.* The commercial diuretics, such as Mercuhydrin, can be freed from the complexing reagents by treatment with aqueous potassium bromide. Mercuhydrin (2 g.) was suspended in 20 cc. of 20% aqueous potassium bromide solution. After standing overnight, the theophylline which precipitated was collected (0.3 g., 58%). Treatment of the filtrate with acetic acid yielded M bromide (0.85 g., 51%, m.p. after recrystallization 163–163.5°).

SUMMARY

The methoxymercuration of N-(β-carboxypropionyl)-N′-allylurea, followed by treatment of the product with aqueous potassium bromide, yielded N-(β-carboxypropionyl)-N′-(2-methoxy-3-bromomercuripropyl)urea (M bromide). No other isomer could be found. The structure of M bromide was proved by degradation to N-(2-methoxy-3-bromopropyl)urea from which two derivatives were made and shown to be identical to known reference compounds.

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tert-BUTYLATION OF β-NAPHTHOL AND 1-CHLORO-2-NAPHTHOL

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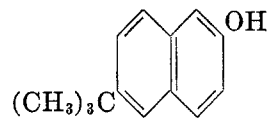
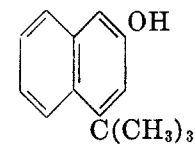
Although the *tert*-butylation of β-naphthol and its methyl ether has already formed the subject of several publications, as yet there is complete uncertainty in the literature as to the constitution of the reaction products.

In 1898, Cahen (1) investigated the Friedel-Crafts reaction of neroline with isobutyl bromide in the presence of aluminum chloride, and obtained a butylneroline of which neither the structure of the alkyl group nor its location in the naphthalene ring was discussed. In 1931, Koenigsberger (2) patented the alkylation of β-naphthol by *tert*-butyl chloride and aluminum chloride; this gave a product melting at about 102°, which he termed "4-*tert*-butyl-2-naphthol" without any proof of constitution. A few years later, a *tert*-butyl-β-naphthol was mentioned without details in two further patents (3); and in 1935, Tschitschibabin (4) described the alkylation of β-naphthol with *tert*-butyl alcohol in the presence of phosphoric acid and described a *tert*-butyl-β-naphthol melting at 113°, whose constitution was also left undecided. These reactions were recently more thoroughly investigated by Contractor, Peters, and Rowe (5), who found that the products described in the patents and by Tschitschibabin were impure samples of a *tert*-butyl-β-naphthol melting at 119–120° (*picrate*, m.p. 142°). In the molecule of this compound, the location of the alkyl group at the 1-position was excluded on the ground that azo derivatives were readily obtained with *m*- and *p*-nitrophenyldiazonium salts; the 6-position was discarded because of the non-identity with a *liquid* naphthol obtained from β-*tert*-butylnaphthalene by sulfonation and subsequent alkaline fusion, and believed to be 6-*tert*-butyl-2-naphthol (I). On these grounds, Contractor, *et al.* assumed the most probable constitution of the compound of m.p. 119–120° to be that of 4-*tert*-butyl-2-naphthol (II).



I

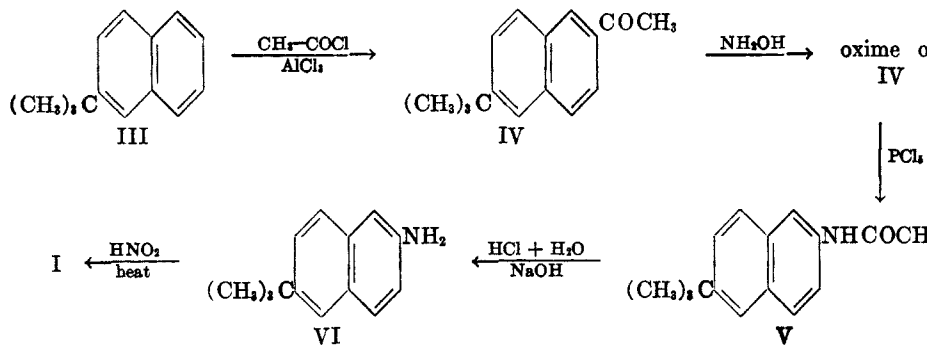


II

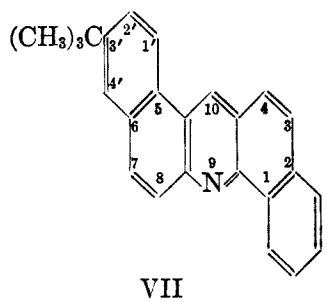
In the course of an investigation into bactericidal and vermifugal drugs, we came to study the same problem. We found that, as well as the procedures already described, β-naphthol was readily *tert*-butylated with isobutyl alcohol or isobutylene. We confirmed the properties found by Contractor, *et al.* for the compound m.p. 119–120°, but the proposed constitution (II) appeared to us improbable since such an alkylation of a phenol at the *meta* position[1] would be

[1] The reported *meta*-ethylation of phenols [*e.g.* Jannasch and Rathjen, *Ber.*, **32**, 2391 (1899)] involved unusual experimental conditions suggesting the intervention of some mechanism (*e.g.* free radicals, Jacobsen's degradation, etc . . .) different from the normal course of a Friedel-Crafts reaction.

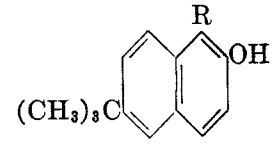
unprecedented (6). It would also be surprising, in view of the outstanding reactivity of the 6-position in 2-substituted naphthalenes (7), if β-naphthol were not *tert*-butylated, at least in part, at the 6-position. The fact that all the 6-alkyl-2-naphthols previously described have relatively high melting points, and the evidence that rearrangements frequently accompany the sulfonation of aromatic hydrocarbons bearing ramified alkyl groups (8), led us to suspect that the substance of m.p. 119–120° might well be 6-*tert*-butyl-2-naphthol, and that the liquid isomer which was given the formula (I) might have another structure than that previously assumed. This has now been confirmed by synthesis in the following way: (a) β-*tert*-butylnaphthalene (III) was acetylated with acetyl chloride and aluminum chloride in cold nitrobenzene, a procedure known to bring about 6-substitution (9); (b) Beckmann rearrangement of the oxime of the resulting 6-*tert*-butyl-2-acetonaphthone (IV) gave 6-*tert*-butyl-2-acetaminonaphthalene (V); (c) 6-*tert*-butyl-2-naphthylamine (VI), obtained by acid hydrolysis of (V), was diazotized and the diazo compound decomposed in aqueous medium to 6-*tert*-butyl-2-naphthol (I). The latter was identified with the product obtained directly from β-naphthol, by mixed melting-point determinations upon the



free naphthols, their picrates, and their methyl ethers. A further proof of this identity was supplied by performing an Ullmann-Fettvadjian reaction (10) with samples of the naphthol (I) from these two sources, α-naphthylamine and paraformaldehyde: in both cases, the same *tert*-butyl-1,2,5,6-dibenzacridine (VII) was obtained.



VII



VIIIa; R = Cl
VIIIb; R = Br
VIIIc; R = $C(CH_3)_3$

In the molecule of 6-*tert*-butyl-2-naphthol, the 1-position was found to be the most reactive, as chlorination gave a monochloro derivative identical to that obtained by *tert*-butylating 1-chloro-2-naphthol, and which must therefore be

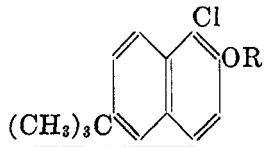
TABLE I

SUBSTITUTED 2-NAPHTHOLS

NAPHTHOL	M.P., °C.	REFERENCE
6-Methyl-2-naphthol	128–129	(12)
6-Ethyl-2-naphthol	97–98	(13)
6-*tert*-Butyl-2-naphthol	119–120	
6-Cyclohexyl-2-naphthol	161–162	(11)
6-*n*-Heptyl-2-naphthol	96–98	(14)
6-*n*-Octyl-2-naphthol	92–93	(15)
6-Chloro-2-napththol	115	(16)
6-Bromo-2-naphthol	127	(17)

TABLE II

NEW ETHERS OF 6-*tert*-BUTYL-1-CHLORO-2-NAPHTHOL



R	FORMULA	M.P., °C.	ANALYSES	
			Chlorine	
			Calc'd	Found
Methyl	$C_{15}H_{17}ClO$	115	14.2	14.0
Ethyl	$C_{16}H_{19}ClO$	80	13.5	13.2
n-Propyl	$C_{17}H_{21}ClO$	60	12.8	12.7
Isopropyl	$C_{17}H_{21}ClO$	58	12.8	12.5
Allyl	$C_{17}H_{19}ClO$	45	12.8	12.5
Isobutyl	$C_{18}H_{23}ClO$	79	12.2	11.9
Isoamyl	$C_{19}H_{25}ClO$	60	11.6	11.5
n-Octyl	$C_{22}H_{31}ClO$	35	10.2	10.0
ω-Undecenyl	$C_{25}H_{35}ClO$	b.p. 275–280/16 mm.	9.2	8.9
n-Octadecyl	$C_{32}H_{51}ClO$	61	7.3	7.0
Benzyl	$C_{21}H_{21}ClO$	94	10.9	10.8
p-Methylbenzyl	$C_{22}H_{23}ClO$	110	10.5	10.2
p-Chlorobenzyl	$C_{21}H_{20}Cl_2O$	132	9.9	9.7
β-Phenylethyl	$C_{22}H_{23}ClO$	112	10.5	10.7
Hydnocarpyl	$C_{30}H_{43}ClO$	b.p. 315–320/17 mm.	7.8	7.5

6-*tert*-butyl-1-chloro-2-naphthol (VIIIa) (this was also proof of the reactivity of the 6-position in the molecule of 1-substituted 2-naphthols). Bromination similarly yielded 6-*tert*-butyl-1-bromo-2-naphthol (VIIIb). Further *tert*-butylation of 6-*tert*-butyl-2-naphthol occurred very easily too, yielding 1,6-di-*tert*-

butyl-2-naphthol (VIIIc), a compound which, like many cryptophenols of the same type, was insoluble in aqueous alkali, but whose hydroxyl group could easily be shown by the Tschugaeff-Zerewitinow procedure; the location of a *tert*-butyl group at the 1-position was deduced from the inability of VIIIc to couple with aryldiazonium salts. The fact that there is no O-ether function in this compound was also established by its stability to boiling pyridine hydrochloride. Compound VIIIc is identical with a substance previously described in the literature (6) as the *tert*-butylether of *tert*-butyl-β-naphthol m.p. 119–120°, apparently because of its alkali insolubility.

The structures which we assigned to the products from the *tert*-butylation of β-naphthol fall well in line with observations previously made by Alberti (11) upon the cyclohexanation of the same naphthol. The melting point of 6-*tert*-butyl-2-naphthol is also consistent with those of already-known 6-alkyl- and 6-halogeno-2-naphthols as listed in Table I.

6-*tert*-Butyl-1-chloro-2-naphthol was found of practical interest as an anthelmintic against the tape-worm; it also has fungicidal properties against *Fusarium graminearum*. The study of similar compounds is under way.

Table II in the experimental part contains a list of ethers of 6-*tert*-butyl-1-chloro-2-naphthol which we prepared for biological testing in view of Sexton's recent work upon fungistatic properties of β-naphthol ethers (18).

EXPERIMENTAL[2]

tert-Butylation of β-naphthol. The three procedures reported by Contractor, *et al.* (5) were followed, except that in each instance, the crude alkylation products were vacuum-distilled, and three fractions isolated. Fraction 1 (b.p. <170°/13 mm.) contained mostly the recovered β-naphthol, fraction 2 (b.p. 175–190°/13 mm.) was chiefly the mono-*tert*-butylnaphthol, and fraction 3 (b.p. >190°/13 mm.) corresponded to the di-*tert*-butylnaphthol. In the first two procedures of Contractor, *et al.* (5), *tert*-butyl chloride could be replaced by isobutylene or isobutyl chloride in equivalent amounts, and in the third one, isobutyl alcohol could be used instead of *tert*-butyl alcohol.

6-tert-Butyl-2-naphthol (I). The fractions of b.p. 175–190°/13 mm. melted indefinitely at around 80–110° as reported in Koenigsberger's patent (2) and by Tschitschibabin (4), but gave after repeated crystallizations from ligroin, long colorless needles with a naphtholic odor, melting at 118–119° (literature: 119–120°). The orange *picrate* of this compound melted at 143–144° (literature: 142°). The mother-liquors from the purification of (I) contained notable amounts of a product crystallizing from ligroin in silky colorless needles melting at about 86–87° (the *picrate* formed deep orange needles from ethanol, m.p. about 118–120°), having the same composition as (I).

Anal. Calc'd for $C_{14}H_{16}O$: C, 84.0; H, 8.0.

Found: C, 83.8; H, 8.3.

This is not, however, a pure isomer of (I), as fractionatal sublimation yielded considerable amounts of the latter; the lower-melting residue (85–86°) could not be freed from traces of (I).

1,6-Di-tert-butyl-2-naphthol (VIIIc). The fractions b.p. >190°/13 mm. were repeatedly recrystallized from methanol and ligroin, giving silky colorless needles melting at 138–139° (in accordance with the melting point recorded by Contractor, *et al.* (5) for "4(?)-*tert*-butyl-2-naphthol *tert*-butylether"). The product was insoluble in aqueous sodium hy-

[2] All melting points were taken with a Maquenne-block.

droxide, nor did it couple with 4-nitrophenyldiazonium chloride, but produced an abundant evolution of methane when added to a solution of methylmagnesium iodide in anisole. Two grams of the substance, refluxed for four hours with redistilled pyridine hydrochloride (15 g.) (a most effective reagent for the splitting of O-ether linkages) were recovered unchanged after treatment with water and crystallization from methanol.

6-tert-Butyl-2-naphthol methyl ether. This compound was obtained from the potassium salt of *6-tert*-butyl-2-naphthol by treatment with methyl sulfate in the usual way. From methanol it formed colorless needles melting at 95°.

Anal. Calc'd for $C_{15}H_{18}O$: C, 84.1; H, 8.4.
Found: C, 84.0; H, 8.6.

6-tert-Butyl-1-chloro-2-naphthol (VIIIa). To a well-stirred mixture of 100 g. (0.56 mole) of 1-chloro-2-naphthol and 5 g. of finely powdered aluminum chloride, 65 g. (0.7 mole) of *tert*-butyl chloride was added, the temperature being kept at about 25°. After the addition, stirring was continued, while the mixture was slowly heated in a water-bath up to 80° and kept at this temperature for one hour. The reaction product was diluted with 150 ml. of ligroin, washed with water, then with an aqueous solution of sodium bicarbonate and again with water. The organic layer was dried over calcium chloride, the solvent removed, and the residue vacuum-distilled (about 170–200°/15 mm.). About half the distillate crystallized on cooling, giving long colorless needles with a sharp odor, which melted at 76° after recrystallization from ligroin.

Anal. Calc'd for $C_{14}H_{15}ClO$: C, 71.6; H, 6.4.
Found: C, 71.5; H, 6.6.

The same compound was obtained when 6-*tert*-butyl-2-naphthol was treated with the calculated amount of chlorine in acetic acid or carbon disulfide (19) in the usual way.

6-tert-Butyl-1-bromo-2-naphthol (VIIIb). A solution of 16.2 g. of bromine in acetic acid (10 ml.) was stirred into a mixture of 6-*tert*-butyl-2-naphthol (20 g.) and acetic acid (50 ml.). The reaction product was poured into water, and the precipitated oil taken up in benzene; the benzene layer was washed with an aqueous solution of sodium bicarbonate and then with water, dried over calcium chloride, the solvent removed, and the residue purified by vacuum-distillation (at about 170–190°/13 mm.). After crystallization from ligroin, long asbestos-like needles melting at 78° were obtained.

Anal. Calc'd for $C_{14}H_{15}BrO$: C, 60.2; H, 5.4.
Found: C, 60.1; H, 5.7.

6-tert-Butyl-2-acetonaphthone (IV). Finely powdered aluminum chloride (120 g., 0.9 mole) was added in small portions to a well-stirred mixture of *β-tert*-butylnaphthalene (20) (150 g.; 0.8 mole), acetyl chloride (72 g.; 0.9 mole), and nitrobenzene (500 ml.). The temperature was kept at around 0° during the addition, and for a further 20 hours. The reaction product was poured onto ice, the nitrobenzene removed by steam-distillation, and the residue taken up in benzene. The benzene solution was washed with dilute sodium hydroxide and then with water, dried over sodium sulfate, the solvent removed, and the residue vacuum-distilled. The portion boiling at 180–210°/15 mm., which solidified on cooling, yielded after recrystallization from methanol 58 g. of colorless prisms melting at 87°.

Anal. Calc'd for $C_{16}H_{18}O$: C, 84.9; H, 7.9.
Found: C, 84.8; H, 8.0.

The corresponding *oxime* formed colorless needles melting at 168° from methanol.

Anal. Calc'd for $C_{16}H_{19}NO$: N, 5.8. Found: N, 5.8.

6-tert-Butyl-2-acetaminonaphthalene (V). A suspension of 10 g. (0.04 mole) of the foregoing oxime in anhydrous ether (100 ml.) was treated at 0° with 13 g. of finely powdered phosphorus pentachloride (0.06 mole). The mixture was kept at 0° for one hour with frequent shaking, and then poured onto cracked ice. The solid product formed after evaporation of the ether was thoroughly washed with sodium carbonate, then with water, dried, and recrystallized from methanol. A 90% yield was obtained of colorless prisms melting at 156°.

Anal. Calc'd for $C_{16}H_{19}NO$: N, 5.8. Found: N, 5.6.

6-tert-Butyl-2-naphthylamine (VI). Hydrolysis of the foregoing *amide* by concentrated hydrochloric acid, followed by basification with sodium hydroxide, yielded a solid *amine* which crystallized from ligroin in almost colorless needles melting at 65–66°, which reddened on exposure to the air.

Anal. Calc'd for $C_{14}H_{17}N$: N, 7.0. Found: N, 6.8.

This amine was further characterized by its *picrate* (which formed yellow prisms from ethanol melting at about 189–191°), and by the reaction product it gave when refluxed for one hour with 2,3-dichloro-1,4-naphthoquinone (21) in ethanol in the presence of sodium acetate. *2-Chloro-3-(6-tert-butyl-2-naphthylamino)-1,4-naphthoquinone* formed long silky dark violet needles melting at 153° from ethanol.

Anal. Calc'd for $C_{24}H_{20}ClNO_2$ N, 3.5. Found: N, 3.5.

Conversion of the amine (VI) into (I). To a well-stirred suspension of 9.5 g. of 6-*tert*-butyl-2-naphthylamine in ice-cooled hydrochloric acid (150 ml. diluted with 100 ml. of water), a solution of sodium nitrite (3.5 g.) in water (35 ml.) was added dropwise. After the diazotization, nitrous acid in excess was destroyed by the addition of urea, and the solution was boiled for some minutes. After cooling, the precipitated naphthol (I) was purified through its sparingly soluble sodium salt. After repeated crystallizations from aqueous methanol, it melted at 117–119°, either alone or mixed with a sample obtained from β-naphthol; the *methyl ether* melted at 94–95°, and the *picrate* at 142–143° (mixed m.p. determinations).

3'-tert-Butyl-1,2,5,6-dibenzacridine (VII). One gram of paraformaldehyde was added in small portions to a boiling mixture of 6-*tert*-butyl-2-naphthol (5 g.) and α-naphthylamine (4.5 g.). When steam-evolution had ceased, the reaction product was brought to the boil for two minutes and then vacuum-distilled. The reddish resin thus obtained solidified on scratching in ethanol, and was recrystallized twice from benzene. A 40% yield of pale yellow needles melting at 208° was obtained, which gave with sulfuric acid a yellow solution with an intense yellow-green fluorescence. The products thus obtained with 6-*tert*-butyl-2-naphthol from both sources were identical, and with the acridine obtained in a similar way from 6-*tert*-butyl-2-naphthylamine, α-naphthol, and paraformaldehyde, by reason of symmetry.

Anal. Calc'd for $C_{25}H_{21}N$: N, 4.1. Found: N, 4.2.

The corresponding *picrate* formed from nitrobenzene fine orange-yellow needles melting with decomposition at about 280°.

Anal. Calc'd for $C_{31}H_{24}N_4O_7$: N, 9.9. Found: N, 9.6.

Ethers of 6-tert-butyl-1-chloro-2-naphthol. These were prepared by refluxing naphthol (VIIIa) with a solution of sodium hydroxide in aqueous ethanol and the required alkyl (or arylalkyl) bromide for some hours. Purification of the resulting ethers was by vacuum-distillation and recrystallization from ethanol and ligroin.

SUMMARY

1. The constitution of the products resulting from the *tert*-butylation of β-naphthol has been investigated, and has been confirmed by synthesis.

2. Several new substitution-products of β-naphthol, some of practical biological interest, have been prepared.

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

2-OXAZOLIDONES: SYNTHESIS FROM N-CARBALKOXY-β-HALOALKYLAMINES[1]

EPHRAIM KATCHALSKI AND DOV BEN ISHAI

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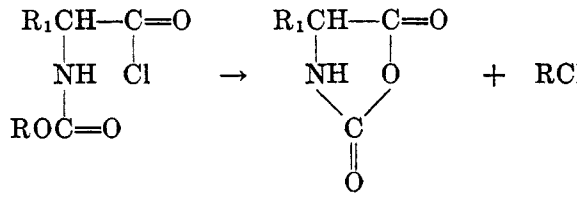
The ease with which N-carbalkoxy-α-amino acid chlorides (I) undergo ring closure to N-carboxy-α-amino acid anhydrides (2,5-oxazolidinedione derivatives) (II) with elimination of alkyl halide (1), suggested that N-carbalkoxy-β-haloalkylamines (III, X = halogen) may suffer a similar cyclization.

Indeed, it was found that at elevated temperatures (120–200°) N-carbalkoxy-β-haloalkylamines (III) split off alkyl halides yielding the corresponding 2-oxazolidones (IV). A new method for the synthesis of 2-oxazolidones is thus available [for other methods, see (2, 3)].



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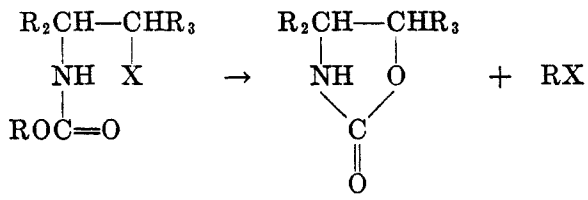


III IV

The influence of the substituents X and R on the temperature of cyclization of N-carbalkoxy-β-haloalkylamines (III, $R_2 = R_3 = H$), was studied systematically. The results are summarized in Table I, which lists the threshold temperatures at which cyclization occurred under the experimental conditions employed. On changing the halogen atom X, it was found that the temperature of cyclization decreases in the order X = Cl, Br, I. A similar decrease was observed, when R was changed from alkyl to benzyl, while in the series R = CH_3, C_2H_5, C_3H_7, C_4H_9, the threshold temperature did not change. The N-phenyl derivative of N-carbobenzoxy-β-chloroethylamine showed the same reaction, leading to N-phenyl-2-oxazolidone.

In order to elucidate the validity of the suggested method in the synthesis of

[1] This paper represents part of a thesis submitted to the Hebrew University, Jerusalem, by Dov Ben Ishai, in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

TABLE I

CYCLIZATION OF N-CARBALKOXY-β-HALOETHYLAMINES

AMINE	M.P., °C.	B.P., °C./MM.	YIELD, %	d_4^{25}	n_D^{25}	ANALYSIS				Cyclization Temp. (°C.)
						Nitrogen		Halogen		
						Calc'd	Found	Calc'd	Found	
$ClCH_2CH_2NHCOOCH_3$	—	113/25	80	1.223	1.4534	10.2	10.2	25.8	25.5	190–200
$ClCH_2CH_2NHCOOC_2H_5$	—	121/24	87	1.156	1.4501	9.3	9.3	23.4	23.3	190–200
$ClCH_2CH_2NHCOOC_3H_7$	—	132/26	88	1.125	1.4511	8.5	8.6	21.4	20.8	190–200
$ClCH_2CH_2NHCOOC_4H_9$	—	143/26	84	1.086	1.4513	7.8	7.9	19.8	20.3	190–200
$ClCH_2CH_2NHCOOCH_2C_6H_5$	—	—	78	1.183	1.5327	6.6	6.6	16.6	16.2	170–180[a]
$BrCH_2CH_2NHCOOCH_3$	—	98/2	75	1.562	1.4822	7.7	7.8	43.9	44.0	170–180
$BrCH_2CH_2NHCOOC_2H_5$	—	118/3	82	1.412	1.4722	7.1	7.0	40.8	41.4	170–180
$BrCH_2CH_2NHCOOC_3H_7$	—	126/4	85	1.341	1.4699	6.7	7.0	38.1	38.4	170–180
$BrCH_2CH_2NHCOOC_4H_9$	24	137/3	90	1.309	1.4686	6.2	6.2	35.7	36.1	170–180
$BrCH_2CH_2NHCOOCH_2C_6H_5$	45	—	92			5.4	5.4	31.0	31.6	140–145[a]
$ICH_2CH_2NHCOOCH_3$	38	116/2	85			6.1	6.4	55.5	56.2	160–165
$ICH_2CH_2NHCOOC_2H_5$	55	—	85			5.8	5.7	52.3	53.0	160–165
$ICH_2CH_2NHCOOC_3H_7$	25	—	78			5.4	5.4	49.4	50.3	160–165
$ICH_2CH_2NHCOOC_4H_9$	48	—	80			5.2	5.4	46.8	46.0	160–165
$ICH_2CH_2NHCOOCH_2C_6H_5$	69	—	84			4.6	4.8	41.6	42.3	130–135[a]

[a] Cyclization carried out at reduced pressure (20 mm.).

2-oxazolidone derivatives, the cyclization of the following homologs of the N-carbalkoxy-β-haloethylamines was studied:

N-Carbobenzoxy-β-chloropropylamine (III, R_2 = H, R_3 = CH_3, R = $CH_2C_6H_5$, X = Cl).

N-Carbobutoxy-β-chloro-*tert*-butylamine (V).

N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl).

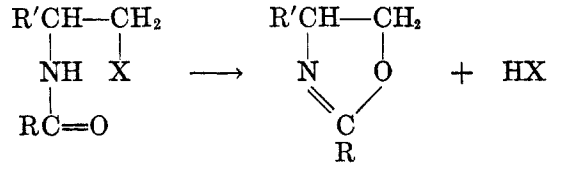
N-Carbobutoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = C_4H_9, X = Br).

N-Carbobenzoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = $CH_2C_6H_5$, X = Br).

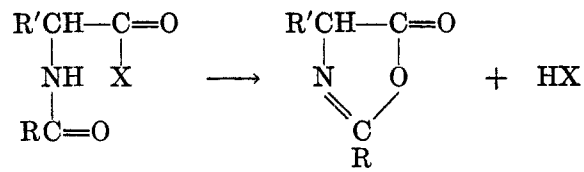
The first substance was obtained by coupling β-chloropropylamine with benzyl chlorocarbonate; the second by the action of thionyl chloride on N-carbobutoxy-β-hydroxy-*tert*-butyl amine; the other three by addition of halogen (chlorine or bromine) to suitable N-carbalkoxy derivatives of allylamine. The first two substances at 160–180° split off benzyl chloride and butyl chloride, respectively, and gave 5-methyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_3) and 4,4-dimethyl-2-oxazolidone (VI). N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl), decomposed to ethyl chloride and 5-chloromethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Cl) previously prepared

by Thomsen (4) and Johnson and Guest (5) in a different manner. It is reasonable to assume that the bromo-compound $C_4H_6BrNO_2$ obtained from the corresponding dibromo-derivatives (with evolution of butyl bromide and benzyl bromide, respectively) is the analogous, but hitherto unknown 5-bromomethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Br).

A comparison of the cyclization of these N-carbalkoxy-β-haloalkylamines (III) with that of N-acyl-β-haloalkylamines (VII) (6) shows that the former are converted into 2-oxazolidone derivatives (IV) with elimination of alkyl halides, the latter into 2-oxazolines (VIII) with liberation of hydrogen halides. An analogous difference has been observed in the case of N-carbalkoxy-α-amino acid chlorides (I) and N-acyl-α-amino acid chlorides (IX) (7, 8): the former decompose into alkyl chlorides and 2,5-oxazolidinediones (11), the latter into azlactones (X) (keto-oxazolines) and hydrogen chloride.

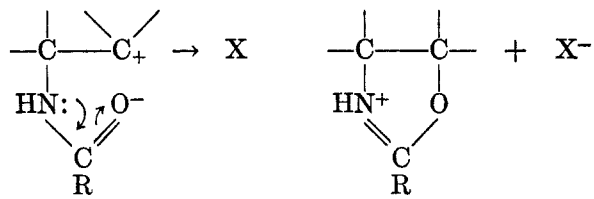


VII VIII

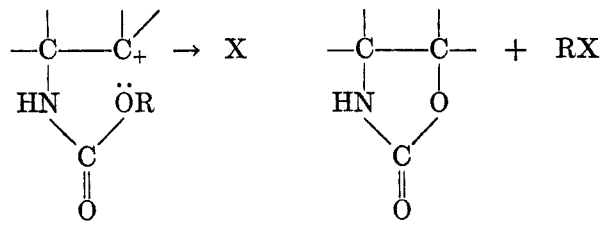


IX X

(a)



(b)



Schemes (a) and (b) may explain this difference in the mode of cyclization of the N-acyl and N-carbalkoxy-β-haloalkylamines. In scheme (a) it is assumed that ring closure of N-acyl-β-haloalkylamines is caused by the interaction between the electrophilic halogen-bearing carbon and the nucleophilic carbonyl-oxygen; the cyclization is accompanied by halogen anion dissociation. A mechanism

similar to (a) has been suggested by Carter (8) for azlactone hydrohalides formation from acyl-α-amino acid chlorides.

In the urethan group of carbalkoxy-β-haloalkylamines [scheme (b)] two nucleophilic oxygens (a carbonyl and an alkoxyl-oxygen) which may react with the electrophilic halogen-bearing carbon are available. A reaction between the carbonyl oxygen and the electrophilic carbon should lead by analogy with the reaction given in scheme (a) to the formation of 2-alkoxy-2-oxazoline hydrohalide. As it has been found experimentally that carbalkoxy-β-haloalkylamines are transformed into 2-oxazolidones with alkyl halide evolution, a reaction between the alkoxyl oxygen and the electrophilic carbon seems to be more plausible. The findings of Gustus, Stevens, and others (9) that acyl halides react with ethers to give esters and alkyl halides suggest that the alkoxyl oxygen of the urethan groups resembles in its nucleophilic character an ethereal oxygen.

The positive character of the halogen-bearing carbon atom is greatly enhanced in the N-acyl- and N-carbalkoxy-α-amino acid chlorides; they undergo therefore, cyclization already at relatively low temperatures (7, 8), but without change in the type of reaction. The greater ease of cyclization of the N-carbobenzoxy-compounds may be due to the pronounced ionization tendency of the benzyl group.

EXPERIMENTAL

β-Chloroethylamine hydrochloride. This amine was prepared from ethanolamine hydrochloride and thionyl chloride according to K. Ward (10).

β-Bromethylamine hydrobromide was obtained from ethanolamine and hydrobromic acid (11).

β-Iodoethylamine hydriodide. Ethanolamine (30.5 g; 0.5 mole) was added to ice-cold 50% hydriodic acid (260 g; 1.0 mole) and the mixture heated in an oil-bath at 160–180° for four hours. During this period, 120 ml. of water distilled off. On cooling, the residue solidified to a brown crystalline mass. It was twice recrystallized from an ethanol-ether mixture. Thus, 115 g. (77%) of β-iodoethylamine hydriodide was obtained; m.p. 191–192°. [Gabriel (32) reports m.p. 192–194°].

General procedure for the preparation of N-carbalkoxy-β-haloakylamines. A quantity of 0.1 mole of the β-haloalkylamine was dissolved in 50 ml. of 2 *N* sodium hydroxide solution. To the ice-cold solution, 0.1 mole of the alkyl chlorocarbonate and 25 ml. of 4 *N* sodium hydroxide solution were added simultaneously with stirring over a period of half an hour, and the stirring was continued for about 20 minutes. The N-carbalkoxy-β-haloalkylamine which separated (as an oil or as a solid) was extracted with ether. After drying with sodium sulfate, the ether was removed *in vacuo* and the residue distilled *in vacuo* or recrystallized from petroleum ether. The properties of the products are recorded in Table I. All these substances dissolve in organic solvents, but not in water.

Preparation of 2-oxazolidone from N-carbalkoxy-β-haloethylamines. Each of the N-carbalkoxy-β-haloethylamines listed in Table I was heated in an oil-bath and the lowest temperature at which liberation of the corresponding alkyl halide occurred was recorded. The alkyl halide formed was collected in a suitably cooled receiver and identified by its boiling point and specific gravity. At the end of the reaction the product, which solidified on cooling, was recrystallized from benzene. The yield of 2-oxazolidone (m.p. 90°) (2, 3) was practically quantitative.

Anal. Calc'd for $C_3H_5NO_2$: N, 16.1. Found: N, 16.0.

Cyclization experiments in solution. In preliminary experiments, it was observed that 2-oxazolidone may be obtained in practically quantitative yield also by refluxing octanol

solutions of the following N-carbalkoxy-β-haloethylamines: *N*-carbomethoxy-β-chloroethylamine, N-carbomethoxy-β-bromethylamine, and N-carbomethoxy-β-iodoethylamine. The 2-oxazolidone thus formed was precipitated from its solution by addition of petroleum ether.

N-Carbobenzoxy-N-phenyl-β-chloroethylamine. N-Phenyl-β-chloroethylamine hydrochloride was prepared from N-phenylethanolamine according to Jones (13) and condensed with benzyl chlorocarbonate. The product was an oil and could not be distilled without decomposition; however, the analysis was reasonably satisfactory.

Anal. Calc'd for $C_{16}H_{16}ClNO_2$: N, 4.8; Cl, 12.2. Found: N, 5.2; Cl, 11.9.

3-Phenyl-2-oxazolidone was prepared from the preceding substance at 165–175° under 20 mm. pressure. Benzyl chloride was evolved, and an oily residue remained which solidified upon cooling. After recrystallization from a mixture of benzene and petroleum ether, the product showed the physical properties ascribed to 3-phenyl-2-oxazolidone by Homeyer (3). Yield, 95%.

Anal. Calc'd for $C_9H_9NO_2$: N, 8.6. Found: N, 8.6.

N-Carbobenzoxy-β-chloropropylamine (III, R_2 = H, R_3 = CH_3, R = $CH_2C_6H_5$, X = Cl). β-Chloropropyl amine hydrochloride was prepared from isopropanolamine according to Jones (13). It was condensed with benzyl chlorocarbonate in the usual way. After extraction with ether and removal of the solvent *in vacuo*, an oily residue was obtained which distilled at 149–151°/5 mm. Yield, 75%. Properties: d_4^{25} 1.131; n_D^{25} 1.5202.

Anal. Calc'd for $C_{11}H_{14}ClNO_2$: Cl, 15.6; N, 6.2.
Found: Cl, 15.1; N, 6.3.

5-Methyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_3). The preceding substance was heated at 170–180° and 20 mm. Evolution of benzyl chloride ceased after one hour. The liquid residue distilled at 136–137°/5 mm. Analysis confirmed the structure of the product as 5-methyl-2-oxazolidone; yield, 90%. Properties: d_4^{25} 1.168; n_D^{25} 1.4648.

Anal. Calc'd for $C_4H_7NO_2$: N, 13.9. Found: N, 13.6.

N-Carbobutoxy-β-hydroxy-tert-butylamine was prepared with butyl chlorocarbonate in the usual way. No attempt was made to purify the oily product; yield, 90%.

Anal. Calc'd for $C_9H_{19}NO_3$: N, 7.4. Found: N, 7.2.

4,4-Dimethyl-2-oxazolidone (VI). In the course of 20 minutes, 30 g. of thionyl chloride was added at room temperature to 36 g. of N-carbobutoxy-β-hydroxy-*tert*-butylamine (14). The mixture was refluxed for a few minutes on the water-bath and the excess thionyl chloride removed *in vacuo* (60°). Distillation at 10 mm. was accompanied by vigorous evolution of gas and gave a small head fraction at 127–130° and the desired product at 152–154° (16 g.). It solidified at room temperature and was recrystallized from benzene-petroleum ether mixture.

Anal. Calc'd for $C_5H_9NO_2$: N, 12.2. Found: N, 12.2.

N-Carbethoxyallylamine was prepared according to Bergmann (15); b.p. 92°/15 mm.; yield, 93%.

N-Carbethoxy-β,γ-dichloropropylamine (III, R_2 = H, R_3 = CH_2Cl, R = C_2H_5, X = Cl). An ice-cold solution of 120 g of *N*-carbethoxy-allylamine in 150 ml. of carbon tetrachloride was saturated with gaseous chlorine. The solvent was removed *in vacuo* and the residue distilled; B.p. 166°/32 mm.; d_4^{25} 1.266; n_D^{25} 1.4755. Yield, 85%.

Anal. Calc'd for $C_6H_{11}Cl_2NO_2$: N, 7.0; Cl, 35.5.
Found: N, 7.2; Cl, 35.5.

5-Chloromethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Cl). The cyclization of N-carbethoxy-β,γ-dichloropropylamine set in at 185–195°; the ethyl chloride formed was collected under ice-water and identified by its boiling point and density. The residue was recrystallized from water (charcoal) and showed the m.p. (105–106°) and other properties indicated by Thomsen (4) and Johnson and Guest (5). Yield, 80%.

Anal. Calc'd for $C_4H_6ClNO_2$: N, 10.3; Cl, 26.2.
Found: N, 10.3; Cl, 25.9.

N-Carbobutoxyallylamine. This urethan was synthesized by condensing 30 g. (0.5 mole)

of allylamine with 70 g. (0.5 mole) of butyl chlorocarbonate. It distilled without decomposition at 120–122°/22 mm.; d_4^{25} 0.955; n_D^{25} 1.4425; yield 94%.

Anal. Calc'd for $C_8H_{15}NO_2$: N, 8.9. Found: N, 8.8.

N-Carbobutoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = C_4H_9, X = Br). A solution of 75 g. of bromine in 50 ml. of chloroform was added to an ice-cold solution of 73 g. of N-carbobutoxy-allylamine in 100 ml. of the same solvent. The chloroform was removed *in vacuo* and the solid residue recrystallized from aqueous alcohol; m.p. 56°; yield, 82%.

Anal. Calc'd for $C_8H_{15}Br_2NO_2$: N, 4.4; Br, 50.4.
Found: N, 4.5; Br, 50.3.

5-Bromoethyl-2-oxazolidone (IV, R_2 = H, R_3 = CH_2Br). The cyclization of N-carbobutoxy-β,γ-dibromopropylamine took place at 170–180°; butyl bromide distilled off. The solid product was recrystallized from benzene; m.p. 107°, yield, 70%.

Anal. Calc'd for $C_4H_6BrNO_2$: N, 7.8; Br, 44.4.
Found: N, 7.9; Br, 44.7.

N-Carbobenzoxy-allylamine. Allylamine (12 g.) was condensed with benzyl chlorocarbonate (42 g.). A yield of 90% was obtained.

Anal. Calc'd for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.6.

N-Carbobenzoxy-β,γ-dibromopropylamine (III, R_2 = H, R_3 = CH_2Br, R = $CH_2C_6H_5$, X = Br). This was prepared by bromination of the foregoing product and was recrystallized twice from aqueous alcohol. M.p. 86–87°; yield, 85%.

Anal. Calc'd for $C_{11}H_{13}Br_2NO_2$: N, 4.0; Br, 45.5.
Found: N, 4.3; Br. 45.0.

The product cyclized at 125–145° and 20 mm. with evolution of benzyl bromide. The solid residue which was recrystallized from benzene and then had m.p. 107°, was identical with the product obtained from N-carbobutoxy-β,γ-dibromopropylamine.

SUMMARY

A series of N-carbalkoxy-β-haloalkylamines has been prepared. It has been shown that at elevated temperatures, these compounds undergo cyclization with elimination of alkyl halides, yielding 2-oxazolidones.

A reaction mechanism has been suggested to explain the different mode of cyclization of N-carbalkoxy-β-haloalkylamines and N-acyl-β-haloalkylamines, a difference which is also valid for the N-carbalkoxy- and N-acyl derivatives of α-amino-acids.

REHOVOTH, ISRAEL

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

A STUDY OF THE REDUCTION AND FRAGMENTATION OF SOME TERTIARY CARBINOLS WHEN CONDENSED WITH BENZENE IN THE PRESENCE OF ALUMINUM CHLORIDE

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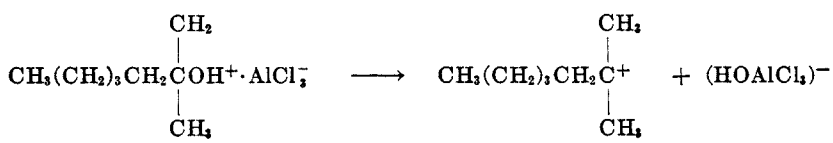
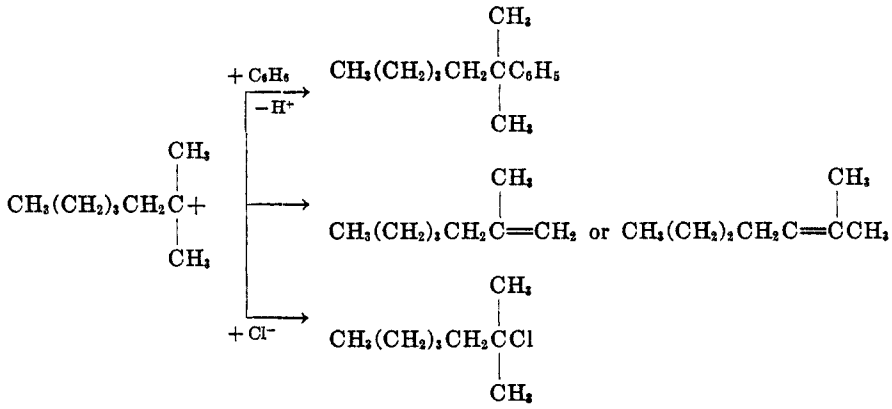
Previous papers (1, 2) from this laboratory showed that when tertiary alcohols having alkyl groups, particularly methyl, on the carbon atom adjacent to the carbinol carbon were condensed with benzene in the presence of aluminum chloride rearrangement followed by fragmentation or fragmentation without rearrangement took place. In any event, the relatively low energy-containing 2-methylpropane and 2-methyl-2-phenylpropane were isolated from the reaction products.

Other investigations (3, 4, 5) in which alkyl aryl carbinols were condensed with benzene and phenol in the presence of aluminum chloride showed that the alcohol was reduced to the corresponding hydrocarbon to an extent of approximately ten percent. In 1945 Dr. G. L. Goerner, of this laboratory, isolated from the condensation products of 3-ethyl-3-hexanol a saturated paraffin hydrocarbon fraction which was tentatively identified as 3-ethylhexane.

Sixteen tertiary alcohols (8 octanols, 4 heptanols, 2 hexanols, 1 pentanol, and 1 butanol) having only primary groups attached to the carbinol carbon have been condensed with benzene in the presence of anhydrous aluminum chloride. Separation of the reaction products showed that reduction of the alcohols to the corresponding hydrocarbons had taken place in varying amounts depending on their size and structure. Fragmentation of those alcohols having methyl groups attached to the second carbon from the carbinol carbon took place without preliminary rearrangement at such a point as to favor the formation of the *tert*-butyl carbonium ion which further reacted to form 2-methyl-2-phenylpropane and 2-methylpropane. Branching on the carbon atom third removed from the carbinol carbon is apparently too distant to bring about appreciable fragmentation.

Making the usual assumptions as to the formation of a dative bond and a carbonium ion, the reactions involved in the condensation of 2-methyl-2-heptanol may be outlined as follows:

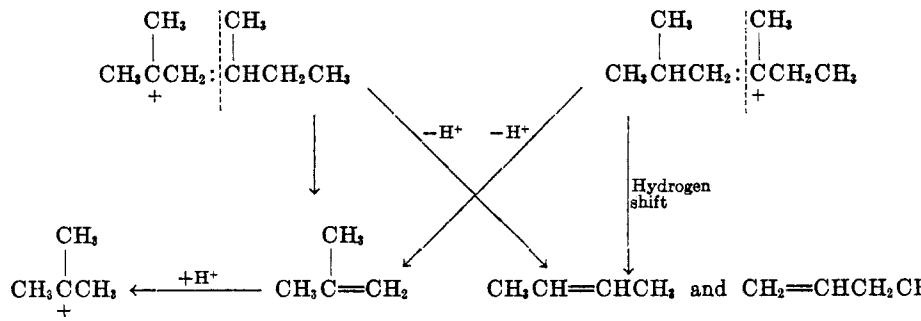




Both olefins and alkyl chlorides have been isolated and both are known alkylating agents. Furthermore either may act as a hydrogen acceptor and would yield, in the presence of a suitable donor, 2-methylheptane.

As examples of fissionable alcohols 2,4-dimethyl-2-hexanol and 2,4-dimethyl-4-hexanol will be used. In both cases the reactions would lead to the formation of an octylbenzene, a mixture of octenes and an octyl chloride.

The carbonium ion from 2,4-dimethyl-2-hexanol or 2,4-dimethyl-4-hexano would undergo fragmentation as follows:



It should be noted that in one case fission takes place between the positive carbon and the adjacent carbon, while in the other case the fission is between the adjacent carbon and the next adjacent. No evidence has been found of the formation of secondary alkylbenzenes; however, secondary alkyl chlorides have been isolated. In either case the 2-methylpropene, the *tert*-butyl carbonium ion or the chloride would condense with benzene to give 2-methyl-2-phenylpropane, or in the presence of a suitable hydrogen donor they would be reduced to 2-methylpropane.

There are many examples of dehydrogenating and hydrogenation effects of aluminum chloride and similar catalysts (6–9). Many of these reactions are accompanied by the formation of biphenyl, anthracene, and indane derivatives, and more generally, by large amounts of resinous material. Each of these side reactions is a possible source of hydrogen.

One can only postulate as to what form the hydrogen acceptor is in during the reduction. If one assumes that the formation of olefin is necessary, some other hypothesis must be advanced to explain the formation of triphenylmethane, when triphenylcarbinol is condensed with benzene in the presence of aluminum

TABLE I

PREPARATION OF ALCOHOLS AND DERIVATIVES

METHOD OF PREPARATION	ALCOHOL	3,5-DINITROBENZOATES		
		M.P., °C.	N	
			Calc'd	Found
$CH_3(CH_2)_4MgBr$ and CH_3COCH_3	2-Methyl-2-heptanol (11)	43–44	8.63	8.40
$CH_3(CH_2)_3MgBr$ and $CH_3COCH_2CH_3$	3-Methyl-3-heptanol (12)	53–54	8.63	8.88
$CH_3(CH_2)_2MgBr$ and $CH_3COOC_2H_5$	4-Methyl-4-heptanol (13)	55–56	8.63	8.59
CH_3CH_2MgBr and $CH_3(CH_2)_2COOH$	3-Ethyl-3-hexanol (12)	62–63	8.63	8.74
$CH_3CH_2CHCH_2MgBr$, CO_2 and CH_3MgBr	2,4-Dimethyl-2-hexanol (14)	48.5–49.5	8.63	8.69
CH_3CH_2MgBr and $CH_3CCH_2CH(CH_3)_2$	2,4-Dimethyl-4-hexanol (15, 16)	52–53	8.63	8.93
$(CH_3)_2CHCH_2CH_2MgBr$ and CH_3COCH_3	2,5-Dimethyl-2-hexanol (17)	61–62	8.63	8.95
$(CH_3)_3COH$, H_2SO_4, HI, and Ag_2O	2,4,4-Trimethyl-2-pentanol (18)	89.5–90.5	8.63	8.81
$CH_3(CH_2)_3MgBr$ and CH_3COCH_3	2-Methyl-2-hexanol (12)	53–54	9.02	8.68
$CH_3(CH_2)_2MgBr$ and $CH_3COC_2H_5$	3-Methyl-3-hexanol (12)	43–44	9.02	9.54
CH_3CH_2MgBr and $C_2H_5OCOOC_2H_5$	3-Ethyl-3-pentanol (19)	118–119	9.02	9.17
CH_3MgBr and $CH_3COCH_2CH(CH_3)_2$	2,4-Dimethyl-2-pentanol (20)	69–70	9.02	9.07
$CH_3(CH_2)_2MgBr$ and CH_3COCH_3	2-Methyl-2-pentanol (12)	71–72		
CH_3CH_2MgBr and $CH_3COC_2H_5$	3-Methyl-3-pentanol (21)	95.5–96.5		

chloride (10). If one assumed that the carbonium ion or complex is reduced, one must postulate the formation of hydride ions.

A free radical mechanism is not favored inasmuch as this would involve the formation of such fragments as $(CH_3)_3C\cdot$ which is not considered as an intermediate in the formation of 2-methyl-2-phenylpropane.

It is perhaps logical to assume that a necessary prerequisite for reduction is the formation of an alkyl chloride which may be reduced by atomic hydrogen

with the formation of a paraffin hydrocarbon and hydrogen chloride. Twelve grams of 2-methylpropane were isolated from a three-mole condensation ($AlCl_3$) of *tert*-butyl chloride with benzene, in contrast to only five grams from a similar run using *tert*-butyl alcohol.

TABLE II

HYDROCARBONS ISOLATED IN THE CONDENSATION OF ALCOHOLS WITH BENZENE

ALCOHOL	YIELD, %				ALKYL BENZENE, %	
	2-Methylpropane	Paraffin Hydrocarbon		2-Methyl-2-phenylpropane		
2-Methyl-2-heptanol	—	2-Methylheptane	8.8	—	2-Methyl-2-phenylheptane (23)	27.4
3-Methyl-3-heptanol	—	3-Methylheptane	9.5	—	3-Methyl-3-phenylheptane	24.2
4-Methyl-4-heptanol	—	4-Methylheptane	12.0	—	4-Methyl-4-phenylheptane (23)	33.1
3-Ethyl-3-hexanol	—	3-Ethylhexane	14.3	—	3-Ethyl-3-phenylhexane (23)	25.1
2,4-Dimethyl-2-hexanol	3.1	2,4-Dimethylhexane	3.8	1.30	2,4-Dimethyl-2-phenylhexane (23)	19.6
2,4-Dimethyl-4-hexanol	4.6	2,4-Dimethylhexane	3.9	2.20	2,4-Dimethyl-4-phenylhexane (23)	19.2
2,5-Dimethyl-2-hexanol	—	2,5-Dimethylhexane	5.7	—	2,5-Dimethyl-2-phenylhexane (23)	21.5
2,4,4-Trimethyl-2-pentanol	4.6	2,4,4-Trimethylpentane	—	20.00	2,4,4-Trimethyl-2-phenylpentane (23)	14.0
2-Methyl-2-hexanol	—	2-Methylhexane	2.1		2-Methyl-2-phenylhexane (24)	31.3
3-Methyl-3-hexanol	—	3-Methylhexane	1.6	—	3-Methyl-3-phenylhexane (24)	30.0
3-Ethyl-3-pentanol	—	3-Ethylpentane	2.3	—	3-Ethyl-3-phenylpentane (24)	33.2
2,4-Dimethyl-2-pentanol	2.2	2,4-Dimethylpentane	—	2.80	2,4-Dimethyl-2-phenylpentane (24)	22.2
2-Methyl-2-pentanol	—	2-Methylpentane	7.0	—	2-Methyl-2-phenylpentane (24)	32.7
3-Methyl-3-pentanol	—	3-Methylpentane	10.2	—	3-Methyl-3-phenylpentane (24)	35.9
2-Methyl-2-butanol	—	3-Methylbutane	1.8	—	2-Methyl-2-phenylbutane (24)	40.0
2-Methyl-2-propanol	2.2			55.0	(*p*-Di-*tert*-butylbenzene) (M.p. 76°)	1.2

EXPERIMENTAL

Preparation of alcohols: Table I gives the methods used in the preparation of all of the alcohols used with the exception of 2-methyl-2-butanol and 2-methyl-2-propanol. These were purified to a boiling-point range of two degrees and their refractive indices and densities were checked against those given in the references. They were further characterized by the preparation and analysis of the new 3,5-dinitrobenzoyl derivatives.

TABLE III

IDENTIFICATON OF PARAFFIN HYDROCARBON FRACTIONS

HYDROCARBON	B.P. °C.	MM.	n_D^{20}	d_4^{20}	MR Calc'd (Found)	INFRARED MAXIMA (in microns at 25°)				
2-Methylheptane (25)	115–116	743	1.3962 (1.3949)	0.7001 (0.6979)	39.16 (39.12)	8.30 8.55 8.75 9.25	9.57 10.41 10.66 10.86	11.17 11.88 12.26 12.99	13.24 13.79	
3-Methylheptane (25)	117.5	749.5	1.3980 (1.3985)	0.7055 (0.7058)	39.16 (39.14)	8.05 8.25 8.70 8.77	9.30 9.89 10.05 10.47	10.72 10.99 11.15 12.95	13.74	
4-Methylheptane (25)	116–117	749	1.3980 (1.3979)	0.7044 (0.7040)	39.16 (39.06)	8.22 8.69 8.76 9.35	9.55 9.70 9.90 10.10	10.48 11.03 11.17 11.44	11.94 12.12 13.06 13.49	
3-Ethylhexane (25)	115–116	746	1.3980 (1.4016)	0.7052 (0.7139)	39.16 (39.02)	7.90 8.03 8.18 8.70	8.90 9.35 9.62 9.75	9.88 9.76 10.95 11.24	12.14 12.88	
2,4-Dimethylhexane (25)	109–109.5	745	1.3970 (1.3953)	0.7012 (0.7004)	39.16 (39.08)	6.81 7.31 7.70 7.79	8.10 8.54 8.69 9.22	9.55 9.87 10.04 10.31	10.85 11.05 11.37 11.61	12.43 13.04
2,5-Dimethylhexane (25)	107–108	736	1.3930 (1.3925)	0.6952 (0.6936)	39.16 (39.14)	6.79 7.22 7.31 7.93	8.17 8.54 9.17 9.58	9.64 10.54 10.69 10.87	11.92 12.28 12.46 13.28	
2-Methylhexane (25)	89.5	750	1.3855 (1.3876)	0.6790 (0.6787)	34.53 (35.26)	6.80 7.23 7.30 7.47	7.72 7.97 8.18 8.53	8.73 9.30 9.53 9.71	9.85 10.88 11.04 11.17	12.16 12.81 13.74
3-Methylhexane (25)	89.5–91	733	1.3895 (1.3887)	0.6890 (0.6870)	34.53 (34.86)	7.24 8.11 8.65 8.72	9.29 9.88 10.16 10.38	10.77 11.36 12.96 13.55		

3-Ethylpentane (25)	92.5–93	741	1.3940 (1.3934)	0.6995 (0.6982)	34.53 (34.73)	6.84 7.25 7.50 7.59	7.66 7.85 8.03 8.57	8.68 8.87 9.59 9.96	11.13 11.83 12.03 12.68	13.05 13.69
2-Methylpentane (25)	60–60.5	742	1.3725 (1.3716)	0.6558 (0.6532)	29.91 (30.18)	7.22 7.29 7.84 8.05	8.52 8.70 9.35 9.62	9.90 10.45 10.65 10.87	11.20 11.59 12.18 13.50	
3-Methylpentane (25)	61.5–62	741	1.3780 (1.3765)	0.6655 (0.6643)	29.91 (30.00)	6.85 7.25 7.69 7.99	8.66 8.88 9.58 9.86	10.15 10.50 11.39 12.85		
2-Methylbutane (25)	26–28	742	1.3552 (1.3537)	0.6197 (0.6212)	25.29 (25.32)					
2-Methylpropane (25)	−10.4	750	1.3518^{-25}							

A preliminary study of the methods of preparation showed the importance of selecting simple Grignard reagents. Isoalkylmagnesium bromides gave relatively small yields of alcohols contaminated with products of side reactions, *i.e.*, reduction, condensation, pinacol formation, enolization coupling, etc.

Condensations: As all condensations were carried out by the same procedure only one will be described. A 3-liter, 3-necked flask equipped with stirrer, dropping-funnel, and condenser to which was attached a solid carbon-dioxide trap, was charged with 1053 grams (13.5 moles) of anhydrous thiophene-free benzene and 179.5 grams (1.35 moles) of anhydrous aluminum chloride. The suspension was heated to reflux, with stirring, cooled to room temperature and 314 grams (2.7 moles) of 2,4-dimethyl-2-hexanol added dropwise at such a rate as to keep the temperature at 35° ± 1°. When the addition of alcohol was complete the mixture was stirred for two hours and then allowed to stand overnight. Cracked ice was used in the hydrolysis.

After hydrolysis the organic layer was separated from the aqueous layer, the latter was extracted with benzene, the combined organic layers washed with dilute sodium carbonate and dried over sodium sulfate. Fractionation was accomplished at atmospheric pressure by means of Fenske-type columns. In the final fractionations of the paraffin hydrocarbons a 92 × 0.8 cm. column, packed with 1/32 in. glass helices, was used.

The gas collected in the solid carbon dioxide-acetone trap was combined with the gas given off during hydrolysis and was identified by its boiling point and refractive index as 2-methylpropane. An adaptation of the method of Grosse (22) for determining refractive indices at low temperatures was used.

Those octyl alcohols in which there was fragmentation gave unsaturated fractions which came over at 190–200°. These indicated the formation of dodecenes (2).

Table II lists the alcohols condensed with benzene and the hydrocarbons isolated.

The identification of 2-methyl-2-phenylpropane was accomplished by its physical constants and the acetamino derivative. The other alkylbenzenes were identified by their physical constants which have been reported in earlier work (23, 24).

Table III lists the isolated paraffin hydrocarbons together with their determined boiling points, densitives, and refractive indices. The figures in parentheses are the "preferred" densities and refractive indices as reported under the American Petroleum Institute Project 44 at the National Bureau of Standards (25).

The infrared absorption maxima were determined at 25° and checked against those of pure samples of the hydrocarbons furnished by the National Bureau of Standards. Those of the octanes and heptanes were also checked against the spectrograms published in mimeograph form by the National Bureau of Standards as a part of the reports of the American Petroleum Institute Research Project 44 (26).

The greatest deviation from the preferred refractive index and density was found in 3-ethylhexane. It is worthy of note in this connection that 3,3-dimethylhexane (25) which is a possible rearrangement product has a lower "preferred" refractive index (n_D^{20} 1.4001) and density (d_4^{20} 0.7100) than 3-ethylhexane (25). The two hydrocarbons have infrared absorption maxima in common at 7.90, 8.20, 8.65, 8.90, 9.85, and 10.92 μ (26). The presence of 3,3-dimethylhexane as a contaminant is not excluded.

SUMMARY

1. Sixteen tertiary alcohols having only primary alkyl groups attached to the carbinol carbon were prepared and condensed with benzene in the presence of aluminum chloride.

2. Fragmentation was shown to take place with those alcohols having branching on the *beta*-carbon. Fission of the alkyl carbonium ion always took place at such a point as to favor the formation of 2-methylpropane and 2-methyl-2-phenylpropane.

3. Reduction was shown to take place as evidenced by the isolation of the paraffin hydrocarbon corresponding to the structure of the alcohol condensed. 2-Methylpropane was isolated in all cases where fragmentation occurred.

4. Possible mechanisms have been proposed to explain the fragmentation and reduction.

5. 3,5-Dinitrobenzoates of the alcohols were prepared.

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

THE REACTION OF NITRILES WITH HYDRAZOIC ACID: SYNTHESIS OF MONOSUBSTITUTED TETRAZOLES

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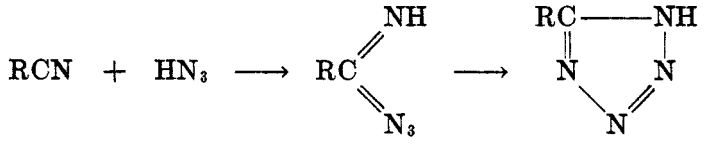
The addition of hydrazoic acid to the cyanide group with the formation of 5-substituted tetrazole derivatives was first observed by Hantzsch and Vagt (1) who prepared 5-aminotetrazole by the interaction of hydrazoic acid and cyanamide. Some twenty years later Stollé (2) showed that the same product could be prepared from the more readily accessible dicyandiamide and hydrazoic acid. Presumably the dicyandiamide dissociated under the conditions of the reaction so that the process was essentially the same as that described by Hantzsch and Vagt. The synthesis of the parent heterocycle was accomplished by Dimroth and Fester (3) by the interaction of hydrazoic acid and hydrocyanic acid in alcoholic solution. These authors suggested that tetrazole formation took place through the formation of an imide azide which immediately cyclized as indicated in the following general reaction:



1.

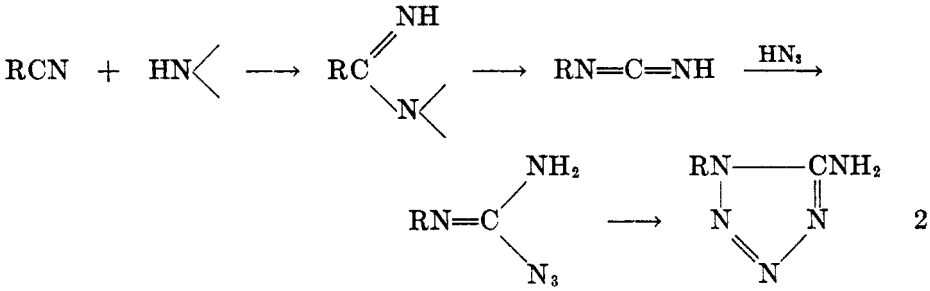
R = H, NH_2, CN, $COOC_2H_5$, $CON(C_2H_5)_2$, Br

Using the same general reaction Oliveri-Mandalà (4) succeeded in preparing 5-bromo-, 5-cyano-, and 5-carbethoxy-tetrazole by the interaction of hydrazoic acid with cyanogen bromide, cyanogen, and ethyl cyanoformate, respectively. More recently the preparation of tetrazole-5-diethylcarboxamide from hydrazoic acid and cyanodiethylformamide has also been described (5). It should be noted that no condensing agents or catalysts were required to bring about interaction of these nitriles with hydrazoic acid and that the reactions took place at relatively low temperatures, in boiling ether, except in the case of hydrocyanic acid. Other methods of preparing 5-substituted tetrazoles have been reviewed recently (6).

In 1932 von Braun and Keller (7) reported attempts to bring about reaction of hydrazoic acid with a number of alkyl and aryl cyanides in the presence of concentrated sulfuric acid. Under these conditions a reaction between two moles of hydrazoic acid and one of the nitrile took place and the formation of 1-alkyl or aryl-5-aminotetrazole derivatives indicated that a rearrangement of the nitrile with a shift of the alkyl group from carbon to nitrogen had taken place during the reaction. They suggested that the reaction involved the addition of an imine radical (HN=) to the cyanide group to form an intermediate which after

[1] Based on a thesis submitted by Joseph S. Mihina to the School of Graduate Studies at Michigan State College in partial fulfillment of the requirements for the Ph. D. degree.

rearrangement added a molecule of hydrazoic acid and cyclized to form the 5-aminotetrazole derivative. The assumption of the existence of the imine radical



was based on the work of Schmidt (8) who had suggested its formation during the decomposition of hydrazoic acid in the presence of sulfuric acid. Since they failed to isolate any 5-alkyl- or 5-aryl-tetrazoles from the reaction, von Braun and Keller concluded that hydrazoic acid would not add to the cyanide group of the nitriles of carboxylic acids.

Repetition of Dimroth's preparation of tetrazole in benzene solution rather than in alcoholic solution as originally suggested has made it possible to develop this procedure into a useful preparative method. Furthermore, a study of the interaction of hydrazoic acid with dicyandiamide in aqueous solution showed this reaction to take place with such remarkable ease that it could be used for the preparation of 5-aminotetrazole in excellent yield in almost any desired quantity. These observations suggested the desirability of studying again the interaction of alkyl and aryl cyanides with hydrazoic acid in the absence of reagents such as sulfuric acid. This was particularly desirable in view of the work of Newman and Gildenhorn (9) and Smith (10) which had demonstrated the readiness with which rearrangement of addition products of hydrazoic acid and unsaturated groupings took place in the presence of proton donors.

When alkyl or aryl nitriles were heated with benzene solutions of hydrazoic acid at temperatures of 120–150° for periods of 96–120 hours, excellent yields of the 5-alkyl- or 5-aryl-tetrazoles were obtained. In many instances the reaction could be carried out equally successfully in isopropyl alcohol solution using equivalent amounts of sodium azide and acetic acid, thus obviating the need of preparing benzene solutions of hydrazoic acid. A series of 5-alkyl- and 5-aryl-tetrazoles prepared in this manner are listed in Table I. Of this group the 5-phenyl-, 5-*p*-tolyl-, and 5-methyl-tetrazoles had been previously described. The first two had been prepared by Pinner (11, 12) by the interaction of benzimino ethyl ether and hydrazine and treatment of the amidrazone so formed with nitrous acid. 5-Methyltetrazole had been prepared in an analogous manner from acetonitrile (13). We have repeated the preparation of these three compounds from benzonitrile, *p*-tolunitrile, and acetonitrile, respectively, by way of the imino ethers and the amidrazones and the products so obtained were identical in every respect with the tetrazoles formed by direct addition of hydrazoic acid to the respective nitriles.

Our results indicate that the conclusion of von Braun and Keller concerning the non-addition of hydrazoic acid to alkyl and aryl cyanides is invalid. The formation of 5-substituted tetrazoles by interaction of hydrazoic acid and nitriles may be explained most easily by the assumption of an intermediate imide azide which rapidly cyclizes to form the tetrazole as suggested by Dimroth and Fester. Although it is unlikely that the imide azide would be stable at the elevated temperature employed, the formation of such an intermediate seems reasonable since Thiele (14) had succeeded in isolating guanyl azide by the interaction of aminoguanidine and nitrous acid and had observed its cyclization to 5-aminotetrazole in boiling aqueous solution. In Reaction 1, the group R may now be considered to include alkyl and aryl groups in addition to those already indicated.

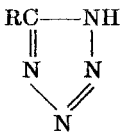
All of the 5-substituted tetrazoles described in Table I are acidic substances. The lower members of the series are quite soluble in water and their aqueous solutions will displace carbonic acid from the alkali bicarbonates. The higher members of the series dissolve readily in water upon addition of alkalies, alkali carbonates or ammonia. The calcium, strontium, and barium salts of the compounds are quite soluble in water and do not lend themselves easily to the characterization of the substances. All the 5-substituted tetrazoles form silver salts that are insoluble in water or dilute nitric acid. In the preparation of the silver salts care should be exercised to avoid an excess of silver nitrate since the precipitates appear to occlude or adsorb excess reagent. The silver salts are light-sensitive and decompose with a flash when heated on a spatula. They do not seem to be sensitive to shock. Two of the products, 5-benzyl- and 5-β-phenylethyltetrazole formed well crystallized complex salts with mercuric chloride in alcoholic solution. Analysis indicated that these compounds were mercuric chloride complex salts of the mercurichloride derivatives, $RHgCl \cdot HgCl_2$. In none of the other cases could characteristic crystalline derivatives be obtained with mercuric chloride.

Dissociation constants and neutralization equivalents of all the 5-alkyl- and 5-aryl tetrazoles were determined potentiometrically. The titration curve for each of the compounds was typical of a weak acid; no abnormalities were observed. The results are summarized in Table I. In most instances the dissociation constants of the tetrazoles were smaller by a factor of about ten than those of the corresponding carboxylic acids in which the carboxyl group replaced the tetrazole ring. The dissociation constant of tetrazole ($K = 1.62 \times 10^{-5}$ at 25°) determined in this way was in good agreement with the value ($K = 1.54 \times 10^{-5}$ at 25°) calculated from conductivity data by Oliveri-Mandalà (15). The most acidic compounds in the group in the order of decreasing strength are 5-phenyltetrazole, 5-*m*-tolyltetrazole, 5-*o*-tolyltetrazole, tetrazole, and 5-*p*-tolyltetrazole.

In an attempt to obtain characteristic derivatives 5-phenyl- and 5-β-cyclohexylethyl-tetrazole were treated with *p*-nitrobenzyl bromide in alkaline, aqueous alcoholic solution. Easily crystallizable, neutral products that gave correct nitrogen analyses for the *p*-nitrobenzyl-5-phenyl- and 5-β-cyclohexylethyl-tetrazoles were formed. In order to determine whether the benzyl group occupied the 1 or the 2 position on the ring the same reaction was carried out with benzyl

TABLE I

5-SUBSTITUTED TETRAZOLES



R	YIELD, %	M.P., °C. (CORR.)	REACTION TIME, HOURS	CRYSTALLIZED FROM	POTENTIOMETRIC TITRATION			
					Average Apparent K × 10⁶	Equivalent Weight		Solvent[a]
						Calc'd	Found	
Hydrogen	42	157.5–158	96	Ethyl acetate	16.2	70.7	70.3	Water
Methyl	76	148–148.5	100	Amyl acetate	2.74	84.1	84.4	Water
Ethyl	66	98–99	75	Ethyl acetate	2.56	98.1	99.0	Water
n-Propyl	76	64–65	108	Isopropyl ether	2.47	112	113	Water
Isopropyl	87	113–114	104	Ethylene chloride	2.80	112	112	Water
n-Butyl	56	47.5–48.5	106	Petroleum ether-ether	2.38	126	126	25% Methanol
Isobutyl	70	53.5–54	104	Isopropyl ether	2.45	126	126	25% Methanol
n-Amyl	77	41–42	109	Acetonitrile	2.22	140	141	25% Methanol
Isoamyl	53	95–96	109	Petroleum ether-ether	1.97	140	141	25% Methanol
n-Hexyl	78	46.5–47.5	125	Acetonitrile	2.12	154	155	23% Methanol
n-Heptyl	56	41.5–42.5	110	Acetonitrile	2.00	168	169	25% Methanol
n-Octyl	84	41.5–42.5	102	Ethyl acetate	1.85	182	184	34% Methanol
Phenyl	75	217–218	101	Water	29.8	146	147	44.4% Methanol
Benzyl	73	125.5–126	103	Ethylene chloride	8.92	160	161	20% Methanol
β-Phenylethyl	86	100.5–101	110	Benzene	3.92	174	176	20% Methanol
γ-Phenylpropyl	59	92.5–93.5	102	Toluene	3.10	188	190	20% Methanol
o-Tolyl	29	157–158	134	Water	23.9	160	162	23% Methanol
m-Tolyl	88	152–152.5	168	Water	25.5	160	162	33% Methanol
p-Tolyl	88	250–250.5	102	Ethanol	12.3	160	162	50% Methanol
Cyclohexyl	61	134–135	102	Water	1.85	152	153	25% Methanol
Cyclohexylmethyl	75	109.5–110	150	Ethyl acetate	2.01	166	167	25% Methanol
β-Cyclohexylethyl	85	143–143.5	120	Ethyl acetate	1.73	180	181	37.5% Methanol
γ-Cyclohexylpropyl	68	94–95	102	Ethyl acetate	1.61	194	195	41% Methanol
δ-Cyclohexylbutyl	67	65.5–66	108	Acetonitrile	1.40	208	210	47.4% Methanol
ε-Cyclohexylamyl	60	71.5–72.5	108	Ethyl acetate	1.18	222	224	56.5% Methanol

[a] Composition of aqueous methanol expressed as percent by weight of methanol.

bromide and 5-phenyltetrazole. A benzyl-5-phenyltetrazole was obtained as glistening needles which melted at 65.5–66°. To check the identity of this compound 1-benzyl-5-phenyltetrazole was prepared from N-benzylbenzamide by a procedure based on the general method of von Braun and Rudolph (16, 17) which involved conversion of the amide to the imide chloride and treatment of the latter with hydrazoic acid. The 1-benzyl-5-phenyltetrazole so obtained crystallized as coarse, granular prisms melting at 92.5–93° and caused depression of the melting point of the lower-melting benzyl derivative. In view of the dissimilarity of the products it is likely that the compounds formed by benzylation and nitrobenzylation of the 5-substituted tetrazoles are the 2-benzyl-5-phenyltetrazole and the 2-*p*-nitrobenzyl derivatives. However, further verification of these structures is necessary before they may be considered unequivocally established.

TABLE II

CYCLOHEXANEALKANOIC ACID CHLORIDES $C_6H_{11}(CH_2)_nCOCl$

n	B.P., °C./MM.	YIELD, %	ANALYSIS		REF.
			Chlorine		
			Calc'd	Found	
1	95–96/21	59	—	—	19
2	109–111/19	88	—	—	20
3	123–124/17	90	18.8	18.8 18.7	
4	143/18	78	—	—	21
5	150–152/17	93	16.4	16.3 16.4	

The nitriles used as intermediates for the tetrazole syntheses were generally available with the exception of those derived from the cyclohexanealkanoic acids. These were prepared from the acids by way of the acid chlorides and amides. Dehydration of the amides was accomplished very smoothly and usually in good yields by treatment with phosphorus oxychloride in the presence of sodium bisulfite (18).

EXPERIMENTAL

PREPARATION OF INTERMEDIATES

Cyclohexanealkanoic acid chlorides. The acid chlorides were prepared by the method of Darzens and Rost (19). In a typical example 274 g. (1.75 moles) of β-cyclohexanepropionic acid was added dropwise to 297 g. (2.5 moles) of boiling thionyl chloride. The mixture was refluxed for an hour after complete addition of the acid when the excess thionyl chloride was removed and the residual acid chloride was distilled under reduced pressure. Physical constants and analyses of the acid chlorides are given in Table II.

Amides of the cyclohexanealkanoic acids. The amides were prepared by a modification of the procedure of Katsnel'son and Dubinin (21). In a typical preparation 250 g. (1.33 moles)

of γ-cyclohexanebutyryl chloride was added dropwise with stirring to a cooled, saturated solution of ammonia in 3 l. of benzene. The mixture was kept below 10° and ammonia was bubbled through the mixture continuously during the addition of the acid chloride. Stirring was continued for an hour after complete addition of the reactants after which the precipitated ammonium chloride was filtered off and thoroughly extracted with benzene. Upon concentration of the combined benzene solutions, the amide separated as colorless plates. Physical properties and nitrogen analyses (Kjeldahl) are recorded in Table III.

TABLE III

AMIDES OF CYCLOHEXANEALKANOIC ACIDS $C_6H_{11}(CH_2)_nCONH_2$

n	M.P., °C.	YIELD, %	ANALYSIS		REF.
			Nitrogen		
			Calc'd	Found	
1	170–171	40	—	—	22
2	120	42	—	—	23
3	112–113	95	8.3	8.4 8.5	
4	124–125	92	—	—	21
5	119–119.5	95	7.1	7.4 7.5	

TABLE IV

NITRILES OF CYCLOHEXANEALKANOIC ACIDS $C_6H_{11}(CH_2)_nCN$

n	B.P., °C./MM.	YIELD, %	ANALYSIS		REF.
			Nitrogen		
			Calc'd	Found	
1	210–212/741	64	—	—	22
2	116.5–117/22	36	10.2	10.1 10.2	
3	132/22	59	9.3	9.3 9.4	
4	141–143/18	81	8.5	8.4 8.5	
5	154/17	77	7.8	7.9 7.9	

Nitriles of the cyclohexanealkanoic acids. Dehydration of the amides was carried out as recommended by Fahrenbach (18). For example, 200 g. (1.09 moles) of δ-cyclohexanevaleramide, 1000 g. (6.54 moles) of phosphorus oxychloride, and 125 g. (0.65 mole) of sodium metabisulfite were mixed in a three-necked flask. The mixture was warmed to 70° on a water bath when the reaction began. The temperature was slowly raised to 96° where it was maintained for two hours. After quenching the reaction with ice, the nitrile was extracted with ether and dried over sodium sulfate. The liquid left upon evaporation of the solvent was distilled under reduced pressure. Physical properties and nitrogen analyses (Kjeldahl) for the nitriles prepared in this manner are reported in Table IV.

PREPARATION OF TETRAZOLES

Tetrazole. Tetrazole was prepared by the interaction of hydrazoic acid and hydrocyanic acid in benzene solution (24). An alternative procedure was also employed. A Pyrex combustion tube was charged with 5.9 g. (0.12 mole) of sodium cyanide, 19 g. (0.3 mole) of sodium azide, 24 ml. of acetic acid, and 35 ml. of isopropyl alcohol. After sealing, the tube was heated for 96 hours at 110°. The contents of the tube were then dissolved in warm water, acidified with nitric acid, and treated with silver nitrate to precipitate silver tetrazole. This was washed and suspended in warm water without drying. After precipitation of the silver with hydrogen sulfide, the aqueous solution was evaporated to dryness and the residual crude tetrazole was recrystallized from ethyl acetate, small needles, m.p. 157.5–158°. The yield was 3.5 g., 42%.

5-Aminotetrazole. The procedure of Stollé (2) for the preparation of this compound was simplified. A suspension of 82 g. (1 mole) of dicyandiamide and 117 g. (1.8 moles) of sodium azide in 200 ml. of water was warmed to 65° on the water-bath under a reflux condenser when 150 ml. (1.8 moles) of concentrated hydrochloric acid was added in small portions with frequent manual agitation. After complete addition of the acid the mixture was kept at 65–70° on the water-bath for 6 hours during which the product began to crystallize. The semi-solid mass was allowed to stand overnight and was chilled thoroughly before the product was filtered off and washed with ice water. The crude 5-aminotetrazole was recrystallized from boiling water, coarse prisms of the monohydrate. The yield was 135 g., 73%, m.p. 206.5–207.5° decompn.

5-Alkyl and 5-aryl-tetrazoles. All the 5-monosubstituted tetrazoles were prepared in a similar manner. The appropriate nitriles and hydrazoic acid in about 1:1.15 molar ratio were heated in benzene solution in a sealed tube at 150° for 96–120 hours. On completion of the reaction the contents of the tube were transferred to a beaker, the solution evaporated to dryness, and the residue taken up in ethanol and decolorized with charcoal. From this point on three different procedures for the isolation and purification of the tetrazoles were employed.

(A) The alcohol was completely evaporated on a steam-bath after which the crude tetrazole was recrystallized twice from the solvent indicated in Table I. This method was employed when the original nitrile had a sufficiently low boiling point to permit complete removal on the steam-bath. The following products were purified in this manner: 5-methyl-, 5-ethyl-, 5-*n*-propyl-, 5-isopropyl-, 5-*n*-butyl-, and 5-isoamyl-tetrazole.

(B) The ethanol was removed by distillation and the residue was distilled under reduced pressure. The tetrazole fraction in the distillate usually solidified and could be purified further by crystallization from suitable solvents. 5-Isobutyltetrazole (b.p. 156–158°/3.5 mm.), 5-*n*-amyltetrazole (b.p. 158–159°/2 mm.), and 5-*n*-hexyltetrazole (b.p. 167.5–168.5°/2.1 mm.) were purified in this manner. The 5-*n*-heptyltetrazole could not be distilled under reduced pressure without extensive decomposition.

(C) The alcoholic solution of the crude product was evaporated to dryness and the residue subjected to steam-distillation to remove unreacted nitrile. After evaporating the water from the aqueous suspension of the non-volatile material, the residue of crude tetrazole was purified by recrystallizing twice from an appropriate solvent. In addition to the 5-*n*-heptyl- and 5-*n*-octyl-tetrazoles, all of the 5-aryl- and 5-cyclohexylalkyl-tetrazoles were isolated in this way.

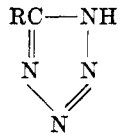
A typical example is the preparation of 5-benzyltetrazole. Benzyl cyanide (23.4 g., 0.2 mole) and 55 ml. of a 20.6% solution of hydrazoic acid (0.27 mole) in benzene were sealed into a Pyrex combustion tube and heated for 102 hours at 150°. After completion of the reaction the contents of the tube were washed into a beaker with ethanol and the solvent removed by evaporation. The residue was taken up in 100 ml. of ethanol, decolorized with charcoal, and the solution again evaporated to dryness. The crude product was then subjected to steam-distillation to remove unreacted benzyl cyanide and after evaporation of the water from the aqueous suspension, the residual 5-benzyltetrazole was twice re-

crystallized from the minimum amount of ethylene dichloride from which it separated as coarse, colorless prisms, m.p. 125.5–126°.

An alternative procedure was especially useful with those tetrazoles which were quite insoluble in water and which were relatively high melting. A mixture of 7 g. (0.108 mole) of sodium azide, 11.7 g. (0.1 mole) of *p*-tolunitrile, 8.5 ml. (0.14 mole) of glacial acetic acid, and 25 ml. of absolute isopropyl alcohol was sealed into a combustion tube and heated at 150°

TABLE V

ANALYTICAL DATA FOR THE 5-SUBSTITUTED TETRAZOLES AND THEIR SILVER SALTS



R	TETRAZOLES			SILVER SALTS		
	Empirical Formula	N		Empirical Formula	N	
		Calc'd	Found		Calc'd	Found
Methyl	$C_2H_4N_4$	66.6	66.8	$C_2H_3AgN_4$	29.4	29.3
Ethyl	$C_3H_6N_4$	57.1	56.8	$C_3H_5AgN_4$	27.3	27.1
n-Propyl	$C_4H_8N_4$	50.0	49.7	$C_4H_7AgN_4$	25.6	25.3
Isopropyl	$C_4H_8N_4$	50.0	50.1	$C_4H_7AgN_4$	25.6	25.5
n-Butyl	$C_5H_{10}N_4$	44.4	44.1	$C_5H_9AgN_4$	24.1	23.8
Isobutyl	$C_5H_{10}N_4$	44.4	44.4	$C_5H_9AgN_4$	24.1	24.0
n-Amyl	$C_6H_{12}N_4$	40.0	40.0	$C_6H_{11}AgN_4$	22.7	22.5
Isoamyl	$C_6H_{12}N_4$	40.0	40.0	$C_6H_{11}AgN_4$	22.7	22.7
n-Hexyl	$C_7H_{14}N_4$	36.3	36.3	$C_7H_{13}AgN_4$	21.5	21.7
n-Heptyl	$C_8H_{16}N_4$	33.3	33.1	$C_8H_{15}AgN_4$	20.4	20.2
n-Octyl	$C_9H_{18}N_4$	30.7	30.4	$C_9H_{17}AgN_4$	19.4	19.5
Phenyl	$C_7H_6N_4$	38.3	38.4	—	—	—
Benzyl	$C_8H_8N_4$	35.0	35.0	$C_8H_7AgN_4$	21.0	21.0
β-Phenylethyl	$C_9H_{10}N_4$	32.1	31.8	$C_9H_9AgN_4$	19.9	20.0
γ-Phenylpropyl	$C_{10}H_{12}N_4$	29.8	29.5	$C_{10}H_{11}AgN_4$	19.0	19.0
o-Tolyl	$C_8H_8N_4$	35.0	35.0	$C_8H_7AgN_4$	21.0	20.7
m-Tolyl	$C_8H_8N_4$	35.0	34.9	$C_8H_7AgN_4$	21.0	20.7
p-Tolyl	$C_8H_8N_4$	35.0	34.7	—	—	—
Cyclohexyl	$C_7H_{12}N_4$	36.8	36.9	$C_7H_{11}AgN_4$	21.6	21.4
Cyclohexylmethyl	$C_8H_{14}N_4$	33.7	33.6	$C_8H_{13}AgN_4$	20.5	20.2
β-Cyclohexylethyl	$C_9H_{16}N_4$	31.1	31.0	$C_9H_{15}AgN_4$	19.5	19.4
γ-Cyclohexylpropyl	$C_{10}H_{18}N_4$	28.3	28.8	$C_{10}H_{17}AgN_4$	18.7	18.6
δ-Cyclohexylbutyl	$C_{11}H_{20}N_4$	26.9	26.9	$C_{11}H_{19}AgN_4$	17.8	17.5
ε-Cyclohexylamyl	$C_{12}H_{22}N_4$	25.1	24.8	$C_{12}H_{21}AgN_4$	17.0	17.3

for 108 hours. After completion of the reaction the solvent was evaporated and the residue was taken up in hot water. Upon acidification with hydrochloric acid 5-*p*-tolyltetrazole precipitated from the aqueous solution. The product was recrystallized from 95% ethanol from which it separated as fine, colorless needles, m.p. 250–250.5°. 5-Phenyl-,5-*o*-tolyl-, 5-*m*-tolyl-, and 5-*p*-tolyl-tetrazole were prepared by the procedure just outlined as well as by the interaction of the appropriate nitriles with hydrazoic acid in benzene solution.

All of the 5-substituted tetrazoles prepared by these procedures are described in Table I. Analytical data for all the compounds are summarized in Table V.

For reference purposes 5-phenyltetrazole and 5-*p*-tolyltetrazole were also prepared by the procedure described by Pinner (11, 12). The nitriles were converted into the imino ethyl ethers and interaction of the latter with hydrazine gave the amidrazones. Conversion to the respective tetrazoles was accomplished by treatment of the amidrazones with nitrous acid. The products were identical in every respect with the tetrazoles made by direct addition of hydrazoic acid to the nitriles and no depression was observed when mixed melting points were taken.

Silver salts of the tetrazoles. The silver salts of the 5-substituted tetrazoles were prepared by dissolving a weighed amount of the tetrazole in ethanol and adding the equivalent amount of a standard silver nitrate solution. Excess of either component was avoided since its adsorption or occlusion on the precipitate gave rise to erroneous nitrogen values. The precipitated silver salt of the tetrazole was digested for two hours in the supernatant liquid, filtered hot, washed with hot 50% ethanol, and dried for analysis for two hours at 90°. Analytical data are recorded in Table V. None of the silver salts listed in Table V could be detonated by shock. All of them were stable to sharp blows with a hammer on an anvil. On heating over a flame on a spatula all of them eventually decomposed with a flash, but they could be burned in the usual micro-Dumas apparatus without special precautions. On exposure to daylight most of the silver salts discolored rapidly.

Mercuric chloride complexes of the tetrazoles. On addition of an alcoholic solution of mercuric chloride to an alcoholic solution of 5-benzyltetrazole a complex of mercuric chloride with the mercurichloride derivative of the tetrazole separated as fine, colorless needles, m.p. 223° decompn.

Anal. Calc'd for $C_8H_7N_4 \cdot HgCl \cdot HgCl_2$: N, 8.4. Found: N, 8.3.

The mercuric chloride complex of 5-β-phenylethyltetrazole mercurichloride separated from alcoholic solution slowly in the form of very small, colorless prisms, m.p. 206° decompn.

Anal. Calc'd for $C_9H_9N_4 \cdot HgCl \cdot HgCl_2$: N, 8.2. Found: N, 8.2.

Although most of the other tetrazoles formed precipitates with mercuric chloride in aqueous or aqueous-alcoholic solution, the products were not crystalline and did not lend themselves to the characterization of the compounds.

p-Nitrobenzyl-5-phenyltetrazole. A solution of the potassium salt of 5-phenyltetrazole was prepared by dissolving 1.46 g. of the tetrazole in a small amount of ethanol and adding 0.7 g. of potassium carbonate and sufficient water to form a clear solution. After addition of 2 g. of *p*-nitrobenzyl bromide the mixture was refluxed for 3 hours. On cooling the product separated as needles which were recrystallized from methanol, m.p. 121.5–122°.

Anal. Calc'd for $C_{14}H_{11}N_5O_2$: N, 24.9. Found: N, 24.7.

p-Nitrobenzyl-5-β-cyclohexylethyltetrazole. A solution of the potassium salt of 5-β-cyclohexylethyltetrazole prepared by dissolving 1.8 g. of the tetrazole and 0.7 g. of potassium carbonate in aqueous alcohol was treated with 2 g. of *p*-nitrobenzyl bromide. After boiling under reflux for 3 hours the product separated as small yellow plates on cooling and was recrystallized from methanol, m.p. 82–82.5°.

Anal. Calc'd for $C_{16}H_{21}N_5O_2$: N, 22.2. Found: N, 21.9.

Benzyl-5-phenyltetrazole. A solution of 1.46 g. of 5-phenyltetrazole and 0.7 g. of potassium carbonate in aqueous ethanol was prepared. After addition of 1.7 g. of benzyl bromide the solution was boiled under reflux for 3 hours. The product separated as an oil which solidified on cooling. Recrystallization was effected from methanol from which it separated as glistening needles, m.p. 65.5–66°.

Anal. Calc'd for $C_{14}H_{12}N_4$: N, 23.7. Found: N, 23.1.

1-Benzyl-5-phenyltetrazole. A solution of 54 g. (0.25 mole) of N-benzylbenzamide in 600 ml. of benzene was prepared in a 2 l. three-necked flask equipped with a reflux condenser, benzene-sealed stirrer, and an addition tube. To the stirred solution 52 g. (0.25 mole) of phosphorus pentachloride was added. After the pentachloride had dissolved completely, 100 ml. of a 16% solution of hydrazoic acid in benzene was added in several small portions. Stirring was continued for 2 hours when the solution was gradually warmed to the boiling

point and allowed to reflux for 3 hours. The solvent was now removed under reduced pressure and the residue was treated with about 500 g. of ice and water. The aqueous suspension was gradually warmed and then boiled under reflux for 3 hours. After cooling the mixture the aqueous layer was decanted and the oily residue was boiled under reflux with 300 ml. of 10% sodium hydroxide solution. The insoluble material was taken up in benzene, the benzene solution washed with water, dried, and the solvent removed under reduced pressure. The crude product remained as a viscous oil which crystallized slowly. After three recrystallizations from ethanol the product was obtained as colorless, dense prisms, m.p. 92.5–93°. The yield was 29 g., 50%. The product depresses the melting point of the benzyl-5-phenyltetrazole prepared by benzylation of 5-phenyltetrazole.

Anal. Calc'd for $C_{14}H_{12}N_4$: N, 23.7. Found: N, 23.7.

DETERMINATION OF DISSOCIATION CONSTANTS OF THE 5-SUBSTITUTED TETRAZOLES

The acid dissociation constants of all the tetrazoles described in Table I were determined by titration of a weighed sample of the compound in aqueous or aqueous methanolic solution with standard alkali. Titration was carried out in a thermostat at 25° and the *p*H was determined after each addition of alkali with a Beckman *p*H Meter, Model G. From these data acid dissociation constants were calculated using the following expression (25):

$$K = C_{H^+}\left(\frac{x}{x_e - x}\right)$$

where C_{H^+} is the hydrogen ion concentration calculated from the *p*H corresponding to the addition of x ml. of alkali. The symbol x_e expresses the number of ml. of alkali required for neutralization of the acid.

The apparent acidic dissociation constants and equivalent weights of all the 5-substituted tetrazoles are recorded in Table I. Each dissociation constant is an average of at least six values calculated from different points near the region of half neutralization of the compound. In each instance the titration curve exhibited the form normally obtained with a weak acid.[2]

The equivalent weight of each of the tetrazoles, calculated from the value for x_e, is recorded in Table I.

SUMMARY

1. A new method for the preparation of 5-alkyl- and 5-aryl-tetrazoles by the interaction of hydrazoic acid and the nitriles of carboxylic acids in benzene or alcoholic solution has been described.

2. A group of twenty-one new 5-alkyl- and 5-aryl-tetrazoles has been prepared and characterized. The silver salts of all the compounds have been prepared and in several instances characteristic mercuric chloride complexes have been described.

3. The 5-substituted tetrazoles are weak acids. The acid dissociation constants of all the compounds have been determined and the effect of various substituent groups in the 5 position on the strength of the compounds as acids has been discussed.

4. Alkylation of a number of 5-substituted tetrazoles with *p*-nitrobenzyl bromide and benzyl bromide is described. Comparison of the products with the

[2] The apparent dissociation constant of 5-methyltetrazole at 25° was 2.74×10^{-6} in water, 2.43×10^{-6} in 25% by weight methanol, and 1.82×10^{-6} in 50% methanol. These values indicate that the tetrazoles may be expected to behave as weaker acids in aqueous methanol solution.

isomeric 1-benzyl-5-substituted compounds indicated that benzylation probably took place in the 2 position on the ring.

5. The preparation of 1-benzyl-5-phenyltetrazole from N-benzylbenzamide has been described.

6. A simple procedure for the preparation of 5-aminotetrazole by the interaction of dicyandiamide and sodium azide in aqueous acid solution has been described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

STEREOCHEMICAL STUDIES IN THE MORPHINE SERIES. THE RELATIVE CONFIGURATION AT CARBONS FIVE AND SIX

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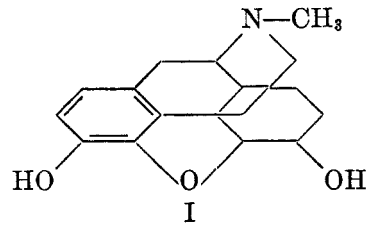
The morphine molecule (I) presents an interesting and important stereochemical problem with its five asymmetric carbons (positions 5, 6, 9, 13, 14) and multiple ring systems. Previous work on the spatial orientation at these asymmetric centers has been confined to some speculative deductions by Schöpf. With the aid of models, Schöpf and Pfeifer (1) interpreted the exclusive formation of dihydrocodeinone from dihydrothebainone by oxide ring-closure at carbon 5 as indicating that the oxygen bond to carbon 5 was *trans* to the ethanamine bond at carbon 13. The hydrogen at carbon 14 was inferred to be *cis* to the ethanamine bond at carbon 13 by analogy with the 14-hydroxy compound. Since degradation of dihydrohydroxycodeinone to nitrogen-free material resulted in a cyclic ether involving the 14-hydroxyl group, this group and the ethanamine chain must be *cis* (2). If one assumes the 14-hydroxyl and 14-hydrogen have the same configuration, then the 14-hydrogen is also *cis*. These conclusions have been supported in a recent re-examination of the evidence (3). The only other data on the subject are the assignments of rotational contributions (plus or minus) to the various asymmetric centers by Emde (4). This, of course, provides no information as to the actual configurations.



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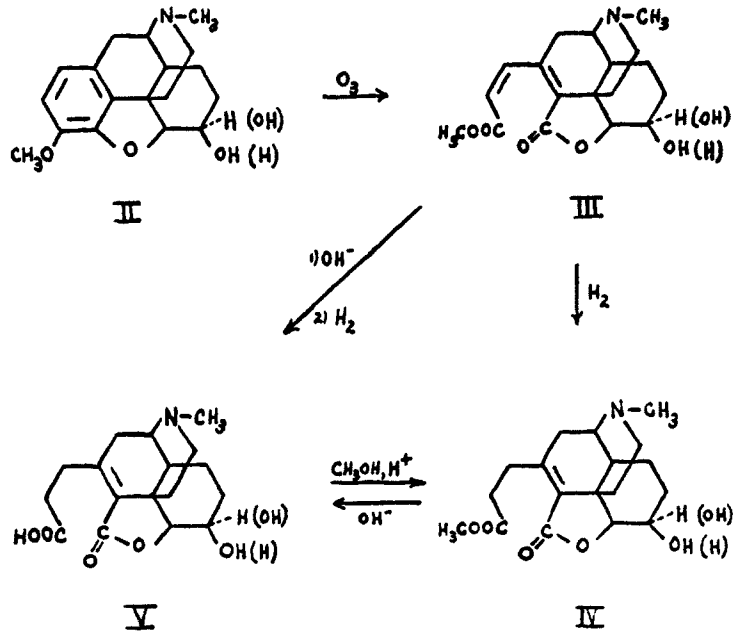
The current studies were undertaken with the objective of determining, by absolute methods, the relative configurations among the various asymmetric centers. This communication is concerned with establishing the relative configuration at carbons 5 and 6.

The epimeric alcohols, dihydrocodeine and dihydroisocodeine (II) constitute the isomeric pair needed for configurational studies at carbons 5 and 6. If the oxide bridge could be opened at carbon 4 instead of at carbon 5, as usually occurs, then a pair of cyclic vicinal diols would result, and their configuration could be determined with the usual reagents (5). Since the requisite opening of the aromatic ring has been achieved by ozonolysis (6), this appeared to be a feasible scheme.

Dihydrocodeine was easily prepared by hydrogenating codeine. However, the preparation of a reasonable quantity of dihydroisocodeine was much more

difficult. The path proceeding from codeine to α-chlorocodide (7), separation of the codeine isomers resulting from hydrolysis of the α-chlorocodide (8), and hydrogenation of the crude isocodeine (8), thus converting any residual pseudocodeine and allopseudocodeine to more easily removed phenolic substances (9), gave only a 6% over-all yield of dihydroisocodeine.

While pseudocodeine is the dominant isomer from the hydrolysis of α-chlorocodide, isocodeine predominates when bromocodide is hydrolyzed (10). Therefore, the preparation and hydrolysis of bromocodide was investigated. Conversion of codeine to bromocodide using thionyl bromide gave a more easily isolated product and in better yield (74%) than the previous phosphorus tribromide procedure (11). A large excess of thionyl bromide should be avoided since



this leads to an appreciable amount of a dibromo compound whose structure was shown to be 1-bromobromocodide by independent synthesis from 1-bromocodeine and thionyl bromide. Hydrolysis of the bromocodide and hydrogenation of the crude isocodeine resulted in a 35% yield (based on codeine) of dihydroisocodeine.

The ozonolysis of dihydrocodeine (II) to ozodihydrocodeine (III) and the characterisation of the latter has been reported by Speyer (6). By substituting aqueous acetic acid for the aqueous formic acid originally used and discontinuing the ozonolysis after the consumption of one mole of ozone, the yield of ozodihydrocodeine was increased from 40% to 75%. Hydrolysis of both the

[1] This nomenclature is based on dihydromorphinic acid (III, methyl ester and lactone hydrolyzed) as the fundamental compound of the series.

methyl ester and lactone groups of ozodihydrocodeine gave dihydromorphinic acid, but it proved too unstable to be used further.

If, however, the ozodihydrocodeine was hydrolyzed and the hydrolysate hydrogenated, the stable tetrahydromorphilactonic acid[1] (V) was isolated. The same compound was also obtained by hydrogenating first to methyl tetrahydromorphilactonate (IV) and saponifying the latter to (V); the methyl ester (IV) was regained by esterifying compound (V).

Speyer (6) has represented the hydrogenation of ozodihydrocodeine (III) as proceeding through hydrogenolysis of the carbon-oxygen bond at carbon 5 to the amino acid (VI) and the saponification of (VI) to give the dibasic acid (VII). The compounds obtained in the present work are identical with those reported previously and are assigned the structures (IV) and (V) instead of the isomeric structures (VI) and (VII) for the following reasons:

A. The hydrogenation product is readily soluble in ether. This would be expected of structure (IV) but not the amino acid (VI).

B. Esterification of the saponified material gives back the original ester with one methoxyl group. This is consistent with structure (V). If the structure of the saponified material was (VII), a dimethyl ester would be expected. Lactone formation conceivably might have occurred with the 6-hydroxyl to give only a monomethyl ester, but the product would then differ from the original ester due to loss of a molecule of water.

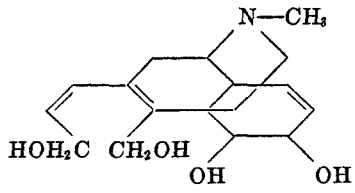
C. Potentiometric titration of the hydrogenation product indicates the absence of any carboxyl group.

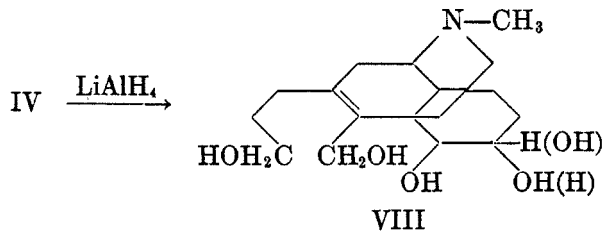
D. Potentiometric titration of the hydrogenated and saponified material shows the presence of one carboxyl and an equivalent weight of 319. This is consistent with structure (V), equivalent weight, 321.

The above evidence clearly eliminates structures (VI) and (VII) and supports the alternative formulations, (IV) and (V). The position of the double bond in these compounds has not been proved but is assumed to be as shown since only one mole of hydrogen is absorbed at atmospheric pressure and room temperature. The endocyclic double bond would be more likely to be resistant to hydrogenation.

A compound suitable for stereochemical examination was obtained by reducing methyl tetrahydromorphilactonate (IV) with lithium aluminum hydride (12). The resulting compound, tetrahydromorphitetrol[2] (VIII), although not

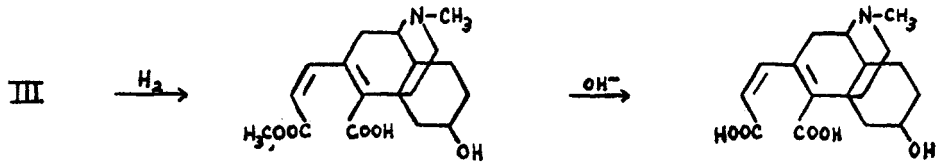
[2] In analogy with already established nomenclature in this series, the parent compound would be morphitetrol with the structure





VIII

obtainable crystalline, was characterized through derivatives and tetraacetate formation. Since the oxygen-carbon bond at carbon 5 is not broken, the configuration at this center remains unaffected (13), and a compound is formed containing a vicinal pair of hydroxyls at carbons 5 and 6 with the original configuration retained.



VI VII

To prepare the epimeric tetrol, dihydroisocodeine (II), differing from dihydrocodeine only in the configuration at carbon 6, was subjected to exactly the same sequence of reactions. Ozonolysis gave ozodihydroisocodeine (III), which was hydrogenated to methyl tetrahydro-α-isomorphilactonate[3] (IV) and the latter saponified to tetrahydro-α-isomorphilactonic acid (V). Lithium aluminum hydride reduction of the ester (IV) then gave tetrahydro-α-isomorphitetrol (VIII).

Of the several methods available for determining the relative configuration of the hydroxyls in a cyclic 1,2-diol (5), the rate of oxidation by lead tetraacetate appeared to be the most suitable. Recent work, especially with cyclic sugar derivatives, has firmly established the original observation (14) that *cis*-1,2-diols are oxidized more rapidly than *trans*.

Oxidation by lead tetraacetate in glacial acetic acid at 15° was applied to the crystalline picrates of both tetrols (VIII), after ascertaining that the presence of picric acid had no effect. The curves obtained are shown in Figure 1. In both cases, only one mole of lead tetraacetate was consumed per mole of tetrol. However, this consumption was complete after two hours with tetrahydromorphitetrol, and required over six hours with tetrahydro-α-isomorphitetrol. An examination of the curves also shows that the rate of oxidation of the one isomer was about three times as rapid as that of the other.

[3] Since the compounds in which the aromatic nucleus has been opened already have the "morphi" designation, the morphine nomenclature has been retained throughout. The alcohol epimeric with morphine is α-isomorphine, therefore all the compounds in this epimeric series have the "α-isomorphi" nomenclature.

From this we may conclude that the hydroxyl pair at carbons 5 and 6 are *cis* in tetrahydromorphitetrol and *trans* in tetrahydro-α-isomorphitetrol. Since the former is derivable from morphine and the latter from α-isomorphine, it follows that the carbon-oxygen bonds at carbons 5 and 6 are *cis* in morphine and *trans* in α-isomorphine.

EXPERIMENTAL

All melting points are corrected, and those above 200° were taken in evacuated tubes. Microanalyses were performed by the Micro Chemical Laboratory, University of California.

Dihydroisocodeine (II). *A. From α-chlorocodide.* Codeine was converted to α-chlorocodide (7) and the codeine isomers were obtained from the latter by the method of Speyer and Krauss (8). The crude isocodeine binoxalate (22.3 g., 21%) thus resulting from the hydrolysis

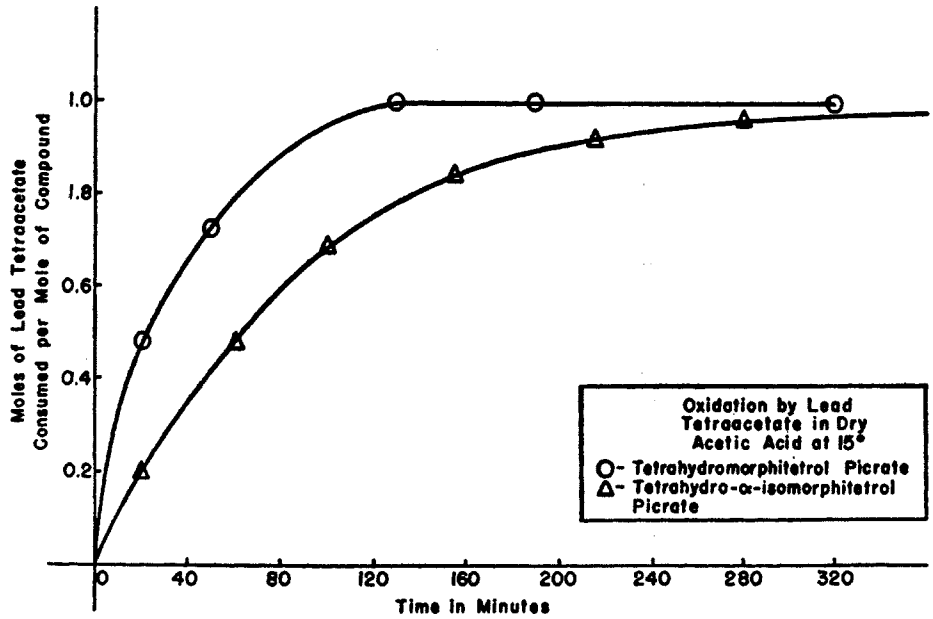


FIGURE 1.

of 88.0 g. of α-chlorocodide was dissolved in 200 ml. of warm water. Basifying with 6 *N* potassium hydroxide liberated an oil which was extracted into 300 ml. of ether, and the aqueous layer was further extracted with two 100-ml. portions of ether. After washing the combined ether solutions with water, drying over potassium carbonate, and evaporating, there was obtained about 16 g. of crude isocodeine. This was dissolved in 70 ml. of hot ethyl acetate and allowed to cool to room temperature. Once crystallization had begun, the solution was cooled overnight at 0°. Filtration gave 7.5 g. of isocodeine melting from 157–164° [reported (15) m.p. 171–172°]. This material, dissolved in 60 ml. of water and 2 ml. of glacial acetic acid, absorbed 1.3 moles of hydrogen when hydrogenated at room temperature and atmospheric pressure in the presence of 1.5 g. of 5% palladium on barium sulfate. Filter aid was added, the mixture was filtered, and the filtrate was basified with excess 6 *N* potassium hydroxide to give a white solid which was washed well with water. The weight of dihydroisocodeine melting from 190–200° was 6.2 g. (6% over-all from codeine). One recrystallization from ethanol gave material melting at 198–200° [reported (8)

m.p. 199–200°] but it was found that this was not necessary, since the crude material was satisfactory for subsequent work.

B. From bromocodide. In an apparatus with stirrer, condenser, dropping-funnel, and protection from moisture, a solution of 17.4 g. (0.084 mole, 6.5 ml.) of thionyl bromide (16) was added dropwise with stirring to a solution of 25 g. (0.084 mole) of dry codeine in 50 ml. of chloroform. A water-bath was used for cooling and the addition was made over a period of two hours. After the addition was complete, the reaction mixture was refluxed gently for three hours and then cooled. The reaction mixture was treated with 100 ml. of water followed by a saturated sodium carbonate solution, and the free base was extracted as an oil into 150 ml. of a 1:1 mixture (by volume) of ether and chloroform. Two additional 50-ml. extractions were made and the combined extracts were washed with 50 ml. of water, dried, and evaporated to give a solid residue of 28–30 g. Recrystallization from 225 ml. of absolute ethanol gave 21.2 g. of pure bromocodide, m.p. 159–160° [reported (11) m.p. 162°]. An additional 1.1 g. was recovered from the mother liquors; total yield, 22.3 g., 74%.

Twenty-five grams (0.069 mole) of bromocodide was suspended in 200 ml. of water and, after adding sufficient glacial acetic acid to bring the base into solution, the mixture was heated under reflux vigorously for four hours and then cooled. The free base was liberated as an oil by the action of excess 6 *N* potassium hydroxide, and this oil was immediately extracted into 150 ml. of a 1:1 mixture of ether and chloroform. The aqueous phase was extracted twice more with 50-ml. portions of ether-chloroform, and then the combined organic layer was washed with two 25-ml. portions of water and evaporated on the steam-bath to give 20 g. of white solid. Recrystallization from about 50 ml. of ethyl acetate gave 14 g. of a solid mixture of isocodeine, pseudocodeine, and allopseudocodeine which was dissolved in 150 ml. of water by adding the necessary amount of glacial acetic acid and hydrogenated at room temperature and 30 p.s.i., using 2.9 g. of a 5% palladium on barium sulfate catalyst. After four hours, hydrogen uptake ceased with a total absorption of 1.3 moles. The catalyst was filtered, washed with warm water, and the filtrate was basified with excess 6 *N* potassium hydroxide to precipitate an oil which solidified on standing. It was filtered, washed with water, and the filtrate and washings were extracted three times with 50-ml. portions of 1:1 ether-chloroform solution. The combined extracts after washing with water, were evaporated to give about 2 g. of solid residue which was added to the 8 g. from the original filtration. Total yield of dihydroisocodeine melting at 190–200° was 10 g. (48% from bromocodide, 35% from codeine). It was sufficiently pure for use in subsequent reactions.

Dihydrocodeine (II) was purified by the method of Homeyer and Shilling (17).

Ozodihydrocodeine (III). A solution of 15 g. (0.05 mole) of dihydrocodeine in 100 ml. of 4.5 *N* acetic acid was ozonized at 0° with a stream of oxygen containing 4% ozone (by volume) at a flow of about 17 liters per hour using the apparatus of Henne and Perilstein (18) and the procedure as described in Organic Syntheses (19). In about five hours, one mole of ozone had been consumed and the ozonolysis was stopped. During the course of the reaction, the solution turned bright yellow and faded to a pale yellow just before the reaction was over. The reaction mixture was brought to about *p*H 6 by the addition of solid sodium bicarbonate, concentrated ammonia was added carefully to *p*H 8 or 9 and the solution extracted five times with 50-ml. portions of chloroform. The combined extracts were washed with 50 ml. of water and evaporated on the steam-bath to a thick oil, which was converted to the hydrochloride by dissolving it in 75 ml. of absolute ethanol and adding 4 *N* alcoholic hydrochloric acid until the solution was acid to Congo Red. Cooling gave 13.5 g. (74%) of hydrochloride decomposing at 235–236°, and recrystallization did not alter the melting point; $[\alpha]_D^{20}$ +78.8° (water, *c*, 2.26); reported (6) m.p. 242°, $[\alpha]_D^{17}$ +78.6° (water, *c*, 5.0).

Ozodihydroisocodeine (III). A solution of 14 g. (0.046 mole) of dihydroisocodeine in 120 ml. of 4.5 *N* acetic acid was ozonized at room temperature as above. At the end of 16 hours about 1.1 moles of ozone had been absorbed and the solution had turned from dark to pale yellow. At that time the reaction was stopped and the product isolated in the same manner as the epimeric compound above. The oily free base was dissolved in 75 ml. of absolute

ethanol and treated with 1 *N* alcoholic perchloric acid until acid to Congo Red. Cooling gave 9.0 g. (45%) of ozodihydroisocodeine perchlorate melting at 203–205°, suitable for use in subsequent reactions without further purification. Recrystallization from ethanol gave material melting with decomposition at 206–208°; $[\alpha]_D^{20}$ +22.6° (water, *c*, 1.106).

Anal. Calc'd for $C_{18}H_{24}ClNO_9$: C, 49.8; H, 5.6; OCH_3, 7.2.

Found: C, 49.8; H, 5.4; OCH_3, 7.4.

Tetrahydromorphilactonic acid (V). A solution of 8.88 g. (24.0 millimoles) of ozodihydrocodeine hydrochloride in 200.0 ml. of 0.59 *N* alcoholic sodium hydroxide (118 millimoles) was heated under reflux in a nitrogen atmosphere for 1½ hours. After cooling, 45.0 ml. of 1 *N* hydrochloric acid was added to give a slightly basic solution. To this was added 1.8 g. of 5% palladium on charcoal, and the solution was hydrogenated at room temperature and 25 p.s.i. After 2 hours, hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added, the solution was filtered, and to the filtrate was added 49.0 ml. of 1 *N* hydrochloric acid to liberate the amino acid from its sodium salt. Evaporation of the resulting solution *in vacuo* gave a solid mixture of sodium chloride and the amino acid which was digested for two hours with 200 ml. of absolute ethanol. Filtration and concentration (to about 75 ml.) of the resulting solution gave, on cooling, 6.5 g. (84%) of tetrahydromorphilactonic acid melting at 240–243° with decomposition. Recrystallization from ethanol gave m.p. 245–246°, $[\alpha]_D^{22}$ +29.0° (water, *c*, 2.38); reported (6) m.p. 245–248°, $[\alpha]_D^{17}$ +28.5°.

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.6; H, 7.2.

Found: C, 63.4; H, 7.3.

By potentiometric titration, the equivalent weight was found to be 319; calc'd 321.

The same compound was obtained by reversing the above procedure, *i.e.*, by first hydrogenating ozodihydrocodeine to methyl tetrahydromorphilactonate (below) and then saponifying the latter. The resulting amino acid melted at 245–246° and showed no depression on admixture with a sample of tetrahydromorphilactonic acid prepared above.

Methyl tetrahydromorphilactonate (IV). A solution of 14 g. (0.038 mole) of ozodihydrocodeine hydrochloride in 250 ml. of water containing 3.3 g. of 5% palladium on barium sulfate was hydrogenated at room temperature and 30 p.s.i. At the end of an hour hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added and the solution filtered and basified with saturated potassium carbonate solution to *p*H 8 or 9. The solution was then extracted five times with 100-ml. portions of ethyl acetate, and the combined extracts were washed with water and dried over magnesium sulfate. On concentration of the solution, crystallization occurred when the volume was reduced to about 50 ml., at which point the solution was cooled and filtered to yield 9.2 g. (73%) of methyl tetrahydromorphilactonate, m.p. 147–148°, $[\alpha]_D^{19}$ +6.3° (ethanol, *c*, 1.026); [reported (6) m.p. 150–151°]. Recrystallization from either ethyl acetate or benzene did not alter the melting point.

Anal. Calc'd for $C_{18}H_{25}NO_5$: C, 64.4; H, 7.5; OCH_3, 9.3.

Found: C, 64.4; H, 7.2; OCH_3, 9.3.

Potentiometric titration indicated the absence of any acidic group.

The *picrate*, prepared in and purified from ethanol, melted at 228–229°, as reported (6).

Methyl tetrahydromorphilactonate could also be prepared by esterification of tetrahydromorphilactonic acid with methanol and sulfuric acid. The product was identical with that prepared above by hydrogenation of ozodihydrocodeine.

Tetrahydromorphilactonic acid amide. A solution of 600 mg. (1.8 millimoles) of methyl tetrahydromorphilactonate in 10 ml. of liquid ammonia was heated overnight at 100° in a bomb. Evaporation of the excess ammonia gave a solid which was twice crystallized from propanol to give 400 mg. of lactonic acid amide melting with decomposition at 226–228°, $[\alpha]_D^{19}$ −3.4° (ethanol, *c*, 1.102).

Anal. Calc'd for $C_{17}H_{24}N_2O_4$: C, 63.8; H, 7.6; N, 8.7.

Found: C, 63.6; H, 7.7; N, 8.4.

Methyl tetrahydro-α-isomorphilactonate (IV). A solution of 6.6 g. (0.015 mole) of ozodihydroisocodeine perchlorate in 150 ml. of 50% aqueous ethanol containing 2.0 g. of 5% palladium on barium sulfate was hydrogenated at room temperature and 20 p.s.i. Within

half an hour the hydrogenation ceased with an uptake of one mole of hydrogen. Filter aid was added, the solution filtered, and the filtrate concentrated to 50 ml. It was then brought to *p*H 8 by the addition of saturated sodium carbonate solution and extracted with six equal volumes of chloroform. The combined extracts were washed with water and evaporated to give 5 g. of residue which could not be induced to crystallize. For analytical purposes the *picrate* was made in and recrystallized from ethanol. It sintered from 213–218° and melted with decomposition at 218°, $[\alpha]_D^{23}$ +2.4° (water, *c*, 0.810).

Anal. Calc'd for $C_{24}H_{28}N_4O_{12}$: C, 51.1; H, 5.0; N, 9.9.

Found: C, 51.1; H, 5.0; N, 9.3.

Tetrahydro-α-isomorphilactonic acid (V). A solution of 560 mg. (1.67 millimoles) of methyl tetrahydro-α-isomorphilactonate in 15.0 ml. of 0.584 *N* alcoholic sodium hydroxide (8.75 millimoles) was heated under reflux in a nitrogen atmosphere for two hours. After adding 8.75 ml. of 1 *N* hydrochloric acid to the cooled solution, it was concentrated to dryness *in vacuo* and the residue of sodium chloride and lactonic acid was digested for two hours with 150 ml. of absolute ethanol. The sodium chloride was removed and the filtrate was concentrated to 25 ml. Thorough cooling precipitated 410 mg. (78%) of tetrahydro-α-isomorphilactonic acid decomposing at 240°. Crystallization from ethanol gave material decomposing at 243–245°, $[\alpha]_D^{19}$ 0.0° (water, *c*, 0.982).

Anal. Calc'd for $C_{17}H_{23}NO_5$: C, 63.6; H, 7.2.

Found: C, 63.3; H, 7.1.

Preparation of a standarizied solution of lithium aluminum hydride in tetrahydrofuran. Fifteen grams of lithium aluminum hydride were crushed into small pieces and added, with cooling, to 250 ml. of pure tetrahydrofuran. The solution was protected from moisture and allowed to reflux for three hours on the steam-bath. After cooling, it was filtered through a plug of glass wool into a 250-ml. graduated cylinder and allowed to stand for several hours at room temperature to settle the suspended material. The solution was standardized before each use by adding a 2-ml. aliquot to 10 ml. of ice-water. Addition of 15.0 ml. of 1 *N* HCl gave a clear solution when warmed on the steam-bath for a few minutes, and back-titration of excess acid was accomplished with 1 *N* sodium hydroxide to a Thymol Blue end-point. The freshly prepared solution contained 1.2 millimoles of lithium aluminum hydride per ml. Blank runs, carried out by titrating known volumes of standard hydrochloric acid with standard base in the presence of aluminum chloride, indicated that this procedure gave results accurate to about 2%.

Tetrahydromorphitetrol (VIII). In a flask equipped with stirrer, condenser, and dropping-funnel, and in a nitrogen atmosphere, was placed a solution of 2.0 g. (6.0 millimoles) of methyl tetrahydromorphilactonate in 50 ml. of pure tetrahydrofuran. To this was added with stirring, over a five-minute period, a standardized solution of 30 millimoles of lithium aluminum hydride in 25 ml. of tetrahydrofuran, and the reaction mixture was heated under reflux overnight. It was then cooled thoroughly before carefully decomposing with water. Sulfuric acid (10%) was added to dissolve the solid hydroxides and render the aqueous solution acidic. To the two-phase mixture was added 50 ml. of ether to effect a better separation, and the lower aqueous phase was separated. The organic layer was extracted with a 50-ml. portion of water and then the combined aqueous solutions were washed twice with 25-ml. portions of ether. After basification with saturated sodium carbonate solution, the aqueous portion was evaporated to dryness *in vacuo* and the resulting solid was digested for two hours by boiling with 200 ml. of ethyl acetate. After filtration, the solution was evaporated to an oily residue of 1.5 g. To remove any lactone-containing impurity, the oil was dissolved in 20 ml. of 0.5 *N* sodium hydroxide and warmed on the steam-bath for two hours. Carbon dioxide was then bubbled in until the basicity was lowered to *p*H 9. Concentration to dryness, followed by repetition of the above isolation procedure gave 1.3 g. (70%) of tetrahydromorphitetrol as an amorphous hygroscopic solid melting from 50–80° when thoroughly dry. All attempts at crystallization failed.

The *picrate* was formed in and recrystallized twice from absolute ethanol. It decomposed at 179–180°, $[\alpha]_D^{20}$ +25.0° (50% acetone-water, *c*, 0.792).

Anal. Calc'd for $C_{23}H_{32}N_4O_{11}$: C, 51.1; H, 6.0.
Found: C, 51.2; H, 5.8.

The *methiodide* was prepared by warming on the steam-bath an ethanolic solution of the tetrol with excess methyl iodide. Two recrystallizations from absolute ethanol gave material melting at 192–194°, $[\alpha]_D^{19}$ +36.7° (water, *c* 1.118).

Anal. Calc'd for $C_{18}H_{32}INO_4$: C, 47.7; H, 7.1.
Found: C, 47.6; H, 7.1.

Tetrahydromorphitetrol tetraacetate methiodide. A solution of 200 mg. (0.65 millimole) of tetrol in a mixture of 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was warmed on the steam-bath for 15 minutes and allowed to stand at room temperature overnight. The solution was then poured into 10 ml. of water and extracted three times with 10-ml. portions of chloroform. The combined extracts were washed first with a dilute sodium carbonate solution and then with water before evaporation to an oily residue which was dissolved in 3 ml. of absolute ethanol and warmed on the steam-bath for a half-hour with excess methyl iodide. Cooling gave a solid methiodide which was recrystallized from absolute ethanol, m.p. 236–237°, $[\alpha]_D^{19}$ +4.5° (water, *c*, 1.013).

Anal. Calc'd for $C_{26}H_{40}INO_8$: C, 50.2; H, 6.5; I, 20.4.
Found: C, 50.6; H, 6.4; I, 20.5.

Tetrahydro-α-isomorphitetrol (VIII). The preparation of this compound from 2 g. of methyl tetrahydro-α-isomorphilactonate was carried out exactly as described above for tetrahydromorphitetrol except that the saponification to remove lactone-containing material was continued under reflux overnight with 1 *N* potassium hydroxide. The yield of α-isotetrol was 1.3 g. (70%). It is a hygroscopic, amorphous solid that could not be induced to crystallize.

The *picrate* was formed by combining a solution of 200 mg. (0.64 millimole) of the α-isotetrol in 1 ml. of absolute ethanol with a solution of 172 mg. (0.75 millimole) of anhydrous picric acid in 2 ml. of benzene. One recrystallization from 50% ethanol-benzene solution gave material melting at 168–169°, $[\alpha]_D^{22}$ −4.5° (water, *c*, 0.837).

Anal. Calc'd for $C_{23}H_{32}N_4O_{11}$: C, 51.1; H, 6.0.
Found: C, 50.8; H, 5.8.

Tetrahydro-α-isomorphitetrol tetraacetate methiodide. A solution of 200 mg. (0.65 millimole) of α-isotetrol in a mixture of 1 ml. of pyridine and 1 ml. (10.6 millimoles) of acetic anhydride was warmed overnight on the steam-bath and the tetraacetate isolated and converted to methiodide in the same manner as was the normal tetrol tetraacetate (above). Two recrystallizations from absolute ethanol gave a methiodide which melted with decomposition at 203°, $[\alpha]_D^{18}$ −8.5° (water, *c*, 1.015).

Anal. Calc'd for $C_{26}H_{40}INO_8$: C, 50.2; H, 6.5; I, 20.4.
Found: C, 50.1; H, 6.4; I, 20.5.

Lead tetraacetate oxidations. The procedure is based on that of Hockett, Dienes, and Ramsden (20). The lead tetraacetate was prepared according to McClenahan and Hockett (21) and a solution in specially dried acetic acid was made up as 0.0986 *N* and dispensed from an all-glass automatic buret protected from moisture by magnesium perchlorate. The weight of dry sample corresponding to 0.25 millimole was dissolved in 46.0 ml. of specially dried acetic acid in a 100-ml. volumetric flask. To this was added (noting the time of first contact) 52.0 ml. (2.56 millimoles) of 0.0986 *N* lead tetraacetate solution. The reaction solution was then made up to 100 ml. with specially dried acetic acid and placed in the thermostat. Samples were removed at intervals with a 10-ml. pipet and added to 25-ml. volumes of a solution containing about one-half gram of sodium iodide and 5 g. of potassium acetate; the pipet was washed down with acetic acid in order to standardize the drainage. Liberated iodine was titrated with 0.0200 *N* sodium thiosulfate, and the results were plotted as the moles of oxidant consumed per mole of substance taken against time in minutes.

1-Bromobromocodide. A. By the action of thionyl bromide on 1-bromocodeine. To a solution of 2.2 g. (5.8 millimoles) of dry bromocodeine, prepared by the method of Speyer and

Rosenfeld (22), in 10 ml. of dry chloroform was added 1.23 g. (0.46 ml., 5.8 millimoles) of thionyl bromide. The reaction mixture was heated on the steam-bath for an hour and the product was isolated as in the preparation of bromocodide. Crystallization of the crude solid from absolute ethanol gave 1.2 g. (47%) of the yellow crystalline 1-bromobromocodide, m.p. 171–173°, $[\alpha]_D^{22}$ +39.0° (dioxane, *c*, 1.065).

Anal. Calc'd for $C_{18}H_{19}Br_2O_2$: C, 49.1; H, 4.1; Br, 36.3.
Found: C, 49.5; H, 4.5; Br, 36.6.

B. By the action of thionyl bromide on codeine. In an apparatus with stirrer, condenser, and protection from moisture, a solution of 14.8 g. (0.071 mole, 6.0 ml.) of thionyl bromide was added over a ten-minute period to a solution of 10 g. (0.035 mole) of dry codeine in 20 ml. of chloroform, cooled with an ice-salt bath and stirred vigorously during the addition. After completion of the addition, the reaction mixture was heated under reflux for two hours and the alkaloidal material isolated as in the preparation of bromocodide. Crystallization of the crude solid from 200 ml. of absolute ethanol gave 7.9 g. of yellow-brown material melting from 162 to 169°. Four more recrystallizations from the same solvent gave 3.4 g. (23%) of 1-bromobromocodide, m.p. 171–173°, no depression in melting point when mixed with the material prepared above.

SUMMARY

An improved preparation of bromocodide and dihydroisocodeine is described. It is shown by the rate of lead tetraacetate oxidation of suitable derivatives that the carbon-oxygen bonds at carbons 5 and 6 are *cis* in morphine and *trans* in α-isomorphine.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

THE PREPARATION OF SOME DIHYDRO KETONES IN THE MORPHINE SERIES BY OPPENAUER OXIDATION

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Among the more important morphine derivatives are the ketones dihydromorphinone (V) and dihydrocodeinone (VI). They have been used directly as analgesics themselves and also are key intermediates in the syntheses of metopon (1) and 6-methyldihydromorphine (2), two of the more promising morphine derivatives (3).

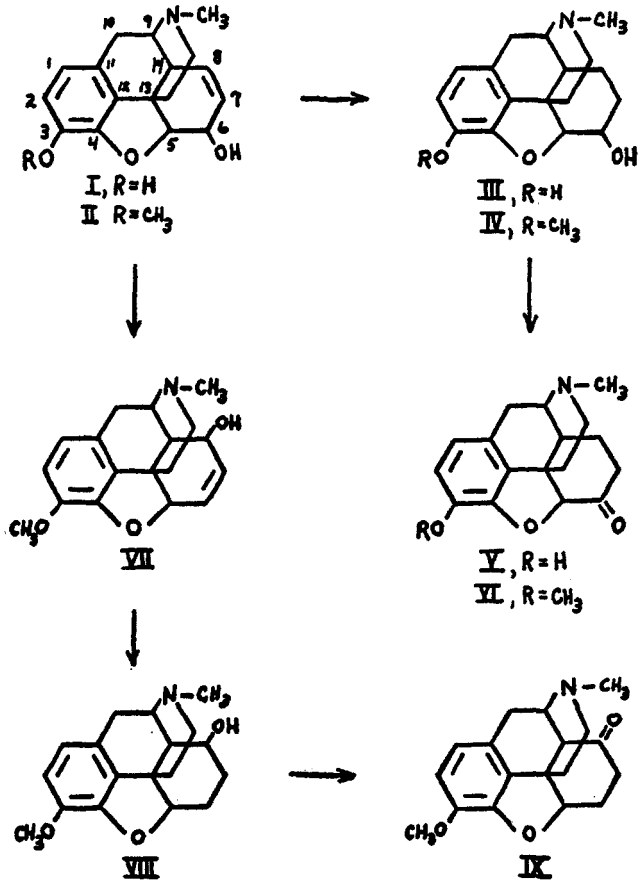
An attractive method for preparing these ketones easily and in yields approaching theoretical has been claimed, in the patent literature (4), to be the rearrangement of the parent morphine or codeine to the corresponding ketone under the catalytic influence of finely divided palladium or platinum, with or without the presence of hydrogen. However, after thorough investigation (5), we were unable to obtain yields higher than 50% by this method. Dihydrocodeinone is available by an alternative path from thebaine through dihydrothebaine (6), but the yield is only 36% and the starting material is relatively rare.

For these reasons, we have sought a better method for preparing the ketones, and have examined the Oppenauer oxidation of the dihydro alcohols. Codeine and morphine were reduced to dihydrocodeine (IV) and dihydromorphine, respectively, in practically quantitative yield, and the latter were subjected to oxidation. The best conditions found were the use of potassium *tert*-butoxide as catalyst and benzophenone as oxidant (7) in refluxing benzene. A benzene solution of potassium *tert*-butoxide free of *tert*-butyl alcohol was conveniently prepared by removing the excess alcohol, after dissolution of the potassium, by azeotropic distillation with benzene. The dihydro alcohol and benzophenone were then added and the solution heated under reflux for $2\frac{1}{2}$ hours, resulting in an 83% yield of dihydrocodeinone and a 71% yield of dihydromorphinone.

To test the generality of this reaction in the morphine series, it was applied to the codeine isomers. Dihydroisocodeine (IV), differing from codeine only in the configuration of the hydroxyl group at carbon 6, was recovered unchanged with no evidence of ketonic material when subjected to the same conditions that had resulted in an 83% yield of ketone from dihydrocodeine. At higher temperatures (refluxing toluene), a small amount of dihydrocodeinone (about 3%) was formed and isolated as the oxime.

With the isomers at carbon 8, dihydropseudocodeine and dihydroallopseudocodeine (VIII), the same striking difference was observed in the reactivity of the epimers. The conditions under which dihydrocodeine was oxidized gave only recovered starting material when applied to dihydropseudocodeine. More drastic conditions resulted in lower recoveries, and no ketonic material could be obtained. Dihydroallopseudocodeine, on the other hand, was easily oxidized to

dihydropseudocodeinone (IX) in 40% yield. This conversion could probably be improved, but there was insufficient dihydroallopseudocodeine on hand to examine the reaction more thoroughly.



Thus we find a marked distinction, on the basis of susceptibility to Oppenauer oxidation, between the pair dihydrocodeine and dihydroallopseudocodeine, which are easily oxidized, and the pair dihydroisocodeine and dihydropseudocodeine, which are resistant to oxidation. Eddy (8) has observed the same parallel in the physiological activity of codeine and allopseudocodeine as contrasted to that of isocodeine and pseudocodeine.

A possible explanation of these pairings might be provided by stereochemical considerations. It has been recently shown (9) that on Meerwein-Ponndorf reduction of a large variety of α-substituted cyclic ketones, the principal reduction products were alcohols with the *cis*-configuration. This is in agreement with other strong evidence for the pseudo-six membered ring intermediate in oxidation-reduction reactions involving carbonyl-carbinol systems and catalyzed by various metal alkoxides (10). Since the more stable (less hindered) configuration of this intermediate would be that one with the pseudo-ring *trans* to the α-sub-

stituent, the chief reduction product of a ketone should be the *cis*-alcohol, and the *cis*-alcohol should be more easily oxidized than the *trans*.

On the basis of this mechanism and the Oppenauer oxidation data presented above, it would follow that the hydroxyl group in codeine is *cis* to the carbon-oxygen bond at carbon 5, while in isocodeine the hydroxyl is *trans* to this bond. For the carbon-8 epimers, the hydroxyl of pseudocodeine would be *trans* to the 9,14 carbon-carbon bond and that of allopseudocodeine would be *cis*. These deductions for the codeine-isocodeine pair are confirmed by recent independent findings on their stereochemistry (11).

EXPERIMENTAL

All melting points are corrected, and those above 200° were taken in evacuated tubes. Microanalyses were performed by the Micro Chemical Laboratory, University of California.

Dihydrocodeine (IV). Codeine was hydrogenated (11) in dilute acetic acid using a palladium on barium sulfate catalyst to give a 93% yield of dihydrocodeine, m.p. 109–111°.

Dihydrocodeinone (VI). *tert*-Butyl alcohol (50 ml.), previously distilled from sodium, was redistilled from a small amount of sodium directly into a thoroughly-dried three-necked flask equipped with a mercury-sealed stirrer and a reflux condenser. To the alcohol was added 150 ml. of dry benzene followed by 4 g. (0.1 mole) of potassium in small portions. After the potassium had dissolved, the reflux condenser was replaced with a two-foot Vigreux column, and, with stirring, the excess *tert*-butyl alcohol was distilled as the benzene azeotrope (12), adding more benzene, when necessary, to keep the potassium *tert*-butoxide in solution. When the boiling point reached 80° and remained constant for 25 ml. of distillate, the column was replaced with a reflux condenser, the system was flushed with nitrogen, and a solution of 10 g. (0.033 mole) of dihydrocodeine and 60.1 g. (0.33 mole) of benzophenone in 50 ml. of dry benzene was added. In a nitrogen atmosphere, the reaction mixture was then heated under reflux for 2½ hours after which it was thoroughly cooled and 50 ml. of 3 *N* hydrochloric acid was added. The benzene layer was separated, extracted with three more 50-ml. portions of 3 *N* hydrochloric acid, and the combined aqueous extract washed with two 50-ml. portions of ether. After basifying the aqueous solution with concentrated sodium hydroxide, it was extracted with three 100-ml. portions of ethyl acetate, and these were combined, dried over magnesium sulfate, and evaporated on the steam-bath to about 25 ml. at which point appreciable crystalline material had separated from the hot solution. Cooling gave 8.3 g., 83%, of *dihydrocodeinone*, m.p. 194–195° [reported (13) m.p. 197–198°]; *oxime*, m.p. 264–265° [reported (14) m.p. 266°]; *methiodide*, m.p. 253–255° [reported (13) m.p. 250–255°].

Dihydromorphine (III). Morphine was hydrogenated in the same manner as described above for codeine to give a 97% yield of dihydromorphine, m.p. 153–155°. After crystallization from ethanol it melted at 155–157° [reported (13) m.p. 155–157°].

Dihydromorphinone (V). The oxidation of dihydromorphine to the ketone was carried out by the same procedure as described above for oxidizing dihydrocodeine except for the following modifications: the molar ratio of potassium to alkaloid was increased from 3:1 to 4.5:1, and the benzophenone and dihydromorphine were added as solids rather than as a benzene solution due to the insolubility of the latter in benzene. The combined acid extract of the reaction mixture was basified with concentrated aqueous ammonia, extracted exhaustively with ethyl acetate, and the ethyl acetate solutions were dried and concentrated on the steam-bath until solid material began to precipitate. Cooling at this point followed by filtration gave the first crop of ketone and an additional portion was isolated by further concentration of the filtrate. From 9.7 g. (0.034 mole) of dihydromorphine there was obtained 6.9 g., 71% yield, of dihydromorphinone (5.5 g., m.p. 266–267°, and 1.4 g., m.p. 260–263°). Repeated crystallization from ethanol did not raise the melting point above 266–267° [reported (4) m.p. 262–263°]; $[\alpha]_D^{25}$ −194° (dioxane, *c*, 0.98).

The *oxime* was prepared by warming a suspension of 0.5 g. of dihydromorphinone in 50 ml. of water containing 0.15 g. of hydroxylamine hydrochloride until solution was complete. After heating an additional hour, the solution was basified with aqueous ammonia to precipitate the oxime, m.p. 234–235° [reported (15) m.p. 231–232°].

Oxidation of dihydroisocodeine (IV). After substituting toluene for benzene and increasing the reflux period from 2½ to three hours, the general oxidative procedure described above for dihydrocodeine was applied to 3.0 g. (0.01 mole) of dihydroisocodeine (11). Evaporation of the ethyl acetate extracts of the reaction mixture left 1.5 g. of an oily residue from which the non-alcoholic portion was obtained by sublimation at 125–150°/0.01 mm. after esterifying with 1.5 g. of *p*-phenylbenzoyl chloride in 10 ml. of pyridine (16). The sublimate (about 200 mg.) was heated on the steam-bath for two hours with 0.5 g. of hydroxylamine hydrochloride in 10 ml. of water, after which the mixture was filtered and the filtrate basified with sodium carbonate. Crystallization of the precipitate from aqueous ethanol gave 50 mg. of pure dihydrocodeinone oxime, m.p. 264° (14).

Attempted oxidation of dihydropseudocodeine (VIII). Using the general oxidative procedure described above, twelve attempts were made to oxidize dihydropseudocodeine (17) to dihydropseudocodeinone, varying the time of reflux, the temperature (refluxing benzene, toluene, and xylene), and the oxidant (benzophenone and fluorenone). In no case was any ketone obtained, and the amount of dihydropseudocodeine recovered decreased as the conditions became more drastic. Esterification with *p*-phenylbenzoyl chloride in pyridine was employed to separate alcoholic from non-alcoholic material (16), but the only product isolated was the *p-phenylbenzoate of dihydropseudocodeine*, m.p. 191–192° after several crystallizations from absolute ethanol; $[\alpha]_D^{25}$ +44.7° (dioxane, *c*, 1.04).

Anal. Calc'd for $C_{31}H_{31}NO_4$: C, 77.3; H, 6.5.

Found: C, 77.1; H, 6.6.

Dihydropseudocodeinone (IX). Exactly the same procedure used for oxidizing dihydrocodeine (above) was applied to the free base from 2.0 g. (0.0044 mole) of dihydroallopseudocodeine acid tartrate (18). The oily reaction product was separated into alcoholic and non-alcoholic fractions by sublimation after esterifying with *p*-phenylbenzoyl chloride in pyridine (16), and 0.55 g., 40% yield, of dihydropseudocodeinone, m.p. 93–110°, was obtained. Crystallization from ether gave ketone melting at 113–114°, $[\alpha]_D^{25}$ +38° (ethanol, *c*, 0.92) [reported (19) m.p. 114°, $[\alpha]_D^{25}$ +37° (ethanol, *c*, 0.62)].

The *oxime* was prepared as directed (19) and melted at 245–247° [reported (19) m.p. 244–245°]; $[\alpha]_D^{25}$ −24.6° (dioxane, *c*, 1.017).

SUMMARY

Dihydromorphinone, dihydrocodeinone, and dihydropseudocodeinone have been prepared in 71, 83, and 40% yield, respectively, from dihydromorphine, dihydrocodeine, and dihydroallopseudocodeine by Oppenauer oxidation.

Dihydroisocodeine and dihydropseudocodeine have been found to be relatively inert to Oppenauer oxidation.

Stereochemical considerations, based on the mechanism of the Oppenauer oxidation, indicate that the hydroxyl and α-substituent in codeine and allopseudocodeine are *cis*, whereas they are *trans* in isocodeine and pseudocodeine.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT, UNIVERSITY OF MISSOURI]

PHENOXYQUINONES. I. 2-PHENOXY-*p*-BENZOQUINONE AND 2-PHENOXY-5-METHYL-*p*-BENZOQUINONE

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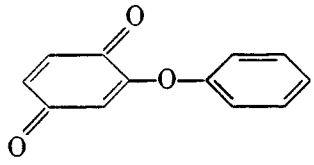
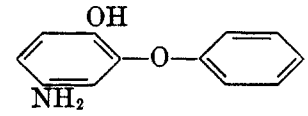
While complex aryloxy-*p*-benzoquinones have been described previously as oxidative degradation products of depsidones (1), the parent substance, 2-phenoxy-*p*-benzoquinone (I) has not been prepared before. The present investigation is concerned with the synthesis and the properties of this compound and one of its homologs.

An amino group is introduced in the 5-position of 2-hydroxyphenyl ether by coupling with diazotized sulfanilic acid and reduction of the resulting azo compound with sodium hydrosulfite according to the method perfected by Smith (1a). The quinone (I) is obtained by oxidizing the hydrochloride of the amino-



I

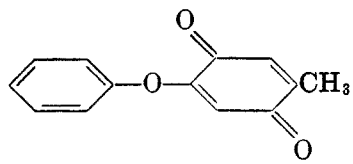


II

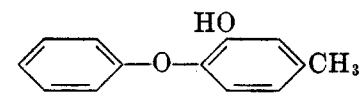
phenol (II) with chromic acid. Its structure has been confirmed by an independent synthesis of the corresponding hydroquinone from authentic 2,5-dimethoxyphenyl ether.

The yellow phenoxyquinone (I), m.p. 70–71.8°, is easily reduced with zinc and acetic acid to the colorless hydroquinone, m.p. 156–157°, with which it forms a purple quinhydrone, m.p. 118–120°.

The normal potential of the quinone-hydroquinone system in aqueous alcohol is 0.584 v., corresponding to a potential lowering of 0.131 v. for the phenoxyl group. A potential lowering of about the same magnitude is arrived at from the normal potential of 2-phenoxy-5-methyl-*p*-benzoquinone (III), m.p. 120–121° (2),



III



IV

which has been prepared from 3-hydroxy-4-phenoxytoluene (IV) by a sequence of reactions analogous to (I).

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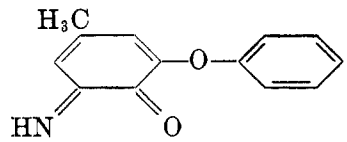
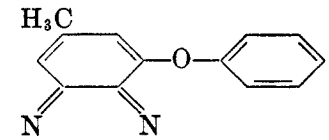
2-Phenoxybenzoquinone forms a dioxime and undergoes the Thiele reaction (3). Preliminary tests indicate that it does not possess any appreciable *in vitro* bacteriostatic activity in the very dilute aqueous solutions necessitated by its small solubility.

Phenoxy-*o*-benzoquinones are unknown in the literature and exploratory work has shown that they are difficult to obtain. The silver oxide oxidation of 2-phenoxy-4-methyl-6-aminophenol yields an intensely red solution. Although attempts to isolate a crystalline product have failed, it is believed that the solution contains some 3-phenoxy-5-methyl-*o*-benzoquinone imine (V) because it was possible to convert it to the phenazine (VI) of the corresponding quinone in small yield.



V



VI

EXPERIMENTAL

All temperatures uncorrected.

2-Hydroxyphenyl ether. Demethylation of 2-methoxyphenyl ether (4) with hydriodic acid in acetic acid (5) gave a nearly quantitative yield of the hydroxyphenyl ether. For preparative purposes the substance was obtained by demethylation of the methyl ether (45 g.) with sodium hydroxide (180 g.) in diethylene glycol (900 cc.) by refluxing for 18 hours in a copper flask. The mixture was poured still warm into 4 l. of water and was acidified with hydrochloric acid. The precipitate was filtered and dried. It weighed 40.1 g. and melted at 103–105°. Recrystallization from petroleum ether (b.p. 60–70°) gave 37 g. (91%) of product melting at 104–105°.

2-Hydroxy-5-aminophenyl ether. A cold diazonium solution prepared from 10.5 g. of sulfanilic acid was added slowly with stirring to a cold solution of 7 g. of 2-hydroxyphenyl ether dissolved in a solution of 11 g. of sodium hydroxide in 60 cc. of water. The mixture was allowed to stand for at least two hours, preferably overnight. Then it was heated to 40–50° and treated with 23 g. of sodium hydrosulfite. The mixture was stirred for two hours. The precipitate was filtered and recrystallized from aqueous hydrochloric acid containing stannous chloride (6). An additional crystallization of the product (5.5 g.) from the same mixture yielded 4.8 g. (53.7%) of 2-hydroxy-5-aminophenyl ether hydrochloride. On heating this substance decomposed gradually with darkening.

Anal. Calc'd for $C_{12}H_{12}ClNO_2$: C, 60.63; H, 5.08; N, 5.89.

Found: C, 60.59; H, 5.21; N, 5.89.

Acetyl derivative. Acetylation of the hydrochloride (1 g.) with acetic anhydride and aqueous sodium hydroxide (7) gave 0.48 g. of acetyl compound, m.p. 125.6–126.7° (from aqueous ethanol).

Anal. Calc'd for $C_{14}H_{13}NO_3$: C, 69.12; H, 5.38; N, 5.76.

Found: C, 69.20; H, 5.32; N, 5.48.

2-Phenoxy-p-benzoquinone. Attempts to oxidize the above amine hydrochloride with ferric chloride (8) gave only 18% yield of quinone. A far better yield was obtained as follows. A solution of the hydrochloride (1.4 g.) in water (21 cc.) was treated with 2 cc. of concentrated sulfuric acid and the mixture was heated. The boiling solution was added with stirring to a mixture of 80 cc. of benzene and 1.4 g. of potassium dichromate dissolved

in 20 cc. of water. Stirring was continued for ½ hour. The benzene layer was separated, washed with water, and distilled under reduced pressure. The residual quinone crystallized on scratching. It melted at 70–71.8°, yield 0.42 g.

Anal. Calc'd for $C_{12}H_8O_3$: C, 71.99; H, 4.02.

Found: C, 72.04; H, 4.11.

Dioxime. A mixture of 2-phenoxy-*p*-benzoquinone (0.5 g.), hydroxylamine hydrochloride (0.5 g.), pyridine (2.5 cc.), and absolute ethyl alcohol (2.5 cc.) was refluxed for two hours on a steam-bath. The solvents were removed by evaporation and the residual material was stirred with water. The remaining solid dioxime was crystallized from aqueous alcohol. The tan solid decomposed at 160°, yield 0.32 g.

Anal. Calc'd for $C_{12}H_{10}N_2O_3$: C, 62.00; H, 4.31; N, 12.05.

Found: C, 62.13; H, 4.39; N, 12.35.

2-Phenoxyhydroquinone.[3] The above quinone (0.75 g.) dissolved in 0.7 cc. of glacial acetic acid and 0.52 cc. of water was reduced with 0.175 g. of 20-mesh granulated zinc. The mixture was refluxed for 30 minutes. Boiling water (0.7 cc.) was added and the liquid was decanted from the metal. The hydroquinone crystallized when this liquid was cooled to 0°. The first crop (0.11 g.) melted at 152.7–154.7°. Recrystallization from acetic acid and from petroleum ether (b.p. 60–70°) raised the melting point to 156–157°.

Anal. Calc'd for $C_{12}H_{10}O_3$: C, 71.22; H, 4.98; Mol. wt., 202.2.

Found: C, 71.18; H, 4.97; Mol. wt., 199.3 (Rast).

The substance was also obtained by starting with 2-bromohydroquinone dimethyl ether (9).

2,5-Dimethoxyphenyl ether. The Ullmann reaction of 2-bromohydroquinone dimethyl ether (69 g.), potassium hydroxide (25.5 g.), a slight excess of phenol, and 0.3 g. of copper powder at 200° as described previously for an analogous compound (9) gave 29 g. of pure dimethoxyphenyl ether which melted at 46–47° after crystallization from petroleum ether (b.p. 60–70°).

Anal. Calc'd for $C_{14}H_{14}O_3$: C, 73.03; H, 6.13; Mol. wt., 230.

Found: C, 73.01; H, 6.01; Mol. wt., 229 (Rast).

Demethylation. A mixture of 2,5-dimethoxyphenyl ether (1 g.), acetic acid (5 cc.), hydriodic acid (5 cc., *d.* 1.5), and acetic anhydride (2.5 cc.), was refluxed for 45 minutes and poured still warm into water. The solution was brought to boiling and cooled in an ice-bath. The dihydroxy compound crystallized on scratching. The product melting at 149–151° weighed 0.75 g. Recrystallization from petroleum ether (60–70°) raised the melting point to 153–155°. The mixed melting point with the reduction product of 2-phenoxy-*p*-benzoquinone was 155–157°.

Quinhydrone. Equal amounts (0.095 g.) of 2-phenoxy-*p*-benzoquinone and 2-phenoxyhydroquinone, dissolved in benzene, were mixed and heated to remove the solvent. The residual dark purple crystals were recrystallized from benzene, yield 0.15 g., m.p. 118–120°.

Anal. Calc'd for $C_{24}H_{18}O_6$: C, 71.11; H, 4.50.

Found: C, 71.00; H, 4.63.

2,4,5-Triacetoxyphenyl ether. 2-Phenoxy-*p*-benzoquinone (1 g.) was added in small portions with stirring to a solution of 1.2 g. of concentrated sulfuric acid and 1.8 g. of acetic anhydride maintained at 40–50°. The mixture was allowed to stand for four hours. A colorless precipitate separated when it was poured into 20 cc. of cold water. The mixture was cooled to 10° and filtered. After crystallization from 5 cc. of 95% ethanol the product melted at 80–82°, yield 0.2 g.

Anal. Calc'd for $C_{18}H_{16}O_7$: C, 62.78; H, 4.68.

Found: C, 62.63; H, 4.79.

Normal potential. EMF values were determined in a series of buffer solutions each containing 50% ethyl alcohol and sufficient phenoxyquinhydrone (m.p. 118–120°) to give a

[3] The senior author is indebted to Dr. L. I. Smith for this procedure.

saturated solution in a cell containing a platinum electrode, a standard calomel electrode (3.5 *N* KCl), and a stirrer. The EMF values (Table I) were interpolated to *p*H 0.

3-Methoxy-4-phenoxytoluene. The Ullmann reaction with 3-methoxy-4-hydroxytoluene (10 g.), potassium hydroxide (4.05 g.), and bromobenzene (11.4 g.) (4) at 230–240° (four hours) gave 4 g. of pure methyl ether, m.p. 74–75° (from aqueous methanol) (10).

3-Hydroxy-4-phenoxytoluene. Demethylation of the material (0.5 g.) in 3 cc. of acetic acid with 3 cc. of hydriodic acid (*d.* 1.5) and 1.5 cc. of acetic anhydride yielded 0.42 g. of pure hydroxy compound, m.p. 78–79° (from aqueous methanol).

Anal. Calc'd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04.

Found: C, 77.80; H, 6.16.

3-Hydroxy-4-phenoxy-6-aminotoluene. The diazonium solution prepared from 0.85 g. of sulfanilic acid was mixed with 12 g. of ice and added to a cold solution of 3-hydroxy-4-phenoxytoluene (1 g.) in 6 cc. of 14% aqueous sodium hydroxide. The azo dye was reduced by addition of sodium hydrosulfite. The precipitated amine was dissolved in methanol and reprecipitated with 1% aqueous sodium hydrosulfite. The dry substance weighed 0.3 g., m.p. 171–172.5°.

Anal. Calc'd for $C_{13}H_{13}NO_2$: C, 57.62; H, 6.08.

Found: C, 57.76; H, 6.24.

TABLE I

OXIDATION POTENTIALS

*p*H[a]	EMF (in volts)
3.28	0.450
3.51	.443
5.49	.367
6.31	.329
7.49	.288

[a] The precise *p*H values of the solutions were determined potentiometrically.

2-Methyl-5-phenoxy-p-benzoquinone. Concentrated nitric acid (2 cc.) was added with stirring at 25° to a solution of 3-hydroxy-4-phenoxy-6-aminotoluene (0.3 g.) dissolved in 10 cc. of glacial acetic acid. The dark red solution was diluted with cold water and extracted with two 25-cc. portions of ether. The combined ether extracts yielded a solid yellow residue which was crystallized from Skellysolve B. The pure quinone, m.p. 120–121°, weighed 0.26 g.

Anal. Calc'd for $C_{13}H_{10}O_3$: C, 72.89; H, 4.70.

Found: C, 72.80; H, 4.84.

Absorption spectra.[4] Ultraviolet absorption spectra of the two quinones were determined in dioxane solution in concentrations of 0.0018 g. per 25 cc. in the range of 240–430 mμ. 2-Phenoxybenzoquinone showed maxima at 250 mμ (log ε, 3.90) and 355 mμ (log ε, 2.90). The 5-methyl homolog had λ max 260 mμ (log ε, 4.22) and 360 mμ (log ε, 2.86).

2-Phenoxy-4-methyl-6-aminophenol hydrochloride. 3-Bromo-4-hydroxytoluene (11) was methylated with methyl sulfate (yield 75%). The Ullmann reaction with the methyl ether and potassium phenoxide gave 42.6% of 2-methoxy-5-methylphenyl ether, m.p. 68–69° (12). Demethylation of this substance with hydriodic acid yielded 98.4% of 2-hydroxy-5-methylphenyl ether, m.p. 65.7–66.5°. Coupling of this material (6 g.) with diazotized sulfanilic acid furnished a solution of the hydroxyazo compound which was immediately reduced with sodium hydrosulfite in the usual way (13). The recrystallized amine hydrochloride weighed 2.7 g. (36.2%). It decomposed on heating.

[4] Ultraviolet absorption spectra by Dr. E. E. Pickett, University of Missouri.

Anal. Calc'd for $C_{13}H_{14}ClNO_2$: C, 62.02; H, 5.60; N, 5.56.
Found: C, 62.22; H, 5.70; N, 5.28.

3-Phenoxy-5-methyl-o-benzoquinone imine. The amine hydrochloride (0.8 g.) dissolved in anhydrous ether (75 cc.) was shaken for one hour with 6 g. of dry silver oxide and 2 g. of anhydrous sodium sulfate. Filtration of the reaction mitxure gave a bright red filtrate.

Phenazine. The above ether solution was mixed with *o*-phenylene diamine dissolved in very little acetic acid and the mixture was allowed to stand for two days. A brown oil remained after removal of the ether. This was redissolved in 20 cc. of ether. The solution was washed repeatedly with water, dried, and evaporated. The residue (0.16 g.) was taken up in benzene and adsorbed on aluminum oxide. The zones which fluoresced under ultraviolet light were eluted with the same solvent and the solutions were evaporated. The residual light tan crystals were recrystallized from benzene-ligroin giving the pure phenazine, m.p. 100.5–101.8° (yield 0.12 g.).

Anal. Calc'd for $C_{19}H_{14}N_2O$: C, 79.33; H, 4.93; N, 9.78.
Found: C, 79.15; H, 4.80; N, 9.38.

SUMMARY

2-Phenoxy-*p*-benzoquinone and its 5-methyl homolog have been prepared. The structure of the former has been established by an independent synthesis of the corresponding hydroquinone. The compounds have been characterized by physical properties and chemical reactions.

COLUMBIA, MISSOURI

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

REARRANGEMENT OF DIETHYL 3-PHENYLPHTHALIDYL-3-MALONATE TO DERIVATIVES OF 3-PHENYLINDONE-2-CARBOXYLIC ACID

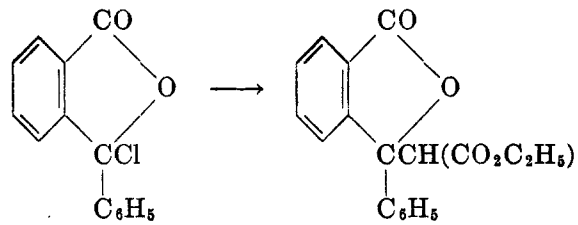
WILLIAM L. YOST[1] AND ALFRED BURGER

Received May 3, 1950

In contrast to the phthalein indicators in which the lactone ring is extremely sensitive to dilute alkali, 3,3-diphenylphthalide is remarkably stable to both acids and bases (1), and to amines, ammonia, and hydrazine (2). Certain 3,3-dialkylphthalides (3) possess nearly as great a stability.

It was desired to prepare a number of 3-alkyl-3-arylphthalides and to investigate the effect of various functional groups in the aliphatic side chain on the stability of the furanone ring. Of the 3-alkyl-3-arylphthalides, only 3-methyl-3-(α-naphthyl)phthalide (4) and 3-methyl-3-phenylphthalide (5) have previously been described.

Diethyl 3-phenylphthalidyl-3-malonate (I) was prepared by treatment of the pseudo chloride of *o*-benzoylbenzoic acid with diethyl ethoxymagnesium malonate in ethanol-ether solution. The structure of this pseudo chloride has been the subject of much consideration (6, 7) and the results of the present work support the earlier assignment of structures. The condensation with diethyl malonate was adapted from the method given by Hauser (8) for the preparation of substituted acetophenones.



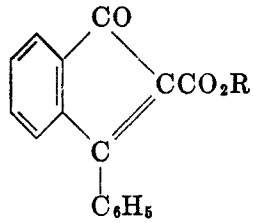
I

The colorless diethyl 3-phenylphthalidyl-3-malonate is accompanied in the preparation by a nearly equal amount of a deep yellow substance which has been shown to be ethyl 3-phenylindone-2-carboxylate (II). This compound is also formed with remarkable ease when the colorless phthalide derivative is warmed gently with dilute sodium carbonate solution. The rearrangement evidently takes place in acids as well, since acid hydrolysis of I produces the brilliant red 3-phenylindone-2-carboxylic acid (III).

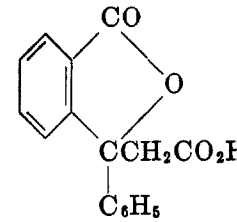
The structure of the ester (II) was established by hydrogenation of the double bond and hydrolysis and decarboxylation to the known 3-phenyl-1-indanone (9). When hydrogenated, the red acid spontaneously decarboxylated to yield the same ketone. The latter was synthesized for comparison by cyclization of

[1] Du Pont Research Fellow, 1947–1949.

β,β-diphenylpropionic acid, and its semicarbazone (10) was found to be identical with those of our two degradation products.



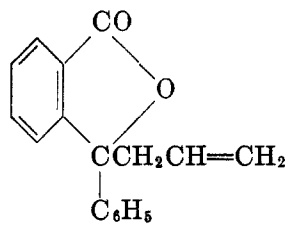
II. R = C_2H_5
III. R = H



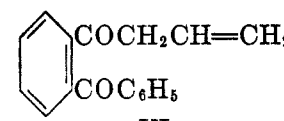
IV

When hydrolyzed with alcoholic potassium hydroxide, diethyl 3-phenylphthalidyl-3-malonate was extensively decomposed, but a very small amount of 3-phenylphthalidyl-3-acetic acid (IV) could be isolated. In order to establish with more certainty the cyclic nature of this latter compound, it was prepared independently by oxidation of 3-allyl-3-phenylphthalide (V), and the acids from the two sources were shown to be identical. Very recently, a synthesis of 3-phenylphthalidyl-3-acetic acid by another route has appeared in the literature (11).

That the previously unknown 3-allyl-3-phenylphthalide had the cyclic (V) rather than the tautomeric open structure (VI) was determined by comparing its ultraviolet absorption spectrum with those of 3-methyl-3-phenylphthalide and of phthalide itself (12).



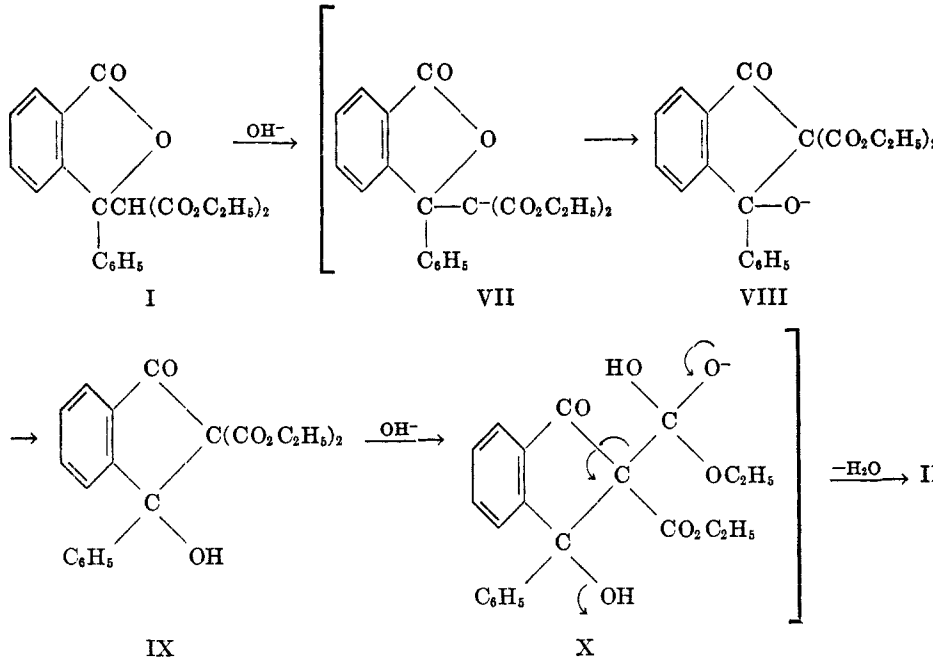
V



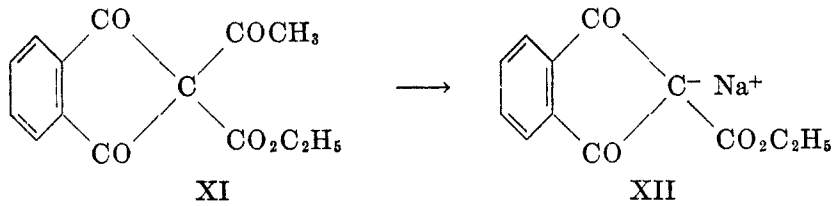
VI

In the light of the extraordinary inertness of 3,3-dialkylphthalides to bases, the solubility of diethyl 3-phenylphthalidyl-3-malonate in sodium carbonate solution indicates an initial attack of the base on the remaining active hydrogen atom of the malonic ester grouping. This observation is supported by the fact that 3-phenylphthalidyl-3-acetic acid, with less active *alpha* hydrogens, is quite stable to strong bases. If the carbanion VII is first formed, it might be expected to undergo an internal Claisen condensation. Attack by hydroxide ions on the ester carbonyl of the corresponding molecule IX would lead to X which must lose water in a process simulating the base-induced dehydration of an aldol.

Once the ester II has been precipitated by acidification, it cannot be redissolved in base. This observation could be explained on the basis of its inability to form a sodium salt. Such salts have been shown to exist in other cases, for



example, in XII which results from the loss of the acetyl group from 2-acetyl-2-carbethoxy-1,3-indandione (XI) in the presence of base (13).



We wish to acknowledge valuable suggestions from Drs. T. A. Geissman of the University of California, and J. W. Wilson of Smith, Kline, and French Laboratories for the preparation of 3-allyl-3-phenylphthalide.

EXPERIMENTAL

Diethyl 3-phenylphthalidyl-3-malonate (I). The pseudo chloride of *o*-benzoylbenzoic acid was prepared by treating 45.2 g. (0.20 mole) of the keto acid with 95.2 g. (0.80 mole) of thionyl chloride at room temperature. The resulting solution was warmed to 50° and maintained at this temperature while a stream of carefully dried air, preheated to 50°, was passed over the surface at atmospheric pressure. After 20 hours dry air was sucked through the mixture for five hours, or until the excess thionyl chloride had apparently been removed. The amber syrupy residue was allowed to cool to room temperature. It was dissolved in 100 cc. of absolute ether and was added rapidly with good stirring to the magnesium diethyl malonate derivative prepared from 5.35 (0.22 atom) of magnesium and 35.2 g. (0.22 mole) of diethyl malonate according to the directions of Walker and Hauser (8). A pale, greenish, thick syrupy precipitate formed. Stirring and reflux were

maintained for an additional hour, the reaction mixture was allowed to stand overnight cooled, and then decomposed with 130 cc. of ice-cold 37% sulfuric acid. The layers were separated, the aqueous solution was extracted with 25 cc. of ether, the ether layers were combined and washed with water, extracted with three 50-cc. portions of 10% sodium carbonate solution, and again washed with water. The oily residue from the ether was dried by distilling benzene from it to near dryness. Addition of absolute ether to this residue gave a precipitate of 17.6 g. (24%) of the colorless diethyl 3-phenylphthalidyl-3-malonate, which melted, after three recrystallizations from absolute ether, at 77–79°.

Anal. Calc'd for $C_{21}H_{20}O_6$: C, 68.47; H, 5.47.

Found: C, 68.74; H, 5.39.

Ethyl 3-phenylindone-2-carboxylate (II). (*a*) The sodium carbonate extracts and water washings from the preparation of diethyl 3-phenylphthalidyl-3-malonate were turbid and yellow. They were combined and washed with ether. Acidification caused the precipitation of a small amount of deep yellow, highly refractive crystals melting at 86–87.5°.

(*b*) The filtrate from the colorless diethyl malonate derivative was evaporated to near dryness. A dark viscous oil remained, which was distilled *in vacuo*. After removing a small amount of unreacted diethyl malonate, the distilland began to decompose. It was cooled, taken up in absolute ether, and refrigerated overnight. The solution deposited 13.0 g. (23.4%) of the same deep yellow crystals, m.p. 87–88° after recrystallization from absolute ether.

(*c*) Ten grams (0.0272 mole) of diethyl 3-phenylphthalidyl-3-malonate was dissolved in 100 cc. of 10% sodium carbonate solution by warming to about 50° for 20 minutes, during which time a yellow color developed and gradually deepened as the temperature increased. After the solution became clear, it was cooled to 15° and cautiously neutralized with 6 *N* hydrochloric acid. The ester crystallized directly at this temperature, melted at 84–87°, and weighed 6.7 g. (88.8%).

Anal. Calc'd for $C_{18}H_{14}O_3$: C, 77.68; H, 5.07.

Found: C, 77.81; H, 5.21.

3-Phenylindone-2-carboxylic acid (III). To a colorless solution of 3.68 g. (0.01 mole) of diethyl 3-phenylphthalidyl-3-malonate in 10 cc. of glacial acetic acid was added 1 cc. of water containing 5 drops of concentrated sulfuric acid. On heating, the color of the solution deepened quickly from yellow to deep vermillion. Distillation of ethyl acetate through a short column was complete after one hour. The cooled residue was diluted with 20 cc. of water, and the red oil which separated was dissolved in benzene, washed with water, and extracted into three 10-cc. portions of 10% sodium carbonate solution. Acidification of these extracts with 6 *N* hydrochloric acid caused the quantitative precipitation of the acid as brilliant red felted needles, which, after repeated recrystallization from 50% ethanol-water, melted at 153.5–156°.

Anal. Calc'd for $C_{16}H_{10}O_3$: C, 76.79; H, 4.03.

Found: C, 76.98; H, 4.35.

Structure of ethyl 3-phenylindone-2-carboxylate. Ethyl 3-phenylindone-2-carboxylate (1.8 g., 0.0065 mole) was hydrogenated in 25 cc. of absolute ethanol at atmospheric pressure and 34° in the presence of Raney nickel catalyst. The crude ethyl 3-phenylindanone-2-carboxylate was isolated as nearly colorless crystals, m.p. 86–87.5°, but decomposed as attempts were made to purify it. The ester was hydrolyzed in 10 cc. of glacial acetic acid containing a trace of 50% sulfuric acid by heating to 90° for one hour. The residue was diluted with water, and the liberated oil dissolved in benzene. After washing with water, the benzene solution was extracted with sodium carbonate solution, but only a trace of alkali-soluble material was isolated. The ketone, formed by decarboxylation during the hydrolysis, could not be isolated in a pure state, but was converted directly to the semicarbazone, m.p. 217.5–219.5° (sintering at 211.5°).

Structure of 3-phenylindone-2-carboxylic acid. This acid (1.28 g., 0.0051 mole) was hydrogenated in 25 cc. of absolute ethanol at atmospheric pressure and 34° in the presence of palladium chloride. Decarboxylation of the reduction product was detected in the readings

of the hydrogen buret. The resulting ketone, after liberation from the catalyst and solvent, was converted to its *semicarbazone*. After purification, the latter melted at 218.5–220.5° (after sintering at 212°). The reported melting point of 3-phenyl-1-indanone semicarbazone is 225° (10).

Anal. Calc'd for $C_{16}H_{15}N_3O$: N, 15.84. Found: N, 15.66.

A mixture of this semicarbazone with that derived from ethyl 3-phenylindone-2-carboxylate (9, 10) melted at 217.5–219.5° (intering at 211.5°). A mixture of the authentic semicarbazone with that derived from the corresponding acid melted at 216–218° (sintering at 212°).

3-Phenylphthalidyl-3-acetic acid (IV). 1. *Hydrolysis of diethyl 3-phenylphthalidyl-3-malonate.* To a solution of 2.5 g. of the diester (I) in 10 cc. of absolute ethanol was added 10 cc. of 40% aqueous potassium hydroxide solution. The mixture began to darken instantly. It was refluxed gently for one hour during which time decomposition continued. Water was added portionwise, and water and ethanol were distilled out until a total of 30 cc. of water had been added and 30 cc. of distillate had been collected. The residue was extracted with benzene to remove tarry decomposition products, and the alkaline layer was acidified with concentrated hydrochloric acid. The liberated oil was extracted into benzene and the solution dried and evaporated. Addition of a small amount of chloroform to the residue caused precipitation of a microcrystalline material which was filtered, washed quickly with cold chloroform, and dried. After recrystallization from 50% ethanol-water, the acid melted constantly at 175–177°.

2. *Oxidation of 3-allyl-3-phenylphthalide.* A mixture of 1 g. of 3-allyl-3-phenylphthalide, 1.7 g. of potassium permanganate, and 20 cc. of water was refluxed for 35 minutes and then cooled. Manganese dioxide was removed by filtration, and the filtrate was acidified carefully with concentrated hydrochloric acid. The liberated oil was extracted into benzene and treated as under 1. Colorless crystals melting at 173–175° were obtained. A mixture melting point with the material obtained by the previous method showed no depression.

Anal. Calc'd for $C_{16}H_{12}O_4$: C, 71.63; H, 4.51; Neut. equiv., 268.24.

Found: C, 71.64; H, 4.44; Neut. equiv., 267.72.

3-Allyl-3-phenylphthalide. (V). Allylmagnesium chloride was prepared by an adaptation of the method of Van Campen (14) for the preparation of substituted benzylmagnesium halides. A suspension of 24.3 g. (1.0 atom) of magnesium turnings in 500 cc. of anhydrous ether was treated with a solution of 38.5 g. (0.5 mole) of allyl chloride in 450 cc. of anhydrous ether at the rate of about 2 cc. per minute. After addition of the allyl chloride was complete (3.5 hours), the mixture was stirred and refluxed for an additional 15 minutes, and then the yield was estimated by titration to be about 85%.

On the basis of this result, an amount of *o*-benzoylbenzoic acid was added so that the ratio of Grignard reagent to keto acid was approximately 3:1. A solution of 33.9 g. (0.15 mole) of *o*-benzoylbenzoic acid in 280 cc. of anhydrous ether was added to the suspension of Grignard reagent during 1.25 hours, and the ether was simultaneously distilled out at the same rate. After addition was complete, 930 cc. of anhydrous benzene was added portionwise and distillation of ether continued until the liquid temperature reached 80°. The solution was then refluxed for an additional 11 hours without stirring.

Hydrolysis of the reaction complex was effected by cautious addition of 100 cc. of ice-cold water. Excess magnesium was removed by decantation and the material further hydrolyzed with 300 cc. of 9% hydrochloric acid. The benzene layer was separated, washed with water, extracted with saturated sodium bicarbonate solution until neutral, and again washed with water. Acidification of the alkali extracts liberated 8.3 g. (24.4%) of starting acid.

The benzene layer was dried and evaporated at atmospheric pressure and the oily residue was distilled *in vacuo*. A first fraction boiled at 180–186° (1.0 mm.) and weighed 21.4 g. (57.1%), n_D^{25} 1.5797. A second fraction was very high-boiling, dark and viscous, and was discarded with the residue. A second fractionation through a short column gave a pale amber distillate boiling at 168–169.5° (0.4 mm.), n_D^{25} 1.5808, and this oil was finally obtained

as a nearly colorless material, boiling at 153–154° (0.2 mm.), n_D^{25} 1.5848. It could also be purified by passing a solution in petroleum ether through a column packed with alumina.

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.58; H, 5.64.
Found: C, 81.03; H, 5.87.

SUMMARY

o-Benzoylbenzoic acid pseudo chloride condenses with diethyl ethoxymagnesium malonate to diethyl 3-phenylphthalidyl-3-malonate. This ester can either be hydrolyzed and decarboxylated to 3-phenylphthalidyl-3-acetic acid, or rearranged to ethyl 3-phenylindone-2-carboxylate. The structures of these two compounds have been established by independent methods, that of 3-phenylphthalidyl-3-acetic acid by oxidation of 3-phenyl-3-allylphthalide, and that of the indone derivative by conversion to the known 3-phenyl-1-indanone. A mechanism for the novel rearrangement reported in this work has been proposed.

CHARLOTTESVILLE, VIRGINIA

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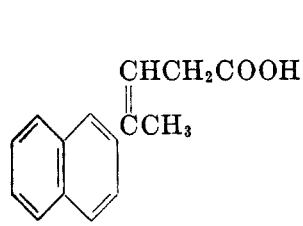
[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

REACTIONS OF 1,2,3,4-TETRAHYDROPHENANTHRENE AND DERIVATIVES. VI. COMPOUNDS DERIVED FROM 1-METHYLTETRAHYDROPHENANTHRENE

W. E. BACHMANN AND R. F. EDGERTON[1]

Received May 8, 1950

In continuation of the work on the reactions of 1,2,3,4-tetrahydrophenanthrene and its derivatives (1), 1-methyl-1,2,3,4-tetrahydrophenanthrene (III, R = H) and 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (III, R = CH_2CH_3) have been prepared and subjected to Friedel-Crafts condensations with acetyl chloride. 1-Methyl-1,2,3,4-tetrahydrophenanthrene was prepared by two methods, which utilized both isomeric naphthoylpropionic acids formed on succinoylation of naphthalene. In one, 1-methyl-3,4-dihydrophenanthrene, which can be prepared in quantitative yield by acetic anhydride dehydration of the carbinol formed from 1-keto-1,2,3,4-tetrahydrophenanthrene by the Grignard reaction (2), was hydrogenated in the presence of Adams' catalyst to the tetrahydro compound. In the second method 4-(2-naphthyl)-3-pentenoic acid (I), prepared from methyl β-(2-naphthoyl)propionate and methylmagnesium iodide (3), was reduced catalytically to γ-(2-naphthyl)valeric acid. Cyclization of the acid chloride by anhydrous stannic chloride yielded 1-methyl-4-keto-1,2,3,4-tetrahydrophenanthrene (II), which was reduced by the Clemmensen method to 1-methyl-1,2,3,4-tetrahydrophenanthrene. The hydrocarbon has now been obtained in crystalline form, and the picrate derivative has been prepared. Palladium dehydrogenation of a sample of the hydrocarbon proceeded without migration of the methyl group and yielded 1-methylphenanthrene.



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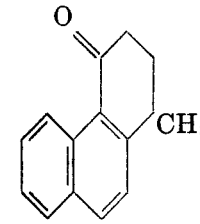

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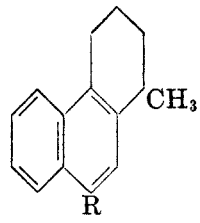
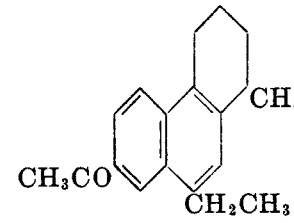


III



IV

[1] From the Ph.D. dissertation of R. F. Edgerton, 1944. Present address: Eastman Kodak Company, Rochester, N. Y.

Acetylation of 1-methyl-1,2,3,4-tetrahydrophenanthrene in a carbon disulfide—*sym*-tetrachloroethane solution of acetyl chloride and aluminum chloride gave 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene (III, R = $COCH_3$) in high yield. In agreement with the results of Bachmann and Cronyn (4) on the parent hydrocarbon, only the 9-isomer was formed by this procedure. That the acetyl group was located in the 9-position was established by Clemmensen reduction of the ketone to 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene, which was dehydrorgenated by palladium on charcoal to 1-methyl-9-ethylphenanthrene. The latter hydrocarbon was found to be identical with that prepared from the known 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene (5) by reaction with methylmagnesium iodide, followed by dehydration and dehydrogenation of the carbinol with palladium.

By oxidation of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene with sodium hypochlorite 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid (III, R = COOH) was produced. By the Willgerodt reaction with ammonium polysulfide the acetyl compound was converted into 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetamide, which was hydrolyzed to the corresponding acid. Decarboxylation and dehydrogenation of the substituted acetic acid yielded 1,9-dimethylphenanthrene. Beckmann rearrangement of the oxime of the acetyl compound gave the 9-acetylamino compound, which was hydrolyzed to 1-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene.

Acetylation of 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene gave a crystalline ketone in good yield. Although the position of the acetyl group was not proved, by analogy with the acetylation of 9-ethyl-1,2,3,4-tetrahydrophenanthrene (6) the ketone is undoubtedly 1-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene (IV).

The antimalarial activities of a number of compounds which were prepared from the two acetyl derivatives are reported in the survey of antimalarial drugs of the Committee on Medical Research (7).

EXPERIMENTAL

1-Methyl-1,2,3,4-tetrahydrophenanthrene. (*a*) *From 1-keto-1,2,3,4-tetrahydrophenanthrene.* A solution of 60 g. of the ketone (m.p. 95–96°) in 300 cc. of dry benzene was added with stirring to the Grignard reagent which had been prepared from 45 cc. of methyl iodide, 15 g. of magnesium, and 600 cc. of ether; throughout the addition the temperature was kept at 0°. After having been stirred for 36 hours at 0–10° the mixture was added slowly to a vigorously stirred (to prevent local superheating which causes a decrease in the yield of carbinol) mixture of ice and ammonium chloride solution. The 1-methyl-1-hydroxy-1,2,3,4-tetrahydrophenanthrene, which was obtained by evaporation of the solution at room temperature, crystallized from benzene-ligroin in clusters of colorless needles; yield, 58.7 g. (90%); m.p. 84–86° [reported (2), 86–86.5°].

A solution of 60 g. of the carbinol in 400 cc. of acetic anhydride was heated on a steam-cone for 45 minutes and poured while hot into 1600 cc. of cold water. The colorless precipitate of the unsaturated hydrocarbon, which remained after the cooled mixture had been stirred until the acetic anhydride was hydrolyzed, was washed repeatedly with a dilute acetone-water solution until the filtrate was neutral to litmus; yield, 55 g.; m.p. 81–83.5°. After one recrystallization from methanol, the 1-methyl-3,4-dihydrophenanthrene formed colorless nacreous platelets; m.p. 85.5–86.5° [reported (2) 86–86.5°].

Five 10-g. portions of the crude unsaturated hydrocarbon, each with 0.1 g. of Adams' catalyst in 125 cc. of acetic acid, were shaken with hydrogen at 25 pounds pressure for 4–7 hours. The combined filtered solutions were diluted with water, and the product, which was extracted with benzene, was distilled at 130–133°/0.05 mm. The *1-methyl-1,2,3,4-tetrahydrophenanthrene* gradually crystallized in a refrigerator; m.p. 28-29°. The *picrate* crystallized from absolute alcohol in yellow needles; m.p. 100.5–101.5°.

Anal. Calc'd for $C_{21}H_{19}N_3O_7$: N, 9.9. Found: N, 9.8.

A mixture of 0.42 g. of 1-methyl-1,2,3,4-tetrahydrophenanthrene and 0.05 g. of palladium-charcoal catalyst was heated at 300–320° in a nitrogen atmosphere for 45 minutes. From a solution of the product in hot alcohol 1-methylphenanthrene crystallized in colorless leaflets; yield 0.31 g. (75%); m.p. 119.5–120.5° [reported (2) 120–121°].

(*b*). *From 1-methyl-4-keto-1,2,3,4-tetrahydrophenanthrene.* Refluxing a mixture of 45 g. of β-2-naphthoylpropionic acid, 150 cc. of methanol, and 4.5 cc. of sulfuric acid for 12 hours yielded 45.6 g. (96%) of the methyl ester; m.p. 74–77°. Following Robinson and Slater (3) and Kloetzel (8) for a similar reaction 18.4 g. of crude 4-(β-naphthyl)-3-pentenoic acid (m.p. 124–126°) was obtained from 30 g. of methyl β-2-naphthoylpropionate in 100 cc. of benzene and methylmagnesium iodide (from 4.2 g. of magnesium and 11 cc. of methyl iodide in 80 cc. of ether); after the addition of water and dilute hydrochloric acid the acid was extracted from the organic layer with aqueous sodium carbonate; 3.8 g. of unchanged methyl ester was recovered from the organic layer. After one recrystallization from dilute acetic acid, the compound formed colorless platelets, m.p. 133–135°. Two further recrystallizations from chloroform raised the melting point to 139–140.5° [reported (3) 141–142°].

A solution of 7.1 g. of 4-(β-naphthyl)-3-pentenoic acid (m.p. 133–135°) in 150 cc. of glacial acetic acid and 0.1 g. of Adams' catalyst was shaken with hydrogen for seven hours at 25 pounds pressure. The reaction mixture was diluted with water and the product was distilled at 0.05 mm. A solution of the distillate in hot 30–60° petroleum ether deposited 6.1 g. (85%) of *4-(β-naphthyl)valeric acid* as colorless prisms on cooling; m.p. 69.5–70.5°. Two recrystallizations from ether-petroleum ether gave m.p. 70–70.5°.

Anal. Calc'd for $C_{15}H_{16}O_2$: C, 78.9; H, 7.1.
Found: C, 78.4; H, 7.9.

To a stirred solution of 5 g. of the substituted valeric acid in 20 cc. of benzene, 4.8 g. of pulverized phosphorus pentachloride was added portionwise. Stirring was continued for one hour at room temperature and for five minutes on a steam-cone. To the mixture which was chilled to 0°, a solution of 5 cc. of stannic chloride in 5 cc. of dry benzene was added rapidly; stirring was continued for 15 minutes. Evaporative distillation under reduced pressure of the product obtained on hydrolysis gave 4 g. of 1-methyl-4-keto-tetrahydrophenanthrene as a liquid. The *semicarbazone* crystallized from absolute alcohol in colorless needles; m.p. 206.5–207.5°.

Anal. Calc'd for $C_{16}H_{17}N_3O$: C, 71.9; H, 6.4.
Found: C, 72.6; H, 6.3.

To 20 g. of amalgamated zinc covered with a mixture of 25 cc. each of glacial acetic acid and concentrated hydrochloric acid was added 3 g. of the above ketone dissolved in 15 cc. of toluene. The mixture was refluxed for 24 hours, during which time 25 cc. of concentrated hydrochloric acid was added in portions. The 1-methyl-1,2,3,4-tetrahydrophenanthrene (2.4 g.) after purification by evaporative distillation formed a picrate which melted at 100–101° alone and when mixed with the picrate prepared in (a).

Acetylation of 1-methyl-1,2,3,4-tetrahydrophenanthrene. Following the procedure of Bachmann and Cronyn (4), a clear solution of the acetylating agent and catalyst was prepared by stirring a mixture of 32.3 g. of aluminum chloride, 350 cc. of carbon disulfide and 17.2 cc. of acetyl chloride for 15 minutes, then adding 250 cc. of *sym*-tetrachloroethane and stirring for half an hour with slight warming. To the stirred and chilled (0°) solution 21.6 g. of 1-methyl-1,2,3,4-tetrahydrophenanthrene in 40 cc. of carbon disulfide was added dropwise; stirring was continued for 15 minutes at 0° and for one-half hour at room temperature, and finally the mixture was kept in a refrigerator for 16 hours. The crystalline

complex which had precipitated was washed with carbon disulfide and hydrolyzed with ice and hydrochloric acid. The filtrate was hydrolyzed separately. The ketone after distillation at 173–175° and 0.1 mm. solidified after several days in a refrigerator; m.p. 23–25°; yield, 15.7 g. (from the solid complex) + 8.2 g. (from the filtrate) (91%). When the *1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene* was regenerated from its picrate, a higher-melting polymorphic form was obtained, which crystallized from methanol in colorless needles; m.p. 41–42°. The liquid ketone originally obtained on distillation crystallized in the higher-melting form when seeded with crystals of the latter.

Anal. Calc'd for $C_{17}H_{18}O$: C, 85.7; H, 7.6.

Found: C, 85.6; H, 7.9.

Proof of structure of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. 1-Methyl-9-ethylphenanthrene. (a) From the acetyl compound. To 220 g. of amalgamated zinc and 300 cc. each of concentrated hydrochloric acid and glacial acetic acid was added a solution of 36.5 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene in 200 cc. of toluene. The mixture was refluxed for 30 hours, during which time an additional 300 cc. of hydrochloric acid was added in portions. The organic layer was washed with dilute hydrochloric acid, water, and sodium bicarbonate. Distillation of the product at 125–127°/0.01–0.05 mm. gave 32.7 g. of 1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene as a colorless liquid (*trinitrobenzene complex*, orange needles; m.p. 106.5–107°).

Heating 0.79 g. of the hydrocarbon with 0.05 g. of palladium-charcoal catalyst at 300–320° in a nitrogen atmosphere for one-half hour gave *1-methyl-9-ethylphenanthrene*, which crystallized from acetone-methanol solution in fine colorless needles; yield, 0.54 g. (70%); m.p. 69.5–70.5°. Two more recrystallizations raised the melting point to 70.5–71°.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.4.

Found: C, 92.8; H, 7.3.

The *picrate* formed orange-yellow needles from absolute alcohol; m.p. 132.5–133°.

Anal. Calc'd for $C_{23}H_{19}N_3O_7$: N, 9.3. Found: N, 9.2.

(b) From 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene. A solution of 0.19 g. of 1-keto-9-ethyl-1,2,3,4-tetrahydrophenanthrene (5) in 10 cc. of benzene was added dropwise with swirling to the Grignard reagent made from 0.39 g. of magnesium and 1.16 cc. of methyl iodide in 20 cc. of dry ether. The solution was kept at 0° throughout the addition of the ketone and then in a refrigerator for 48 hours. The product obtained on hydrolysis with ice-cold ammonium chloride solution was heated with 40 mg. of palladium-charcoal catalyst at 300–315° in a nitrogen atmosphere for one-half hour. The 1-methyl-9-ethylphenanthrene and its picrate proved to be identical with the compounds prepared in (a).

Reactions of 1-Methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene. (a) Haloform reaction. A mixture of 2 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 50 cc. of sodium hypochlorite solution prepared according to Newman and Holmes (9), and 25 cc. of dioxane was stirred for two hours at 60–65°. The cooled solution was poured slowly into a mixture of hydrochloric acid, sodium bisulfite, and ice; yield of colorless acid, 1.94 g. (96%); m.p. 168–170.5°. Recrystallized once from dilute acetic acid and twice more from ethyl acetate, a sample of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-carboxylic acid* formed colorless plates; m.p. 173.5–174.5°.

Anal. Calc'd for $C_{16}H_{16}O_2$: C, 80.0; H, 6.7.

Found: C, 79.5; H, 6.7.

(b) Willgerodt reaction. By the method of Fieser and Kilmer (10), except that the mixture was heated for 48 hours at 170°, 1.55 g. (54%) of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetamide* was obtained from 2.68 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene; m.p. 173–174.5°. Recrystallized twice from acetone, a sample formed colorless needles; m.p. 175–176°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.5.

A solution of 1 g. of the amide in 20 cc. of acetic acid and 10 cc. of hydrochloric acid was refluxed for 24 hours. After the addition of 50 cc. of concentrated hydrochloric acid the

mixture was cooled; yield of *1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid* as colorless needles, 0.94 g. (93%); m.p. 160–161.5°. A sample formed colorless needles when recrystallized twice from ethyl acetate; m.p. 165.5–166.5°.

Anal. Calc'd for $C_{17}H_{18}O_2$: C, 80.3; H, 7.1.
Found: C, 80.6; H, 7.2.

A solution of 0.51 g. of crude 1-methyl-1,2,3,4-tetrahydrophenanthrene-9-acetic acid in 10 cc. of methanol was treated with an equivalent of methanolic sodium methoxide, the solvent was removed, and the salt was triturated with ether and filtered. A mixture of the dry salt and 2 g. of soda-lime was heated for four hours at 300–340°/0.01–0.05 mm. in a subliming-tube and the distillate was heated with palladium-charcoal at 310° for 45 minutes. The picrate of the resulting 1,9-dimethylphenanthrene formed orange needles after two recrystallizations from ethanol; m.p. 160–160.5°. Regenerated from the picrate and recrystallized from methanol, the hydrocarbon formed colorless needles; m.p. 86–87° [reported (11) 163.5° and 88° respectively].

(*c*) *Oximation and rearrangement.* A quantitative yield of the oxime was obtained by refluxing 29.1 g. of 1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene, 20.5 g. of hydroxylamine hydrochloride, 100 cc. of absolute ethanol, and 35 cc. of pyridine for four hours. Recrystallized three times from ether-petroleum ether, a sample of *1-methyl-9-acetyl-1,2,3,4-tetrahydrophenanthrene oxime* formed colorless prisms; m.p. 129.5–131.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.3.

A Beckmann rearrangement of 3.8 g. of the crude oxime in 80 cc. of benzene by heating with 4 g. of phosphorus pentachloride for 15 minutes on a steam-cone followed by treatment with water yielded *1-methyl-9-acetylamino-1,2,3,4-tetrahydrophenanthrene;* weight, 2.14 g. and m.p. 171–176° after recrystallization from ethanol. After evaporative distillation under reduced pressure and two recrystallizations from ethanol the amide formed colorless needles; m.p. 183–184.5°.

Anal. Calc'd for $C_{17}H_{19}NO$: N, 5.5. Found: N, 5.6.

The amide was hydrolyzed with alcoholic hydrochloric acid (4) to the amine, a solid which discolored rapidly. The *picrate* of *1-methyl-9-amino-1,2,3,4-tetrahydrophenanthrene* formed golden platelets from ethyl acetate; m.p. 178–180°.

Anal. Calc'd for $C_{21}H_{20}N_4O_7$: N, 12.7. Found: N, 13.4.

Acetylation of *1-methyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene.* From the crystalline complex which was formed by the reaction of 27.1 g. of the hydrocarbon with a solution of 19 cc. of acetyl chloride, 32.3 g. of aluminum chloride, 375 cc. of carbon disulfide, and 275 cc. of *sym*-tetrachloroethane carried out as described for the previous acetylation, 22.5 g. (70%) of colorless needles, presumably *1-methyl-7-acetyl-9-ethyl-1,2,3,4-tetrahydrophenanthrene*, was obtained after distillation at 170–173° and 0.01–0.05 mm. and crystallization from methanol; m.p. 83–84°. Recrystallized twice from methanol, a sample melted at 84.5–85°.

Anal. Calc'd for $C_{19}H_{22}O$: C, 85.6; H, 8.3.
Found: C, 85.3; H, 8.1.

SUMMARY

1-Methyl-1,2,3,4-tetrahydrophenanthrene has been prepared by two different methods, and a number of reactions of it and its derivatives are described.

ANN ARBOR, MICHIGAN

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[CONTRIBUTION FROM THE CHEMISTRY DIVISION, NAVAL RESEARCH LABORATORY]

SYNTHESIS OF PHENOTHIAZINE DERIVATIVES FOR USE AS ANTIOXIDANTS

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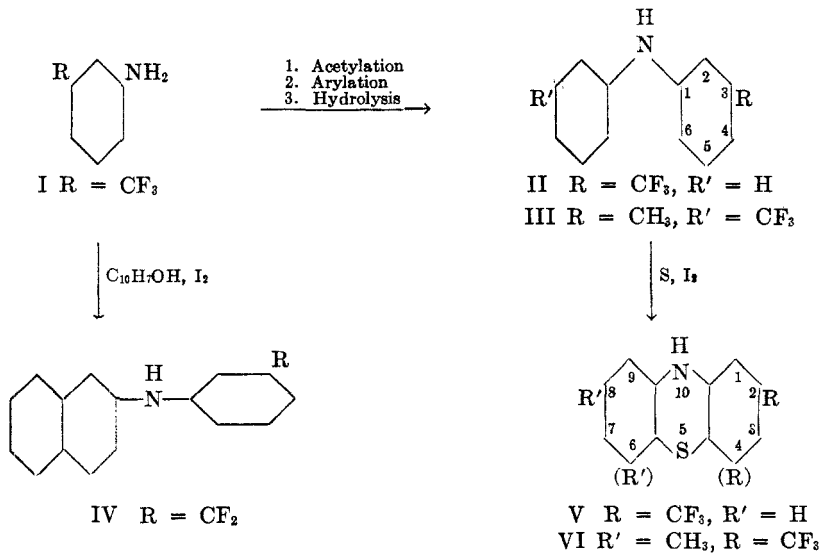
As a result of the interest in phenothiazine as an antioxidant for lubricant application, a project was initiated to synthesize phenothiazine derivatives of interest, to test them as antioxidants, and to study their mode of action.[1] Two objectives of the preparative phase of that investigation are described in this communication: first, the synthesis of some trifluoromethylated phenothiazines from the corresponding aromatic secondary amines, and secondly, the formation and cyclization of β-(10-phenothiazyl)propionic acid. The substituted propionic acid, previously prepared by Cauquil and Cassadevall,[2] was obtained by hydrolysis of the cyanoethylation product of phenothiazine.

Asymmetrical and substituted trifluoromethylated diarylamines provided the corresponding thiazine structures by an iodine-catalyzed modification of Bernthsen's fusion with sulfur (1). For the preparation of the aromatic secondary amines, either the convenient Buu-Hoï condensation of an aryl amine with an aryl hydroxy compound (2) or the Goldberg condensation of a substituted acetanilide with an aryl halide (3) was employed.

The commercially available *m*-trifluoromethylaniline (I)[3] served as convenient starting material for the preparation of 3-trifluoromethyldiphenylamine (II), 3-trifluoromethyl-3′-methyldiphenylamine (III), and 3-trifluoromethylphenyl-β-naphthylamine (IV). Consequently, the thionation products prepared in this investigation from the first two diarylamines must be 2- or 4-trifluoromethylphenothiazine (V) and 2- or 4-trifluoromethyl-6- or 8-methylphenothiazine (VI) depending on the orientation effect of sulfur bridging:



Gilman (4) and Baltzly (5) discussed the position problem with respect to metalation and acylation of phenothiazine, while Calcott (6) considered it for some fluorinated and trifluoromethylated methylene blue compounds and Buu-Hoï (7) for a methyl-substituted benzophenothiazine. The observations of these investigators indicate that position orientation varied with the formation and reactions of thiazines and that chemical methods of identification showed little promise. Since the exact position of the phenothiazine adduct is of considerable interest for inhibitor studies, it was decided to subject trifluoromethylphenothiazine to spectral examination.

Thompson (8) and Barnes (9) have shown that unsymmetrical trisubstituted benzene structures produce a characteristic infrared band in the region 12.0 to 12.5μ, while *vicinal*-trisubstituted benzene compounds produce bands in the retion from about 12.5 to 13.15μ. If these correlations are followed by 2- or 4-trifluoromethylphenothiazine then a strong band in either of these regions is indicative of the corresponding structure.

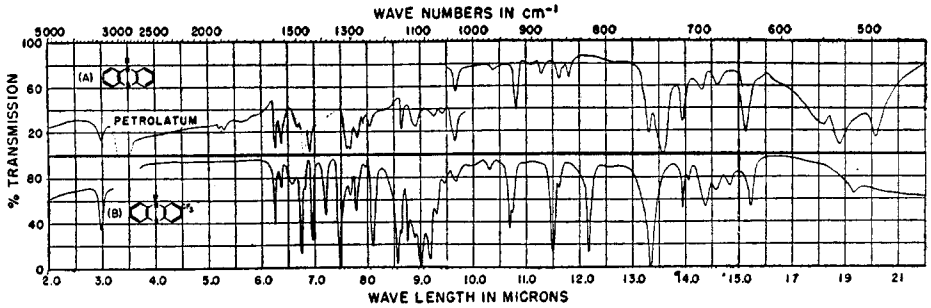


FIGURE 1. A. Infrared Spectrum of Phenothiazine. B. Infrared Spectrum of 2-Trifluoromethylphenothiazine.

The spectra of phenothiazine and trifluoromethylphenothiazine, studied in the solid phase (using the petroleum mull technique) over the range 2–22μ, are shown in Figure 1. It is seen that trifluoromethylphenothiazine has a strong band at 12.17 which is not in the phenothiazine spectrum, indicating that the CF_3 group is attached to the 2-position. Accordingly, the methyl and trifluoromethyl groups in the two phenothiazine compounds prepared by thionation reactions are provisionally assigned to positions 2 and 8. The presence of the sulfur atom seems to orientate the groups to the *para*-positions.

With the object of investigating the use of substituted propionic acids for the preparation of new types of thiazine compounds, the synthesis of β-(10-phenothiazyl)propionic acid (IX) was attempted. Although some or all of the reactions involved have been applied to other heterocyclic compounds (10, 11), apparently

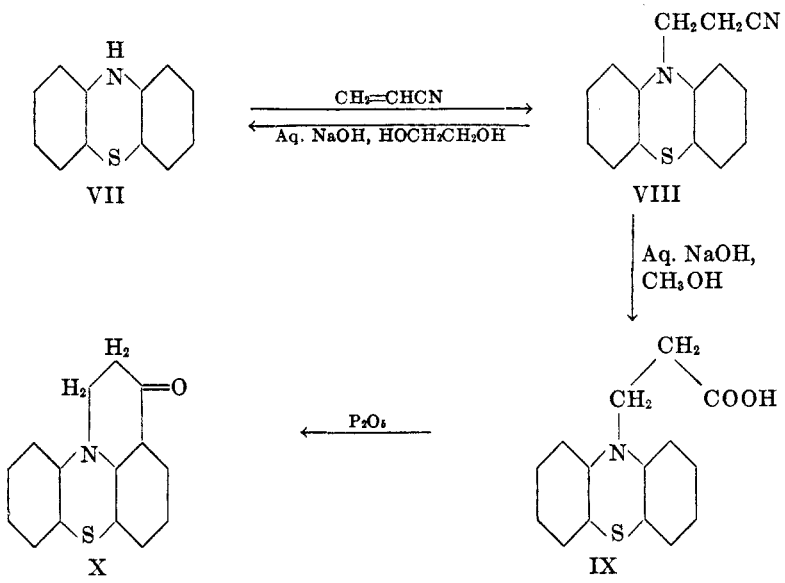
[1] An evaluation of the inhibitor properties of these compounds and a theoretical discussion of their mode of action will be discussed elsewhere.

[2] These authors reported (12) the preparation of this acid by the hydrolysis of the condensation product of ethyl β-bromopropionate with phenothiazine.

[3] Product of Hooker Electrochemical Company, Niagara Falls, N. Y.

no similar process has been described in the chemical and patent literature for phenothiazine.

The synthesis of β-(10-phenothiazyl)propionic acid (IX) *via* the hydrolysis of the cyanoethylation product of phenothiazine (VII), β-(10-phenothiazyl)-propionitrile (VIII), and subsequent cyclization of the substituted propionic acid readily provided 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*] phenothiazine (X):[4]



A vigorous but controllable reaction was initiated when a 40% solution of benzyltrimethylammonium hydroxide[5] was added to a mixture of 0.1 mole of phenothiazine and an excess of acrylonitrile; very efficient cooling was necessary when larger quantities of the reactants were used. The reaction product, β-(10-phenothiazyl)propionitrile, furnished the corresponding propionic acid on hydrolysis with an aqueous methanol-sodium hydroxide solution and subsequent acidification. Replacing the methanol with ethylene glycol resulted in the unexpected rupture of the hetero nitrogen-carbon bond, in addition to the action on the cyano group, liberating β-hydroxypropionic acid and phenothiazine. Apparently, under conditions specified for the reaction, the smaller fragment dehydrates readily, since only acrylic acid was isolated.

β-(10-Phenothiazyl)propionic acid was converted into the anhydride at the boiling point of dry xylene in the absence of a dehydrating agent. When boiled with phosphoric anhydride in benzene, the acid gave the desired ketone in 76% yield. The cyclic ketone was characterized by its phenylhydrazone and 2,4-dinitrophenylhydrazone.

The trifluoromethylated phenothiazines resemble the parent heterocyclic compound in color, crystalline structure, and tendency to discolor on exposure to

[4] Nomenclature recommended by Drs. L. T. Capell and A. M. Patterson.

[5] Triton B, product of Rohm and Haas Company, Philadelphia, Pa.

atmospheric conditions. Furthermore, the color phenomena of diarylamines and phenothiazines with concentrated sulfuric acid were observed with the trifluoromethylated derivatives prepared.

EXPERIMENTAL[6]

3-Trifluoromethyldiphenylamine (II). 3-Trifluoromethylaniline was first converted to the acetyl derivative with acetic anhydride. A mixture of 20.3 g. (0.1 mole) of 3-trifluoromethylacetanilide, m.p. 110°, and 31.4 g. (0.2 mole) of bromobenzene in 100 ml. of nitrobenzene was stirred under reflux for 21 hours in the presence of 15.0 g. of anhydrous potassium carbonate and 0.5 g. of cuprous bromide, after which the nitrobenzene and unchanged bromobenzene were removed by steam. The crude N-acetyl-3-trifluoromethyldiphenylamine, b.p. 125–127° (0.5 mm.), obtained in 72% yield (21.0 g.), was hydrolyzed by refluxing for four hours with 30 ml. of ethanol and 30 ml. of concentrated hydrochloric acid. The product was poured onto ice and the precipitate extracted with ether, washed with alkali and water, dried over sodium sulfate, the solvent removed, and the residue distilled. 3-Trifluoromethyldiphenylamine distilled as a yellow liquid, b.p. 108–110° (0.3 mm.), n_D^{25} 1.5655 and weighed 10.6 g. (56%). A picrate crystallized from benzene in coarse yellow needles, m.p. 147°. The amine is steam-distillable.

Anal. Calc'd for $C_{13}H_{10}F_3N$: N, 5.90. Found: N, 5.90[7].

2-Trifluoromethylphenothiazine (V). To 7.0 g. (0.03 mole) of 3-trifluoromethyldiphenylamine was added 2.0 g. of sublimed sulfur and 0.2 g. of iodine. The mixture was heated at 140–150° for one hour. The reaction product was cooled, dissolved in toluene, treated with Filter-Cel and charcoal, filtered, and the solution allowed to crystallize. The crude 2-trifluoromethylphenothiazine weighed 3.5 g. (44% yield) and was recrystallized from alcohol in yellow platelets, m.p. 188–189°. The compound imparts to concentrated sulfuric acid a brown color which remains unchanged on dilution with water or the addition of nitric acid. The color impurities of this thiazine can be removed by treatment with zinc dust.

Anal. Calc'd for $C_{13}H_8F_3NS$: C, 58.20; H, 3.16.
Found: C, 58.56, H, 3.22.

3-Trifluoromethyl-3'-methyldiphenylamine (III). A mixture of 50.3 g. (0.25 mole) of 3-trifluoromethylacetanilide, 85.5 g. (0.5 mole) of 3-bromotoluene, 33.0 g. of anhydrous potassium carbonate, 1.0 g. of cuprous bromide, and 300 ml. of dry nitrobenzene was heated under reflux for 18 hours. The nitrobenzene and unchanged 3-bromotoluene were steam-distilled, and the residue refluxed for one hour with 75 ml. of concentrated hydrochloric acid and 75 ml. of ethanol. The solvent was removed and the reaction product washed thoroughly with alkali and water. The amine distilled as a yellow oil, b.p. 130–132° (1.0 mm.), n_D^{25} 1.5581 and weighed 24.0 g. (39%). The hydrochloride melted at 228° with decomposition.

Anal. Calc'd for $C_{14}H_{12}F_3N$: N, 5.58. Found: N, 5.92.

The *acetyl* derivative, prepared by boiling the amine with excess acetic anhydride for two hours, was obtained from *n*-hexane in the form of white crystals, m.p. 67–68°.

2-Trifluoromethyl-8-methylphenothiazine (VI). Two grams of 3-trifluoromethyl-3'-methyldiphenylamine, 0.5 g. of sulfur, and a small crystal of iodine were heated in an oil-bath maintained at 145–150° for one hour. The reaction product was cooled, dissolved in benzene, treated with charcoal and Filter-Cel, and recrystallized from benzene as yellow platelets, m.p. 227–228° in 52% yield (1.3 g.). In conc'd sulfuric acid, the thiazine gives a reddish-brown color.

Anal. Calc'd $C_{14}H_{10}F_3NS$: N, 4.98. Found: N, 4.98.

3-Trifluoromethylphenyl-β-naphthylamine (IV). A mixture of 72.0 g. (0.5 mole) of β-naphthol and 80.5 g. (0.5 mole) of 3-trifluoromethylaniline was heated under reflux for 24

[6] All melting and boiling points are uncorrected.

[7] Microanalyses performed by Oakwold Laboratories, Alexandria, Va.

hours in the presence of 0.5 g. of iodine. The dark oil was taken up in toluene, washed with alkali, and dried over sodium sulfate. After the removal of the solvent the residue was distilled *in vacuo*, b.p. 180–185° (2 mm.). The reddish-brown distillate (71.0 g.) solidified on cooling. Recrystallization from alcohol yielded white needles, m.p. 83–84°. No crystalline picrate was formed.

Anal. Calc'd for $C_{17}H_{12}F_3N$: C, 71.00; H, 4.18; N, 4.87.
Found: C, 70.64; H, 4.17; N, 5.22.

β-(10-Phenothiazyl)propionitrile (VIII). A mixture of 200 g. (1.0 mole) of phenothiazine[8] and 300 ml. of acrylonitrile was cooled in an ice-bath and treated with 3.0 ml. of a 40% aqueous solution of benzyltrimethylammonium hydroxide. A sudden reaction took place with considerable evolution of heat. The reaction product was warmed on a steam-bath for an hour and then allowed to cool. The crystalline mass was vacuum-dried yielding 235 g. (93%) of crude product. Recrystallization from acetone gave 171 g. (73% recovery) of thick colorless needles, m.p. 158–159°. No picrate was formed. The nitrile was soluble in benzene and acetone, less soluble in methanol and ethanol.

Anal. Calc'd for $C_{15}H_{12}N_2S$: N, 11.16; S, 12.73.
Found: N, 11.20; S, 12.77.

β-(10-Phenothiazyl)propionic acid (XI). The successful hydrolysis of the nitrile was accomplished by boiling a mixture of 25.0 g. (0.1 mole) of β-(10-phenothiazyl)propionitrile, 25.0 g. of sodium hydroxide, 75 ml. of water, and 250 ml. of methanol under reflux for 15 hours. The hydrolysis product was poured into ice-water, acidified with dilute hydrochloric acid, filtered, and crystallized from ethanol. The acid, 17.5 g. (65%), was recovered in the form of fine needles, m.p. 163°[9]; Neut. equiv., 272.0 (calc'd, 271.4).

An attempt to prepare the acid in ethylene glycol failed. A mixture of β-(10-phenothiazyl)propionitrile, 250 ml. of ethylene glycol, 25 g. of sodium hydroxide, and 40 ml. of water was boiled under reflux for 6.5 hours, cooled, acidified with dilute hydrochloric acid, washed with water, and finally crystallized from alcohol, m.p. 185°. Mixed m.p. with an authentic sample of phenothiazine showed no depression. The other cleavage product found in the filtrate was identified as acrylic acid, b.p. 141°, and characterized by its methyl ester, b.p. 80°.

The anhydride of the acid precipitated from a solution of the acid in dry xylene at the boiling point, m.p. 228° (decomp.). The original acid was recovered from aqueous alkali solution by acidification.

2,3-Dihydro-3-keto-1H-pyrido [3,2,1-kl] phenothiazine (X). β-(10-Phenothiazyl)propionic acid (10 g., 0.04 mole) was treated with 50.0 g. of phosphoric anhydride in 200 ml. of dry benzene. The mixture was heated for one hour on a steam-bath and allowed to remain at room temperature overnight. The reaction product was treated with ice-water, washed with water, then with sodium carbonate solution, again with water, and dried over sodium sulfate. The solvent was removed and the residue taken up with alcohol, diluted with water and allowed to crystallize. Yield: 7.1 g. (76%). Recrystallization from alcohol gave yellow needles, m.p. 112–113°.

Anal. Calc'd for $C_{15}H_{11}NOS$: C, 71.07; H, 4.38; N, 5.53.
Found: C, 71.20; H, 4.25; N, 5.64.

The *2,4-dinitrophenylhydrazone* was obtained from alcohol as brick-red needles, m.p. 90°; the *phenylhydrazone* afforded yellow crystals from alcohol, m.p. 167°.

Anal. Calc'd for $C_{21}H_{17}N_3S$: C, 73.56; H, 4.99; N, 12.23.
Found: C, 73.56; H, 5.11; N, 12.34.

ACKNOWLEDGEMENTS

The author wishes to express his appreciation to the following members of this laboratory; Dr. W. A. Zisman for many helpful discussions, Dr. D. C. Smith

[8] N.F. purified; manufactured by Dow Chemical Company, Midland, Mich.
[9] Reported m.p. 161° (12).

for interpretation of the infrared data, and L. W. Daasch for the infrared analyses.

SUMMARY

A series of seven phenothiazine derivatives and diarylamines were synthesized in a program designed to provide antioxidants of interest for lubricant application.

The aromatic secondary amines—3-trifluoromethyldiphenylamine, 3-trifluoromethyl - 3′ - methyldiphenylamine, 3 - trifluoromethylphenyl - β - naphthylamine —were prepared by condensation reactions with 3-trifluoromethylaniline. Thionation reactions converted two of the amines into the corresponding thiazine structures—2-trifluoromethylphenothiazine and 2-trifluoromethyl-8-methylphenothiazine.

Cyanoethylation of phenothiazine provided β-(10-phenothiazyl)propionitrile, which was hydrolyzed to the corresponding propionic acid. The acid readily cyclized to 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine.

WASHINGTON 25, D. C.

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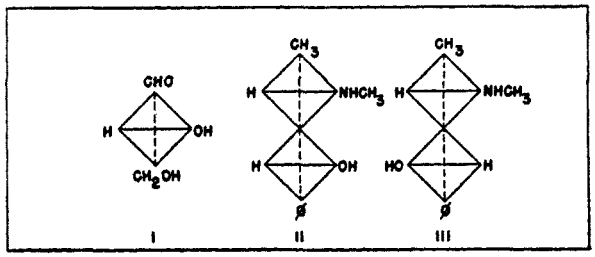
[CONTRIBUTION FROM ABBOTT LABORATORIES]

THE CONFORMATION OF THE EPHEDRINES

W. J. CLOSE

Received May 24, 1950

The chemistry of ephedrine and its three optical isomers has attracted widespread interest because of the physiological significance attached to the structure. (−)-Ephedrine was first isolated by Nagai (1) in 1887 and by 1920 all of the optical isomers had been synthesized (2). Shortly thereafter Freudenberg (3, 4) and Leithe (5) established the relative configuration about the two asymmetric centers for (−)-ephedrine, and hence for its optical isomers, since the configurational relationship between compounds of the ephedrine and pseudoephedrine series is well known.[1] The configurations of (−)-ephedrine and (+)-pseudoephedrine may be represented by Figures II and III, respectively, if D-glyceraldehyde is represented as I.



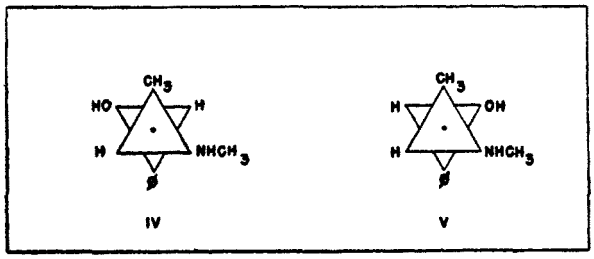
The molecular picture is not complete with the establishment of the relative configuration, however. The *conformation* (11) of the ephedrine molecule is still indeterminate. A consideration of the observed differences in reactivity of ephedrine and pseudoephedrine derivatives has led Fodor and his coworkers (8)

[1] Much confusion has arisen in recent times concerning the configuration about the carbon bearing the methylamino group. Jarowski and Hartung (6) stated that Freudenberg (4) and Leithe (5) arrived at opposite configurations and that the configuration is, therefore, in doubt. Fourneau and Benoit (7) apparently also felt that the configuration had not been established, for they stated that the structures of the diastereoisomers of ephedrine and isoephedrine remain undetermined. More recently, Fodor and coworkers (8) maintained that the configuration at the nitrogen-bearing carbon atom is unsettled, and to indicate this unsettled configuration a double-headed arrow was used in all of the projection formulas relating to the ephedrines. Only Welsh (9) has felt that the configuration has been adequately established.

The authors who believe that the configuration is unsettled may have been misled by an incorrect abstract (10) of Leithe's work, wherein it was stated that "the natural Ephedra bases are not derived from natural *l*-alanine but from the *d*-antipode". Actually, both Freudenberg and Leithe related natural ephedrine to natural L(+)-alanine. Since two independent investigators, by varying technique and by acceptable and logical means, have arrived at identical conclusions, there can be no reasonable doubt concerning the configuration at this asymmetric center.

to the conclusion that there is some restricted rotation about the bond between the carbon bearing the hydroxyl group and the carbon bearing the methylamino group. The evidence pointed to the probability that in the ephedrine molecule the hydroxyl and methylamino groups are relatively distant; in pseudoephedrine, relatively close.

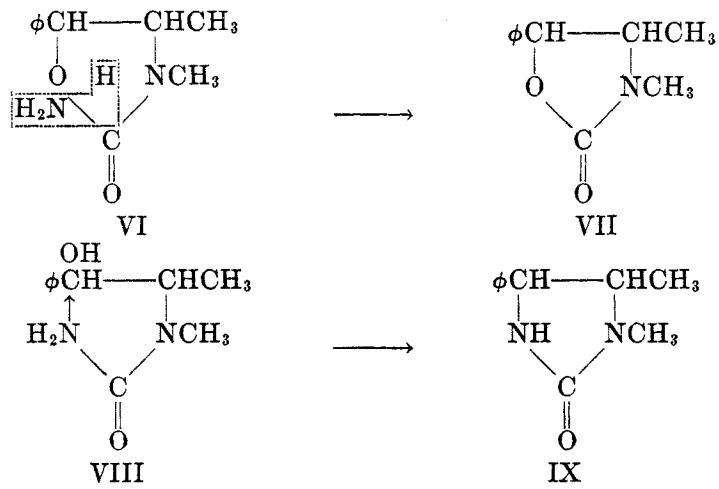
Freudenberg and coworkers (3) had denied that any restricted rotation existed. Recently Welsh (9), interpreting the concept in its strictest sense, also denied its existence on the basis of molecular models. The latter author preferred to explain his data, which was similar to that of Fodor, on the basis of the "differences in the spatial arrangements of the groups in the diastereomers." Welsh concluded that the phenyl and methyl groups in both ephedrine and pseudoephedrine[2] tended to orient themselves *trans* to each other.



The viewpoints of both Fodor and Welsh can be made consistent by assigning the conformations represented by Figures IV and V for (−)-ephedrine and (+)-pseudoephedrine, respectively. These forms preserve the relative configurations established for these molecules.

Experimental evidence of a different type has now been obtained in these laboratories which lends further support to the conformations shown. In the preparation of 2-oxazolidones by the fusion of urea with *beta*-aminoalcohol hydrochlorides, it was found that whereas (+)-pseudoephedrine gave the normal product (VII), *dl*-ephedrine gave an imidazolidone (IX). This difference in behavior can be rationalized by a consideration of the probable mechanism of the urea fusion. At the temperature of the reaction (170–210°) the urea breaks down to cyanic acid, which attacks the basic group to give the intermediate ureido derivative (VI or VIII). Now if the terminal amino group can be brought into close proximity with the hydroxyl group (as in VI), interaction occurs with the formation of the oxazolidone, as shown. Where it is relatively more difficult to bring these groups together (as in VIII), a rearward attack on the carbon atom carrying the hydroxyl group occurs by an S_N2 mechanism, resulting in expulsion of the hydroxyl group. The experimental evidence indicates that (−)-ephedrine corresponds to VIII (and, therefore, to IV), whereas (+)-pseudoephedrine corresponds to VI (and, therefore, to V).

[2] In terms of the usual conventions, Figures III and IV in Welsh's paper represent, respectively, (−)-pseudoephedrine and (+)-ephedrine.



It should not be inferred that the conformations assigned are the only possible geometrical arrangements. Rather, they should be viewed as the most probable arrangements in the resting state of the molecules, or the arrangements which represent the lowest energy states. Although it is probable that similar conformations apply to the norephedrine derivatives (*cf.* Fodor), this could not be demonstrated by the method described above. *dl*-Norephedrine gave the normal oxazolidone. It would appear that the difference in energy levels between the various possible conformations in the *nor*-series is less than in the ephedrine series, and interconversion is accomplished with relatively greater ease. This might be expected in view of the hindering effect of the N-methyl group.

Acknowledgment. The author wishes to thank Drs. R. L. Shriner, M. A. Spielman, and A. L. Wilds, who were kind enough to read the manuscript and offer suggestions for its improvement. It is a pleasure also to acknowledge the assistance of E. F. Shelberg and his staff, who obtained the analytical data.

EXPERIMENTAL[3]

1,5-Dimethyl-4-phenyl-2-imidazolidone (IX). Forty grams of *dl*-ephedrine hydrochloride was mixed with 36 g. of urea and heated for one-half hour at 170–175° followed by one hour at 200–210°. The cooled mixture was treated with water, and the somewhat oily solid which precipitated was washed with 5% hydrochloric acid and water. Recrystallization from alcohol gave 11.8 g., m.p. 140–144°, and 6.6 g., m.p. 139–143° (48%). Further recrystallization brought the melting point to 144.5–145°.

Anal. Calc'd for $C_{11}H_{14}N_2O$: C, 69.5; H, 7.4; N, 14.7.
Found: C, 69.7; H, 7.1; N, 14.6.

Attempts to crystallize the oxazolidone from the filtrate gave only additional small amounts of the imidazolidone. The oily residues were finally distilled at 202–204° (14 mm.). Analysis of the distillate indicated that it contained substantial amounts of the oxazolidone.

Anal. Calc'd for $C_{11}H_{14}N_2O$ (imidazolidone): N, 14.7.
Calc'd for $C_{11}H_{13}NO_2$ (oxazolidone): N, 7.3. Found: N, 10.0.

[3] All melting points are uncorrected.

3,4-Dimethyl-5-phenyl-2-oxazolidone (VII). The procedure described above was followed with 20.2 g. of (+)-pseudoephedrine hydrochloride. The oil which precipitated upon treatment with water was taken up in ether and washed with 5% hydrochloric acid and water. Concentration of the solution gave an oil which solidified readily in Skellysolve B and ether. Fourteen grams (73%) of material melting at 45–49° was obtained. Continued recrystallization from the same solvents brought the melting point to 50–51°.

Anal. Calc'd for $C_{11}H_{13}NO_2$: N, 7.3. Found: N, 7.5.

4-Methyl-5-phenyl-2-oxazolidone. A mixture of 3.6 g. of *dl*-norephedrine hydrochloride and 2.3 g. of urea was treated in the same manner as described. The solid which separated upon the addition of water was extracted with large volumes of ether to remove a small amount of ether-insoluble material. The ether extracts yielded 1.1 g., m.p. 144–146°, and 1.0 g., m.p. 140–143° (62%). An analytically pure sample melted at 146–146.5°. Homeyer (12) records 145–146°.

Anal. Calc'd for $C_{10}H_{11}NO_2$: N, 7.9. Found: N, 7.9.

SUMMARY

It has been found that the fusion of ephedrine with urea gives rise to an imidazolidone, whereas pseudoephedrine yields an oxazolidone. From these data the conformation of the ephedrines is deduced.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE CHEMOTHERAPY OF CANCER. I. SOME ALKOXYMETHYLENE-1-TETRALONES[1]

KENNETH N. CAMPBELL, ALBERT SCHRAGE,[2,3] AND BARBARA K. CAMPBELL[4]

Received December 27, 1949

The alkaloid colchicine has long been known to be a mitotic poison, (1, 2) and as such, acts as a tumor-growth inhibitor in cancer. Although its high toxicity precludes its use in the treatment of human cancer, it is possible that simpler analogs of colchicine might retain some of the growth-inhibitory properties, while losing some of the toxicity of the alkaloid, and a good deal of work is being done in various laboratories on such analogs.

For many years the accepted structure for colchicine was that proposed by Windaus, I (3). On the basis of this structure, it was postulated (4) that the growth-inhibitory properties of colchicine are due to the diarylethylamine chain, and it has been found (4, 5) that simpler diaryl-ethyl- and -propylamines do have some growth-inhibitory action. It seemed to us, however, that the highly unsaturated "C" ring of colchicine might also be responsible, at least in part, for the mitotic poisoning activity. Many compounds with conjugated olefinic and carbonyl groups are growth-inhibitors in one degree or another; as examples may be cited the benzo- and naptho-quinones (6), the unsaturated lactones protoanemonin and hexenolactone (7, 8), and certain α, β-unsaturated ketones (8). It seemed of interest, therefore, to prepare compounds modeled after the "C" ring of colchicine for testing as tumor-growth inhibitors, and as the present work was started before the evidence in support of the tropolone structure of colchicine (II) (10) appeared, the compounds reported in this paper and the next are based on the Windaus structure (I).

In the present paper several derivatives of 2-hydroxymethylene-1-tetralone (III) are described.

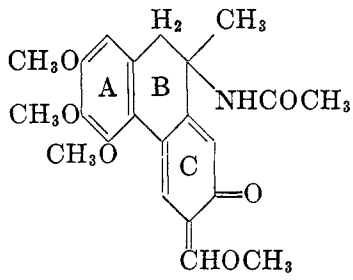
Although 1-tetralone itself can be prepared (in rather poor yield) by oxidation of tetralin, the best route to bz-substituted 1-tetralones is by cyclization of the γ-arylbutyric acids. The 1-tetralones are readily converted, in 50–75% yields, to the 2-hydroxymethylene derivatives by condensation with ethyl formate in the presence of sodium ethoxide (11). The hydroxymethylene compounds are unstable to air, but may be purified by high-vacuum distillation.

[1] This investigation was supported (in part) by a research grant from the National Cancer Institute, U. S. Public Health Service, and the compounds are being tested at the Institute.

[2] Abstracted from the Ph.D. thesis of Albert Schrage, University of Notre Dame, June, 1949.

[3] Reilly Fellow, 1947–1949. Present address: Wellcome Research Laboratories, Tuckahoe, New York.

[4] Present address, Indiana University, South Bend, Indiana.



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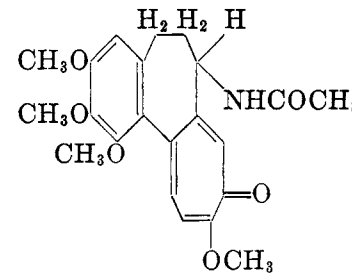
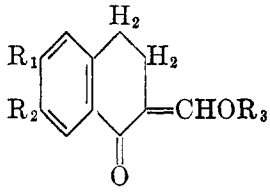


II



(a) $R_1 = R_2 = H; R_3 = C_2H_5$
(b) $R_1 = R_2 = H; R_3 = CH(CH_3)_2$
(c) $R_1 = H, R_2 = CH_3O, R_3 = C_2H_5$
(d) $R_1 = R_2 = CH_3O, R_3 = C_2H_5$

III

Alkylation of a hydroxymethylene ketone can occur either on the oxygen or on the carbon atom of the >C=CHOH system. Johnson and Posvic (12) have shown that methylation of these compounds with methyl iodide in the presence of potassium carbonate gives a high proportion of the C-methyl product. Since in the present work the O-alkyl derivative was the desired one, other methylating agents were investigated, including diazomethane, methyl sulfate under varying conditions, and methanol in the presence of a trace of acid, but we were unable to obtain appreciable yields of a stable O-methyl ether. As Johnson and Posvic have pointed out, isopropyl iodide gives a much higher proportion of O-alkylation. This has also been found true for ethyl iodide, and the O-ethyl ethers were obtained in fair yield by the action of ethyl iodide and potassium carbonate in anhydrous acetone, according to the general procedure of Claisen as described by Auwers (13). These ethers did not give an immediate color with ferric chloride but on standing with aqueous ferric chloride some hydrolysis to the free hydroxymethylene compound occurred, and the typical enol color developed.

Some of the compounds prepared in this work have been screened against sarcoma 37 in the mouse, at the National Cancer Institute. While they were found to be much less toxic than colchicine, they also showed much less growth-inhibitory action. The work is being continued, and compounds modeled after the recently proposed seven-membered "C" ring structure of colchicine (9, 10) are being synthesized.

EXPERIMENTAL[5, 6]

5-Tetralones. 1-Tetralone itself was prepared by air-oxidation of tetralin (14) but the best yield obtained was only 30%, instead of the 44–56% reported. γ-(*p*-Methoxyphenyl)-

[5] Analyses carried out by Mr. Charles Beazley, Micro-Tech Laboratories, Skokie, Illinois.

[6] All melting points are uncorrected.

butyric acid (15) was cyclized by phosphorus pentoxide in benzene to give a 32% yield of 7-methoxy-1-tetralone, m.p. 60–61° (16), and γ-(3′,4′-dimethoxyphenyl)butyric acid was cyclized to 6,7-dimethoxy-1-tetralone, m.p. 99°, in 58% yield by the procedure of Haworth and Marvin (17).

2-Hydroxymethylene-1-tetralones. The procedure was similar to that developed by Johnson and Shelberg (11) for related compounds. Ethyl formate (0.1 mole) was added to alcohol-free sodium ethoxide (from 0.1 gram-atom of sodium and 0.1 mole of absolute ethanol) in dry benzene and the resulting suspension was treated with 0.05 mole of the tetralone in an atmosphere of dry nitrogen. The reaction mixture was stirred at room temperature for 24 hours, evaporated to dryness under reduced pressure, and the residue dissolved in 10% aqueous sodium hydroxide and extracted with ether to remove non-acidic impurities. The aqueous layer was acidified with 2 *N* hydrochloric acid at 5–10° and repeatedly extracted with ether. The combined ether extracts were dried over magnesium sulfate, evaporated, and the residue distilled at *ca.* 0.1 mm. It was essential to avoid exposure to air throughout the preparation.

2-Hydroxymethylene-1-tetralone was obtained in 78% yield as a light yellow oil, b.p. 124–128°/4 mm., n_D^{20} 1.6232–1.6245. Auwers and Weigand (18) reported b.p. 153–154°/10 mm., n_α^{18} 1.6246.

2-Hydroxymethylene-7-methoxy-1-tetralone, formed a yellow oil, b.p. 115–120°/0.1 mm. The yield was 63%.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.37; H, 5.93.
Found: C, 70.16; H, 6.11.

2-Hydroxymethylene-6,7-dimethoxy-1-tetralone, was obtained in 75% yield as straw-colored crystals (from high-boiling petroleum ether) m.p. 147–150°.

Anal. Calc'd for $C_{13}H_{14}O_4$: C, 66.65; H, 6.02.
Found: C, 66.08; H, 5.90.

Ethers of 2-hydroxymethylene-1-tetralones. The general procedure was similar to that described by Auwers (13). A mixture of 0.05 mole of the hydroxymethylenetetralone, 0.05 mole of anhydrous potassium carbonate, and 0.08 mole of alkyl iodide in 25 ml. of dry acetone was refluxed for 24 hours. The mixture was cooled, diluted with two volumes of dry ether, filtered from potassium iodide, the solvents removed, and the residue purified by molecular distillation; this did not permit determination of the boiling points. The products obtained gave slowly developing colors with ferric chloride, but only a very slight instantaneous color, indicating that they were largely, if not entirely, the O-alkyl ethers.

2-Ethoxymethylene-1-tetralone (IIIa) was obtained in 40% yield as a light yellow oil by distillation at 0.005 mm. (bath temperature 110–125°). It had n_D^{20} 1.5824. Auwers and Weigand (18) reported b.p. 170–171°/10 mm., n_α^{18} 1.5853. The material obtained in the present work appeared to be largely the O-ethyl ether.

Anal. Calc'd for $C_{13}H_{14}O_2$: C, 77.20; H, 6.98.
Found: C, 77.52; H, 7.30.

2-Isopropoxymethylene-1-tetralone (IIIb) distilled at 0.005 mm. (bath temperature 115–120°). The yield of oil, n_D^{20} 1.5847, was 79%.

Anal. Calc'd for $C_{14}H_{17}O_2$: C, 77.75; H, 7.46.
Found: C, 77.92; H, 7.68.

2-Ethoxymethylene-7-methoxy-1-tetralone (IIIc) was obtained as a yellow oil after two distillations at 0.008 mm. (bath temperature 95–120°). The oil solidified, and after recrystallization from petroleum ether (b.p. 30–60°) formed white crystals, m.p. 86–87.5°, which gave a slowly developing color with ferric chloride. The yield was 55%.

Anal. Calc'd for $C_{14}H_{16}O_3$: C, 72.39; H, 6.94.
Found: C, 72.38; H, 6.92.

2-Ethoxymethylene-6,7-dimethoxy-1-tetralone (IIId) was obtained as white needles, m.p. 98.5–100° from petroleum ether (b.p. 90–120°); yield, 40%.

Anal. Calc'd for $C_{15}H_{18}O_4$: C, 68.68; H, 6.92.
Found: C, 68.35; H, 6.92.

SUMMARY

Several alkoxymethylene derivatives of 1-tetralones have been prepared for testing as tumor-growth inhibitors.

NOTRE DAME, INDIANA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF NOTRE DAME]

THE CHEMOTHERAPY OF CANCER. II. SOME ARYL-SUBSTITUTED ALKOXYMETHYLENE CYCLOHEXENONES[1, 2]

KENNETH N. CAMPBELL, ALBERT SCHRAGE[3], AND BARBARA K. CAMPBELL[4]

Received December 27, 1949

In continuation of our work (1) on chemotheraputeic agents for cancer, it seemed of interest further to explore compounds related to the unsaturated C ring of colchicine, since this ring may be responsible, in part at least, for the mitotic-poisoning activity of the alkaloid. The Windaus structure (I) for colchicine can be regarded as that of a methoxymethylene aryl-substituted cyclohexadienone where the two rings are linked together by a saturated two-carbon chain. It appeared worthwhile to prepare compounds as closely related to this structure as possible. Meyer and Reichstein (2) have prepared 3-methoxymethylene-4-ketotetrahydrophenanthrene (II) and 2-methoxymethylene-1-ketotetrahydrophenanthrene, but their synthesis did not appear to be easily adaptable to derivatives with one or more alkoxyl groups on the benzene ring. Neither did it seem feasible to prepare hydroxymethylenecyclohexadienones, since these would probably exist almost entirely in the isomeric salicylaldehyde form and therefore could not be alkylated in the desired way.

The method of Horning and Field (3), however, provided an excellent route to a variety of aryl cyclohexenones of the general structure III, starting from readily available aldehydes. These 3-methyl-5-aryl-2-cyclohexen-1-ones were condensed with ethyl formate and the resulting hydroxymethylene ketones, which were usually obtained as non-crystallizable dark red oils, were etherified directly to IV with ethyl iodide and potassium carbonate in dry acetone.

Some of these compounds have been tested against mouse sarcoma 37 at the National Cancer Institute, and have shown little or no activity. Steinegger and Lavan (4) who tested the Meyer-Reichstein compounds for anti-mitotic action found that 3-hydroxymethylene-4-ketotetrahydrophenanthrene showed activity, but the methyl ether did not.

EXPERIMENTAL[5, 6]

3-Methyl-5-aryl-2-cyclohexen-1-ones. These were prepared from the aromatic aldehydes by condensation with acetoacetic ester, cyclization, and decarboxylation without isolation of any of the intermediates, using the procedure described by Horning and Field (3) for the 5-*p*-methoxyphenyl compound.

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[1] Abstracted from Ph.D. thesis of Albert Schrage, University of Notre Dame, June, 1949.

[2] This investigation was supported (in part) by a research grant from the National Cancer Institute, U.S. Public Health Service, and the compounds are being tested at the National Cancer Institute.

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[4] Present address, Indiana University, South Bend, Indiana.

[5] Analyses carried out by Mr. Charles Beazley, Micro-Tech Laboratories, Skokie, Illinois

[6] All melting points are uncorrected.

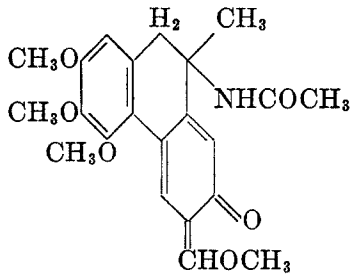
3-Methyl-5-(p-methoxyphenyl)-2-cyclohexen-1-one (IIIa) was obtained in 66% yield, b.p. 168–170°/0.8 mm., m.p. 63° (3).

3-Methyl-5-(3',4'-dimethoxyphenyl)-2-cyclohexen-1-one, (IIIb) b.p. 190°/1.2 mm., was obtained as a light yellow solid, m.p. 90–91° after recrystallization from ethyl acetate-petroleum ether (b.p. 30–60°) mixture. The yield was 22%.

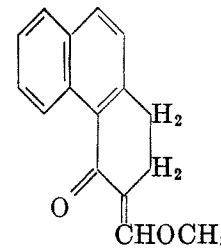
Anal. Calc'd for $C_{15}H_{18}O_3$: C, 73.15; H, 7.39.

Found: C, 73.11; H, 7.45.

3-Methyl-5-(3',4'-methylenedioxyphenyl)-2-cyclohexen-1-one (IIIc) was obtained in 11% yield from piperonal. It had b.p. 201°/2 mm., m.p. 84°, in agreement with Knoevenagel and Hoffmann's value (5).



I



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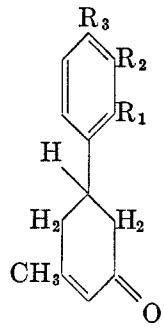
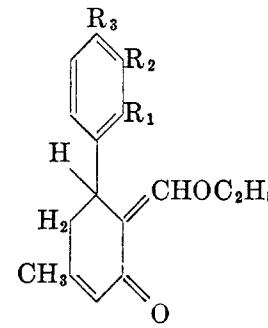


III



IV

(a) R_1, R_2 = H; R = CH_3O
(b) R_1 = H; R_2 and R_3 = CH_3O
(c) R_1 = H; R_2—R_3 = —OCH_2O—
(d) R_1, R_2, R_3 = CH_3O

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-2-cyclohexen-1-one (IIId). 2,3,4-Trimethoxybenzaldehyde was prepared in 90% yield from pyrogallol trimethyl ether as described by Slotta and Heller (6); b.p. 150–155°/10 mm., m.p. 26–28°. It was condensed with acetoacetic ester and converted to the cyclohexenone in 40% yield. The product boiled at 175–180°/0.5 mm. and solidified to light yellow crystals which melted at 101–102° after recrystallization from ethyl acetate-pretroleum ether.

Anal. Calc'd for $C_{16}H_{20}O_4$: C, 69.54; H, 7.30.

Found: C, 69.40; H, 7.47.

3-Methyl-5-aryl-6-ethoxymethylene-2-cyclohexen-1-ones. The cyclohexenones were condensed with ethyl formate in the presence of sodium ethoxide as described previously (1) except that the hydroxymethylene ketones could not be distilled even in a high vacuum, without decomposition. With one exception they could not be crystallized, either, and

therefore the crude red oils were etherified without purification by treatment with ethyl iodide and potassium carbonate in anhydrous acetone. The ethoxymethylene compounds were purified by molecular distillation. They did not give an immediate color with aqueous ferric chloride, but on long standing with the reagent the typical enol color developed.

3-Methyl-5-(p-methoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVa) was obtained as light yellow oil which was purified by distillation at 10^{-5} mm.; the yield was 20%.

Anal. Calc'd for $C_{17}H_{20}O_3$: C, 74.97; H, 7.40.
Found: C, 74.97; H, 7.29.

3-Methyl-5-(3',4'-dimethoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVb). This was obtained in 21% yield as a light yellow oil.

Anal. Calc'd for $C_{18}H_{22}O_4$: C, 71.50; H, 7.34.
Found: C, 71.1; H, 7.36.

3-Methyl-5-(3,4-methylenedioxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVc). This was prepared as described previously; the yield of light yellow oil was 20%.

Anal. Calc'd for $C_{17}H_{18}O_4$: C, 71.3; H, 6.34.
Found: C, 71.07; H, 6.50.

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-6-hydroxymethylene-2-cyclohexen-1-one. This was the only hydroxymethylene compound which crystallized. It formed yellow prisms, m.p. 97.5–99.5° from hexane; yield 76%.

Anal. Calc'd for $C_{17}H_{20}O_5$: C, 67.09; H, 6.62.
Found: C, 67.05; H, 6.37.

3-Methyl-5-(2',3',4'-trimethoxyphenyl)-6-ethoxymethylene-2-cyclohexen-1-one (IVd). This was obtained in 75% yield as a light orange oil which solidified on treatment with ethyl acetate-hexane mixture to yellow needles, m.p. 105–106°.

Anal. Calcd for $C_{19}H_{24}O_5$: C, 68.66; H, 7.28.
Found: C, 68.80; H, 7.47.

SUMMARY

Several 3-methyl-5-aryl-6-ethoxymethylene-2 cyclohexen-1-ones have been prepared as possible tumor-growth inhibitors.

NOTRE DAME, INDIANA

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SYNTHESIS OF THE THREE TRIMETHYL- AND CERTAIN OTHER POLYALKYL-BENZENES

J.E. NICKELS AND W. HEINTZELMAN

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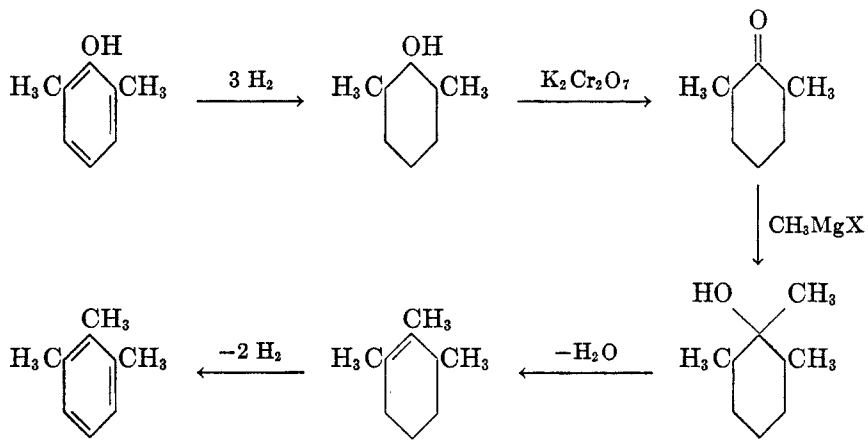
For the development of a spectrographic method of analysis of mixtures of polyalkylbenzene isomers and for a chemical study of the individual isomers and their mixtures, it was necessary to prepare authentic samples of the pure hydrocarbons in quantity for use as reference standards. In the preparation of such authentic compounds it is essential to employ a method of synthesis that avoids reactions that may possibly result in the formation of isomer mixtures. This paper describes a synthesis of the three trimethylbenzene isomers (hemimellitene, pseudocumene, and mesitylene), *o*-diethylbenzene, *m*-xylene, and 1,2,4-triethylbenzene by a method that gives the specific polyalkylbenzene isomer desired in high purity and in good yields. Although the method was used for making polyalkylbenzenes having like alkyl groups, it is equally suitable for the preparation of polyalkylbenzenes containing mixed groups, such as ethyltoluenes and ethylxylenes.

This synthesis involves a combination of known reactions which apparently has not been applied to the preparation of pure polyalkylbenzene isomers from alkylphenols as the starting materials. It comprises the following five distinct steps: (a) hydrogenation of the alkylphenol to an alkylcyclohexanol, (b) oxidation of the cyclohexanol to a ketone, (c) Grignard reaction of the ketone with alkylmagnesium halide, (d) dehydration of the tertiary alcohol to a polyalkylcyclohexene, and (e) dehydrogenation of the latter to a polyalkylbenzene. Although this method may give intermediates comprising geometric and structural isomer mixtures, the product of the final step is a single polyalkylbenzene isomer. The following equations illustrate the synthesis of 1,2,3-trimethylbenzene by this five-step method:



The yields of polyalkylbenzenes obtained by this method were, in general, better than those reported for other methods. For example, the yields of hemimellitene, pseudocumene, and mesitylene were 43, 57, and 61%, respectively, as compared with yields of 24% (1), 35–55% (2, 3, 4) and 14–33% (5, 6), respectively, reported in the literature for other synthetic methods.

TABLE I

ALKYLCYCLOHEXANOL INTERMEDIATES[a]

COMPOUND	B.P.,[b] °C. (20 mm.)	n_D^{20}	d_4^{20}	YIELD,[c] %
2,6-Dimethylcyclohexanol	76–78	1.4600	0.9231	94
3,4-Dimethylcyclohexanol	94	1.4623	.9161	94
3,5-Dimethylcyclohexanol	91	1.4550	.8977	93
2-Ethylcyclohexanol	88–90	1.4660	.9246	93
3-Methylcyclohexanol	82	1.4570	.9158	92
2,4-Diethylcyclohexanol	111.5	1.4658	—	93

[a] Probably mixtures of geometric isomers. [b] Uncorrected distillation temperatures. Based on the alkylphenol.

TABLE II

ALKYLCYCLOHEXANONE INTERMEDIATES[a]

COMPOUND	B.P.,[b] °C. (20 mm.)	n_D^{20}	d_4^{20}	YIELD,[c] %
2,6-Dimethylcyclohexanone	69	1.4470	0.9102	93
3,4-Dimethylcyclohexanone	81	1.4520	.9161	93
3,5-Dimethylcyclohexanone	75	1.4434	.8940	92
2-Ethylcyclohexanone	76	1.4522	.9190	86
3-Methylcyclohexanone	64	1.4460	.9155	88
2,4-Diethylcyclohexanone	104	1.4541	.9021	90

[a] Probably mixtures of geometric isomers. [b] Uncorrected distillation temperatures. [c] Based on the alkylcyclohexanol.

EXPERIMENTAL

Materials. The alkylphenols were, with the exceptions noted, Eastman Kodak Co. chemicals that had been upgraded by distillation and/or crystallization. 2,6-Xylenol was obtained from the Edcan Laboratories. *o*-Ethylphenol was separated from a mixture of ethylphenol isomers by fractional distillation while 2,4-diethylphenol was prepared by Clemmensen reduction of 2-acetyl-4-ethylphenol, obtained by the Fries rearrangement (7) of the acetate of *p*-ethylphenol (8). Hydrogenations were accomplished by means of a powdered nickel catalyst (9) which had been previously reduced at 425° in hydrogen. A 15% chromia-85% alumina catalyst (10) in the form of $\frac{1}{8}'' \times \frac{1}{8}''$ pills was used for the vapor-phase dehydrogenations.

Procedure. The purified alkylphenols (*ca.* 1 kg.) in the presence of about 5% of nickel catalyst, were hydrogenated at 700–1500 p.s.i. and 150–175° in a rotating autoclave of the Ipatieff type fitted with a glass liner. The alkylcyclohexanols (Table I) were isolated from the filtered catalyzates by fractionation at 20 mm. through a 27-plate, all-glass distillation column packed with glass helices.

For oxidation of the alkylcyclohexanols to alkylcyclohexanones, Sandborn's menthol oxidation method (11) was modified by adding the acid-dichromate solution to the stirred alkylcyclohexanols (instead of the reverse) at such a rate as not to exceed a reaction temperature of 60°. This modification decreased the formation of troublesome emulsions during the subsequent extraction of the ketones with ether and also increased the yields of the ketones by 5–15%. In one instance, when the oxidized mixture remained at room temperature for a day before extraction, a low yield of only about 70–75% was realized. The alkylcyclohexanones (Table II) were purified by fractional distillation through the 27-plate column at 20 mm.

TABLE III

POLYALKYLCYCLOHEXENE INTERMEDIATES[a]

COMPOUND	B.P.,[b] °C. (740 mm.)	n_D^{20}	d_4^{20}	YIELD,[c] %
1,2,3-Trimethylcyclohexene-1	151	1.4641	0.8347	80
1,3,4-Trimethylcyclohexene-1	144	1.4546	.8124	82
1,3,5-Trimethylcyclohexene-1	139	1.4468	.7970	87
1,2-Diethylcyclohexene-1	170.5	1.4635	.8451	88
1,3-Dimethylcyclohexene-1	124.5	1.4493	.8051	88
1,2,4-Triethylcyclohexene-1	98[d]	1.4644	.8370	92

[a] Probably a mixture of geometric and structural isomers. [b] Uncorrected distillation temperatures. [c] Based on the alkylcyclohexanone. [d] Distilled at 20 mm.

TABLE IV

POLYALKYLBENZENE ISOMERS

COMPOUND	B.P.,[a] °C., (740 mm.)	n_D^{20}	d_4^{20}	F.P.,[b] °C.	PURITY,[c] MOLE-%	YIELD,[d] %	OVER-ALL YIELD,[e] %
1,2,3-Trimethylbenzene	170.5	1.5131	0.8943	−26.0	99.0	62	43
1,2,4-Trimethylbenzene	164	1.5047	.8758	−44.9	96.9	80	57
1,3,5-Trimethylbenzene	160	1.4993	.8653	−52.6	98.2	82	61
1,2-Diethylbenzene	177	1.5039	.8797	−32.7	95.7	45	32
1,3-Dimethylbenzene	135.5	1.4969	.8640	−48.2	99.1	80	57
1,2,4-Triethylbenzene	106.5[f]	1.5024	.8738	—[g]	—	53	41

[a] Uncorrected distillation temperatures. [b] Determined in a simplified freezing point apparatus (14, 15) using a copper-constantan thermocouple. [c] Computed from observed freezing points and published data (16, 17). [d] Based on the polyalkylcyclohexene. [e] Based on the starting alkylphenol. [f] Distilled at 20 mm. [g] Forms a "glass" at −78°.

The usual Grignard procedure with ketones was followed; the reaction product was hydrolyzed with dilute sulfuric acid and crushed ice. The resulting ether-extracted tertiary alcohol was usually dehydrated without prior distillation, since some of these alcohols dehydrated partially on distillation. Consequently, the yields of these tertiary alcohols were not determined. Only one of these alcohols, *1,2-diethylcyclohexanol* (b.p. 86.5° at 10 mm.; n_D^{20} 1.4691; d_4^{20} 0.9198; yield, 89%), was isolated and purified.

Dehydration of the tertiary alcohols was accomplished in nearly theoretical yields by following a procedure based on either Cook's (12) conversion of 1-naphthyldimethylcarbinol to 1-isopropenylnaphthalene or the alcohol dehydration method of Bachman and Finholt (13). In the first method the tertiary alcohol was refluxed with an ethanol-hydrochloric acid solution (about 30 ml. of concentrated acid and 750 ml. of ethanol per mole of tertiary

alcohol) for 6–10 hours, the product was diluted with a large excess of water and the insoluble olefin layer was separated. In the second method the alcohol was heated with sodium bisulfate and phosphorus pentoxide (about 4 g. of sodium bisulfate and 6 g. of phosphorus pentoxide per mole of tertiary alcohol) at about 210° under such pressure that the olefin and water (but not alcohol) distilled. The resulting polyalkylcyclohexenes (Table III) were dried and fractionated in the 27-plate column at atmospheric pressure.

The polyalkylcyclohexenes were dehydrogenated to the corresponding polyalkylbenzenes in the vapor phase at 525° and 0.5 liquid hourly space velocity (volume of liquid per volume

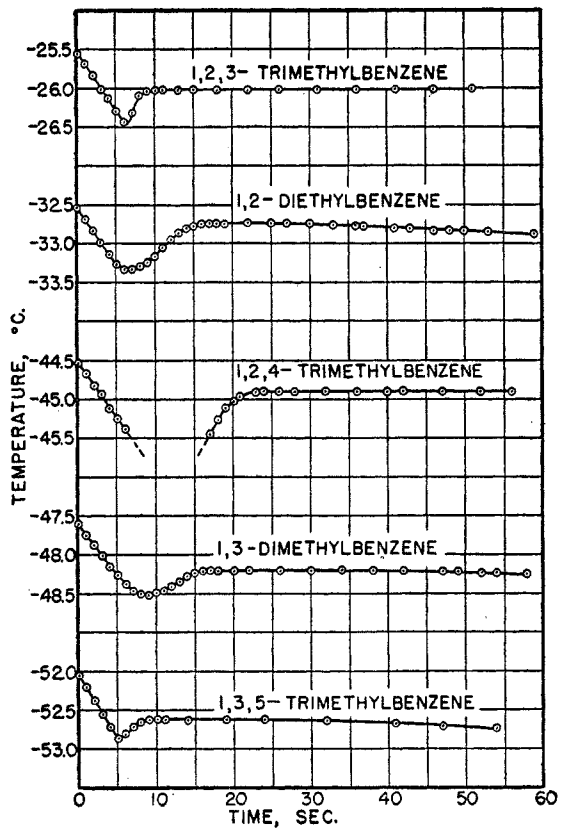


FIGURE 1. FREEZING-POINT CURVES OF POLYALKYLBENZENES

of catalyst per hour), using the equipment and general technique described for the dehydrogenation of isopropylbenzene to α-methylstyrene (10). The liquid catalyzates were distilled through the 27-plate column to effect preliminary purification of the polyalkylbenzenes. The polyalkylbenzenes (Table IV) were further purified by refluxing over sodium at atmospheric pressure for 8–10 hours and by finally fractionating at a reflux ratio of at least 10 to 1 through a 43-plate all-glass distillation column packed with glass helices. The freezing curves (Figure 1) of the polyalkylbenzenes are indicative of their purity.

SUMMARY

1. A five-step, improved synthesis for polyalkylbenzenes was applied to the preparation of the three trimethylbenzenes (hemimellitene, pseudocumene, and mesitylene), *o*-diethylbenzene, *m*-xylene, and 1,2,4-triethylbenzene.

2. The intermediate alkylcyclohexanols, alkylcyclohexanones, and polyalkylcyclohexenes were isolated and characterized by boiling point, refractive index, and density.

PITTSBURGH 13, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, EMORY UNIVERSITY]

THE ACYLATION OF OLEFINS. I. THE ACETYLATION OF CYCLOHEXENE[1]

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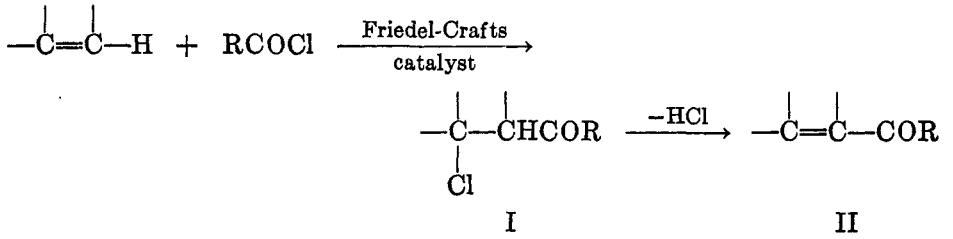
Received March 20, 1950

The acylation of olefins with acyl halides under the influence of Friedel-Crafts type catalysts is a general reaction (1).



I II

Depending upon the catalyst used, the temperature, and other experimental conditions, the product isolated from the acylation reaction may be the chloroketone, I, the unsaturated ketone, II, or a mixture of the two. Standard practice in application of this reaction to the preparation of α,β-unsaturated ketones is to effect (or complete) the dehydrohalogenation of the crude reaction product by heating with dimethylaniline (2), sodium carbonate (3), aluminum chloride (4), or other dehydrohalogenating agent. Aluminum chloride and stannic chloride have been most frequently used as catalysts for the acylation of olefins with acyl halides. Despite the apparent generality of the olefin acylation reaction under the influence of Friedel-Crafts type catalysts, presently published information does not permit its classification as a standard synthetic procedure. There is little agreement in the published literature as to the best experimental conditions for application of the reaction to a given olefin, nor as to the results to be expected from application of a given procedure. The reaction has other drawbacks which will be discussed later in the present paper. A general investigation of the acylation of olefins has been undertaken in this laboratory with the object of developing simple, dependable procedures for the conversion of for the conversion of olefins to pure α,β-unsaturated ketones. In the present paper, we wish to report the results of our study of the acetylation of cyclohexene to 1-acetylcyclohexene.

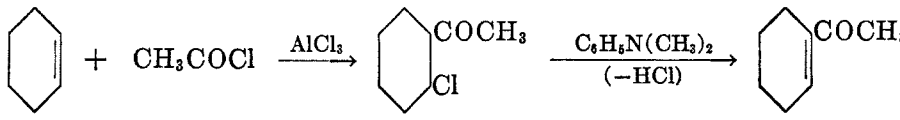
Acetylation of cyclohexene with acetyl chloride. Darzens (2), in 1910, added

[1] Presented in part before the Organic Section, Meeting-in-Miniature of the Georgia Section, American Chemical Society, November 18, 1949.

[2] This paper is taken from a thesis presented by C. M. Hendry to the Graduate Faculty of Emory University in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1950.

[3] Recipient of a grant from the Chemistry Scholarship Fund of the New York Community Trust, administered by Mr. Ralph Hayes, 1949–1950.

aluminum chloride to a solution of acetyl chloride and cyclohexene in carbon disulfide at 0°, and obtained a saturated chloroketone, III, which on treatment with dimethylaniline eliminated hydrogen chloride with formation of 1-acetylcyclohexene, IV.



III IV

The yield of the unsaturated ketone was reported as 42%. Wieland and Bettag (4) reported that at a lower reaction temperature, −18°, the chloroketone, III, is the principal product of the reaction. The latter workers converted the chloroketone into 1-acetylcyclohexene in 60% yield[4] by warming with a small amount of aluminum chloride in carbon disulfide solution. More recent workers have followed the general directions of Darzens and of Wieland and Bettag for acylation of cyclohexene. Thus, Christ and Fuson (3) report the formation of 1-acetylcyclohexene in 62% yield by addition of acetyl chloride to cyclohexene essentially according to the procedure of Wieland and Bettag followed by distillation of the crude chloroketone from sodium carbonate to effect dehydrohalogenation. Nightingale, Milberger, and Tomisek (5) have applied the Wieland and Bettag procedure to the synthesis of several 1-acylcyclohexenes. These workers reported that they were unable to effect complete dehydrohalogenation of the intermediate chloroketones by distillation from sodium carbonate, but that heating for two hours with dimethylaniline at 180° did give chlorine-free products. Colonge and his associates (6, 7) have reported that cyclohexene, as well as other olefins, may be acylated in excellent yields by the use of acid chlorides in the presence of very small amounts of stannic chloride. The use of catalytic amounts of the catalyst is in distinct contrast to the customary (8) employment of somewhat more than one molecular proportion of catalyst in the usual Friedel-Crafts acylation of aromatics with acyl halides.

We have investigated the acetylation of cyclohexene with acetyl chloride using aluminum chloride, zinc chloride, and stannic chloride as catalysts under a variety of experimental conditions. Stannic chloride was easier to handle and gave the smoothest reactions of any of the three catalysts used. We have been unable to reproduce the high yields of 1-acetycyclohexene reported by Christ and Fuson; an attempt to duplicate exactly their described procedure (3) gave only a 37.9% yield. We were also unable to confirm the report of Colonge and associates (6, 7) that catalytic amounts of stannic chloride may be used to effect acylation of alkenes; the use of small ratios of stannic chloride to cyclohexene gave low yields of 1-acetylcyclohexene roughly proportional to the amount of catalyst used. Despite the failure of the reaction to proceed satis-

[4] The yield reported by Wieland and Bettag apparently refers to the dehydrohalogenation step only; this dehydrohalogenation was run on a very small scale. Examination of the figures reported by Wieland and Bettag shows that the over-all yield of 1-acetylcyclohexene from cyclohexene was not greater than 40–50%, perhaps closer to the lower figure.

factorily to completion in the presence of really catalytic amounts of stannic chloride, it was found that a full molecular proportion of stannic chloride is unnecessary. Our best results were obtained using 0.25–1.0 moles of stannic chloride per mole of acetyl chloride with a reaction period of one hour at 0–20° (36.3–40.2% yields).

Chlorocyclohexane was found to be an important by-product from all acetylations of cyclohexene with acetyl chloride; with zinc chloride as catalyst, this by-product accounted for as much as 30% of the cyclohexene reacted. The chlorocyclohexane probably results from addition of hydrogen chloride, eliminated during the reaction from the chloroketone, III, to unreacted cyclohexene. This side reaction has been previously mentioned (7, 9, 10) in the literature, but no indication has been given of its relative importance. It is known (11) that the addition of hydrogen halides to olefins is catalyzed by Friedel-Crafts catalysts.

In agreement with the observation of Nightingale and co-workers (5), we found that the 1-acetylcyclohexene resulting from acetylation of cyclohexene with acetyl chloride and dehydrohalogenation of the crude reaction product with sodium carbonate, even after careful fractionation, contained considerable chlorine. We were also unable to effect complete dehydrohalogenation of the products of acetylation with acetyl chloride by heating with dimethylaniline at 180° for three hours. Indeed, none of our samples of 1-acetylcyclohexene prepared by acetylation of cyclohexene with acetyl chloride followed by dehydrohalogenation with dimethylaniline were completely halogen-free. Parr bomb halogen determinations on several of the products consistently showed the presence of about 4% chlorine even after repeated treatments with dimethylaniline and careful fractionation. It was also noted that most samples of 1-acetylcyclohexene prepared by acetyl chloride acetylation darkened very considerably on standing. Variations in refractive index during fractional distillation also indicated a low order of purity.

Acetylation of cyclohexene with acetic anhydride. Because of the shortcomings indicated above for the acetylation of cyclohexene with acetyl chloride, the use of acetic anhydride as acetylating agent was investigated. Anhydrides have been successfully used (12, 13) in aromatic Friedel-Crafts acylations; such acylations require the use of two or more moles of the Friedel-Crafts catalyst per mole of the anhydride. Only fragmentary reports appear in the literature (14, 15, 16) regarding the use of acid anhydrides as acylating agents for olefins.

Although Experiments 1, 2, and 3 (Table I) gave no better yields of 1-acetylcyclohexene that did acylations using acetyl chloride as acetylating agent, the use of acetic anhydride offers several distinct advantages: (a) The reaction conditions are more easily reproducible, and the experimental procedure is simpler; (b) 1-Acetylcyclohexene is produced directly, thus eliminating the troublesome dehydrohalogenation step; (c) The 1-acetylcyclohexene produced is purer, as is indicated by the constancy of refractive index of successive fractions during distillation, failure of samples to darken on standing, and complete absence of chlorine (sodium fusion tests).

Variations in the procedure for acetylation of cyclohexene. In the experiments thus far described, the acetylation procedure was that used by previous investigators (2–5), namely, the addition of the catalyst portionwise to a mixture of cyclohexene and the acetylating agent. Several variations of this customary procedure were investigated in the present work. Because of the advantages of acetic anhydride over acetyl chloride as acetylating agent enumerated above, major emphasis was placed on variations in the procedure for acetylation with acetic anhydride.

The most advantageous variation in experimental procedure found was that of dropwise addition of acetic anhydride to a mixture of cyclohexene and stannic chloride (Experiments 4, 5, and 6, Table I) during a short reaction period at about room temperature. Under these conditions, 1-acetylcyclohexene was obtained in 54% yield. This product did not darken on standing, and was shown to be chlorine-free, despite the fact that considerable chlorocyclohexane (18%

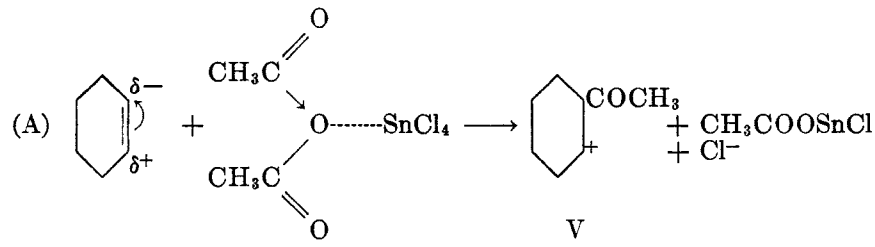
TABLE I

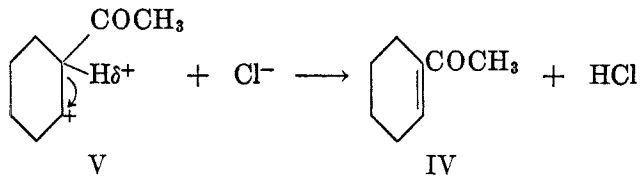
ACETYLATION OF CYCLOHEXENE WITH ACETIC ANHYDRIDE

RUN NO.	MOLES OF C_6H_{12}	MOLES OF Ac_2O	CATALYST USED	MOLES OF CATALYST	REACTION PERIOD IN HOURS	REACTION TEMP., °C.	YIELD OF 1-ACETYL-CYCLOHEX-ENE, %
1[a]	1.0	1.0	$AlCl_3$	2.0	4	0 –5	28.2
2	1.05	2.5	$ZnCl_2$	2.0	4	45–55	40.3
3	1.42	1.0	$SnCl_4$	1.0	2	0 –30	40.3
4	1.0	0.75[b]	$ZnCl_2$	1.0	2.25	30–50	40.0
5	1.50	1.0[b]	$SnCl_4$	1.0	0.75	25–35	54.0[c]
6	1.50	1.0[b]	$SnCl_4$	1.25	2	0 –10	50.0[d]

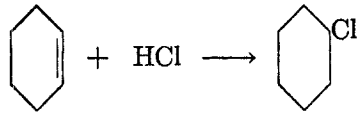
[a] In this reaction, 200 cc. of carbon disulfide was used as solvent. [b] The acetic anhydride was added gradually to the mixture of cyclohexene and catalyst. [c] This reaction also produced 32 g. of chlorocyclohexane. [d] This reaction also produced 37 g. of chlorocyclohexane

based on cyclohexene) was formed as a by-product in this reaction. Since the samples of 1-acetylcyclohexene prepared by acetylation with acetyl chloride invariably contained chlorine, this evidence appears to indicate that the acid chloride is not an intermediate in olefin acylation with anhydrides, as has frequently been suggested (1, 13) for aromatic Friedel-Crafts acylations with acid anhydrides. It seems more probable that the anhydride is the actual acetylating agent, and that the acylation reaction and the side-reaction of chlorocyclohexane formation proceed by some such mechanism as the following:

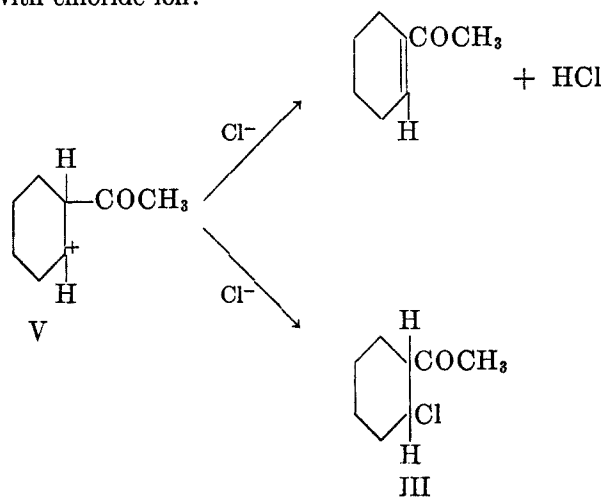


(B) 

V IV

(C) 

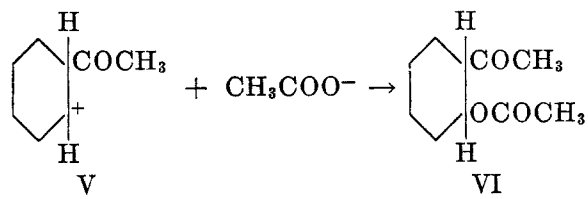
This mechanism is analogous to that usually suggested (17) for the corresponding reaction of cyclohexene with acetyl chloride. The formation of both 1-acetylcyclohexene and 1-acetyl-2-chlorocyclohexane from the acetyl chloride reaction may be rationalized on the basis of a competition between elimination of a proton from the intermediate carbonium ion, V, and combination of this carbonium ion with chloride ion:

(D) 

V III

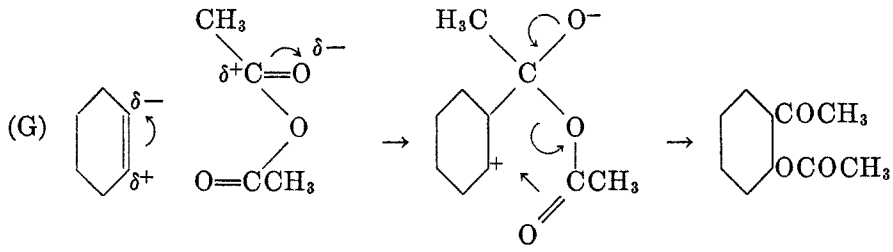
The question might, then, be raised as to why the same intermediate, V, postulated for the acetic anhydride reaction does not also combine with chloride ion to give chloroketone and the same over-all result as though the reaction had been effected with acetyl chloride. The difference probably lies in the fact that acetate ion, actual or potential, is present in the acetic anhydride reaction mixture, and if intermediate V combines with any anion, it is with the more powerfully nucleophilic acetate ion rather than chloride ion:

(E) $$CH_3COOSnCl_3 + Cl^- \rightleftarrows CH_3COO^- + SnCl_4$$

(F) 

V VI

If 1-acetyl-2-acetoxycyclohexene, VI, is an intermediate in the acetic anhydride reaction, and we have no experimental evidence that it is, the postulation of a cyclic intermediate for its formation rather than the sum of equations (A) and (F) is attractive (Equation G). 1-Acetyl-2-acetoxycyclohexane, if formed in the



VI

acetic anhydride reaction, would certainly be expected to decompose during the workup procedure or during distillation to 1-acetylcyclohexene and acetic acid.

Observations on possible side reactions during the acetylation of cyclohexene. Those reactions which led to low yields of 1-acetylcyclohexene gave either incomplete reaction, with recovery of considerable unreacted cyclohexene, or formation of resinous products. Several experiments were carried out in an effort to determine the source of the resinous by-products. It was observed that neither zinc chloride nor stannic chloride was effective in polymerizing cyclohexene at temperatures below 90°. Aluminum chloride effected some polymerization of cyclohexene at 45–50°. It thus appears highly unlikely that the resinous by-products arise from self-polymerization of cyclohexene. The possibility that the resins are produced by polymerization of the product, 1-acetylcyclohexene, was next investigated. 1-Acetylcyclohexene was recovered unchanged after heating with zinc chloride at temperatures below 80°; stannic chloride, however, effected considerable resinification of 1-acetylcyclohexene at temperatures as low as 25°. The presence or absence of cyclohexene had no effect on the polymerization of 1-acetylcyclohexene by zinc chloride or stannic chloride. In the presence of acetic anhydride, however, both zinc chloride and stannic chloride readily effected resinification at moderate temperatures. It would appear, then, that the resinous by-products which occur in the acetylation of cyclohexene with acetic anhydride arise from self-polymerization of 1-acetylcyclohexene and/or further reaction of 1-acetylcyclohexene with acetic anhydride. Hence, the presence of an excess of both stannic chloride and acetic anhydride during the acetylation of cyclohexene is not conducive to high yields. This probably explains the beneficial effect of the experimental procedure of adding the anhydride dropwise to a mixture of cyclohexene and stannic chloride; the excess of stannic chloride always present leads to rapid reaction, but excess anhydride is at no time present.

Other catalysts and reaction variables. Hartough and his associates (18, 19, 20) have reported excellent yields from acetylation of certain heterocyclic com-

pounds with acetic anhydride using as catalysts small amounts of phosphoric acid, iodine, or phosphorus pentoxide. Application of these procedures to the reaction of acetic anhydride with cyclohexene was unsuccessful; at low temperatures, little reaction occurred, while at higher temperatures there was extensive resinification.

Although a few of our experiments utilized a solvent, we have made no general investigation of solvent effects.

EXPERIMENTAL PART

Preparation of 1-acetylcyclohexene using acetic anhydride. The experiment here described represents our best procedure for the preparation of 1-acetylcyclohexene. A mixture of 123 g. (1.5 moles) of cyclohexene and 260.5 g. (1.0 mole) of stannic chloride was placed in a 1-liter, three-necked flask equipped with a dropping-funnel, a reflux condenser, a thermometer extending into the reaction mixture, and a modified Hershberg stirrer (21). All openings were protected by calcium chloride-tubes. The flask was immersed in an ice-bath, and 102 g. (1.0 mole) of acetic anhydride (99–100%) was added dropwise during 30 minutes; the temperature of the reaction mixture varied from 25–35° during the addition. Stirring in the ice-bath was continued for 15 minutes. The reaction mixture was then poured onto 300–400 g. of cracked ice. The resulting mixture was extracted with ether; the ether extract was washed with sodium bicarbonate solution, then with water, and dried over calcium chloride. The ether was stripped off, and the residue fractionally-distilled through an 18-inch helix-packed column under reduced pressure. After a fore-run from which chlorocyclohexane was isolated (see below), there was obtained 67 g. (54%, based on acetic anhydride) of 1-acetylcyclohexene, b.p. 65–69°/5 mm. (202.5°/atms.) n_D^{25} 1.4883, d_4^{30} 0.9641. Reported (22) values: b.p., 201–202°, n_D^{20} 1.4881, d_4^{20} 0.9655. The product gave a semicarbazone, m.p. 220°; reported (22), m.p. 221°. The oxime was prepared and found to melt at 58–59° on crystallization from aqueous alcohol. Darzens (2) reported an oxime, m.p. 99°, from 1-acetylcyclohexene. More recently, Bergs, Wittfeld, and Wildt have reported (23) an oxime, m.p. 60–61°.

Anal. of oxime. Calc'd for $C_8H_{13}NO$: N, 10.07. Found (Kjeldahl): N, 9.91.

General procedure for the acetylation of cyclohexene with acetyl chloride. The chosen quantities of cyclohexene and acetyl chloride were placed in the apparatus just described. The reaction vessel was cooled in an ice or Dry Ice-acetone bath depending upon the temperature desired, and the catalyst was added portionwise with stirring. On completion of the reaction, the reaction mixture was poured onto a mixture of ice and hydrochloric acid, and the resulting mixture was extracted with ether. The ether extracts were washed with sodium bicarbonate solution, then with water, and dried over calcium chloride. The ether and unreacted cyclohexene were distilled off, and the residue was heated with an excess of dimethylaniline for three hours at 180°. This mixture was cooled, washed with dilute hydrochloric acid, taken up in ether, and dried over calcium chloride. The product was then isolated by fractional-distillation through an 18-inch, helix-packed column. Samples of 1-acetylcyclohexene prepared by this general procedure showed the following properties: b.p., 65–69°/5 mm., n_D^{25} 1.4921–1.4950, chlorine content (Paar bomb), 4.0 ± 0.1%. The samples darkened considerably on standing.

Characterization of by-products. Chlorocyclohexane was isolated from the fore-runs in most of our acetylation experiments. This material showed the following properties: b.p., 142° (uncorr.), n_D^{25} 1.4597, d_4^{30} 0.9880. Reported (24) values: b.p., 142°, d_4^{20} 1.000, n_D^{20} 1.46264.

Anal. Calc'd for $C_6H_{11}Cl$:Cl, 29.8. Found (Parr bomb): Cl, 29.8.

Very small amounts of cyclohexyl acetate were isolated from several acetylations using acetic anhydride. Only one experiment (in which cyclohexene was added to a mixture of acetic anhydride and stannic chloride) afforded a large amount of this by-product. The cyclohexyl acetate isolated from this experiment showed the following properties: b.p.

174–175° (uncorr.), n_D^{25} 1.4379. Alkaline hydrolysis gave cyclohexanol, b.p. 158–160°; phenylurethan, m.p. 81–82°; reported (25) m.p. 82°.

SUMMARY

A study has been made of factors affecting the yield of 1-acetylcyclohexene from the acetylation of cyclohexene with acetyl chloride and with acetic anhydride in the presence of various Friedel-Crafts type catalysts. The best procedure found involves the portion-wise addition of acetic anhydride to a mixture of cyclohexene and stannic chloride during a reaction period of about one-half to one hour at 25–35°. This procedure affords 1-acetylcyclohexene in 54% yield. The product of this reaction is much purer than that resulting from acetylation of cyclohexene with acetyl chloride, and the experimental procedure is considerably simpler. The mechanism of the reaction and the nature of side reactions are briefly discussed.

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[CONTRIBUTION FROM THE NOYES CHEMICAL LABORATORY, UNIVERSITY OF ILLINOIS]

THE REACTION OF ARYLLITHIUM COMPOUNDS WITH HINDERED DIARYL KETONES

REYNOLD C. FUSON, GEORGE P. SPERANZA, AND RUSSELL GAERTNER[1]

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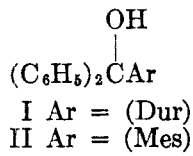
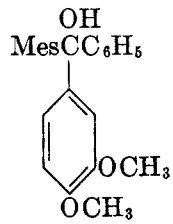
The synthesis of triarylcarbinols containing radicals such as mesityl is difficult because of the hindrance provided by such groups to the types of condensation that might serve. The only example of the class, in fact, is diphenylmesitylcarbinol, prepared by the reaction of mesitylmagnesium bromide with benzophenone (1).

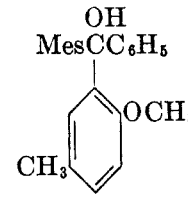
Since organolithium compounds exhibit a greater tendency than Grignard reagents to add to α,β-unsaturated carbonyl compounds in the 1,2 manner (2), it seemed probable that aryllithium compounds might produce carbinols from hindered diaryl ketones which undergo *ortho*-arylation with phenylmagnesium bromide (3).

Experiments with phenyl-, mesityl- and duryl-lithium have made possible the synthesis of a number of new carbinols containing one mesityl or duryl radical. Duryl- and mesityl-lithium combine with benzophenone to yield duryldiphenyl- (I) and mesityldiphenyl-carbinol (II), respectively.





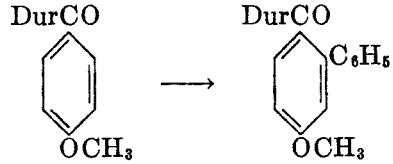
III



IV

Phenyllithium reacts with mesityl 3,4-dimethoxyphenyl ketone and mesityl 2-methoxy-5-methyl ketone to yield, respectively, 3,4-dimethoxyphenylmesitylphenylcarbinol (III) and mesityl-2-methoxy-5-methylphenylphenylcarbinol (IV). The yields of III and IV are 18% and 57%, respectively.

This type of behavior proved not to be general, however. Duryl 4-methoxyphenyl ketone (V) and mesityl 3-methoxyphenyl ketone (VII), for example, are phenylated in an *ortho*-position by phenyllithium, yielding the dihydro derivatives of VI (52.5% yield) and VIII (7.5% yield), respectively.



V VI

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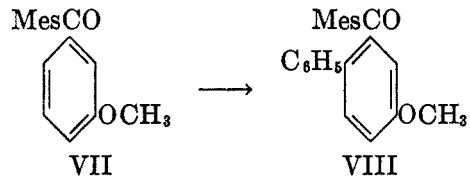

VII VIII

In a similar way duryl phenyl ketone reacted with phenyllithium to give duryl 2-phenylphenyl ketone (IX) in a 28% yield and with duryllithium to produce duryl 2-durylphenyl ketone (X) in a 40% yield.

IX X

Reaction of mesityl- and phenyl-lithium with dimesityl ketone, which cannot undergo arylation in an *ortho*-position, had been shown by Faber and Nauta not to yield carbinols (4). It is to be noted that duryllithium, not previously reported, can be made satisfactorily by treatmentof bromodurene with lithium.

EXPERIMENTAL[2]

Arylation of p-anisyl duryl ketone with phenyllithium. To a solution of phenyllithium prepared from 23.6 g. of bromobenzene and 2.1 g. of lithium metal in 75 ml. of ether was added a solution of 10 g. of the ketone (5) in 50 ml. of benzene over a period of 30 minutes. A slight warming was observed and a brown color developed. Stirring was continued for one hour and the mixture was poured on ice. The solvent layer was washed with water three times, then with hydrochloric acid, again with water, and finally dried over sodium sulfate. Distillation of the solvents left 19 g. of red-brown, viscous material, which was dissolved in methanol. The solution deposited 6.85 g. (52.5%) of duryl 2-phenyl-4-methoxy-1,2-dihydrophenyl ketone; m.p. 137–139° (corr.). It crystallized from ethanol in white plates, m.p. 140.5–141° (corr.).

Anal. Calc'd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56; Mol. wt., 346.
Found: C, 83.05; H, 7.65; Mol. wt. (ebullioscopic in benzene), 333.

The compound reacted with a solution of potassium permanganate in water and acetone within ten minutes. Dehydrogenation was accomplished by heating 1 g. of the material with 0.1 g. of a palladium-on-charcoal catalyst (10%) at 300–325° for 25 minutes and finally at 350° for five minutes. A solution of the mixture in ethanol was filtered and cooled; 0.35 g. of crystals separated; m.p. 141–143° (corr.). Duryl 2-phenyl-4-methoxyphenyl ketone separated from methanol in white crystals; m.p. 146.5–147.5° (corr.). It did not react with potassium permanganate.

Anal. Calc'd for $C_{24}H_{24}O_2$: C, 83.69; H, 7.02.
Found: C, 83.53; H, 7.25.

3,4-Dimethoxyphenyl mesityl ketone. This ketone has been prepared previously (6) by condensing veratroyl chloride with mesitylene by the Friedel-Crafts method. It was prepared in higher yield from mesitoyl chloride and catechol dimethyl ether by the same type of reaction. A solution of 46.0 g. of the acid chloride in 100 ml. of carbon disulfide was added with mechanical stirring to a mixture of 33.4 g. of catechol dimethyl ether, 32.2 g. of alumi-

[2] Microanalyses by Miss Rachel Kopel and Miss Emily Davis; infrared absorption data and interpretations by Miss Elizabeth Petersen and Mrs. J. L. Johnson.

num chloride, and 150 ml. of the solvent over a period of 20 minutes and stirring continued for four hours. The mixture was decomposed with cold dilute hydrochloric acid, and the solvent layer was washed with water and 10% sodium hydroxide solution. The solvent was removed by distillation; there was obtained, after recrystallization of the residue from ethanol, 56.3 g. (80%) of product; m.p. 103–104°. The pure ketone melted at 105–106°. The mixture melting point with the product obtained from veratroyl chloride and mesitylene showed no depression.

Reaction of 3,4-dimethoxyphenyl mesityl ketone and phenyllithium. A solution of 6 g. of the ketone in 25 ml. of benzene was added over a period of 15 minutes to a reagent prepared from 13.2 g. of bromobenzene and 1.2 g. of lithium in 50 ml. of ether. After being stirred for an additional hour, the purple mixture was decomposed in the usual manner. There was obtained from methanol 1.5 g. (18%) of light yellow powder; m.p. 189–192° (uncorr.). 3,4-Dimethoxyphenylmesitylphenylcarbinol crystallized from a mixture of benzene and methanol, then from ethyl acetate as white sandlike crystals; m.p. 201–202° (corr.). It did not react with a solution of potassium permanganate in acetone and water.

Treatment of the carbinol with bromine in carbon tetrachloride gave only tar. The infrared absorption spectra of this compound and that of the one obtained by the reaction of phenyllithium and mesityl 2-methoxy-5-methylphenyl ketone reveal several features of their structures. Both samples possess hydroxyl absorptions at 3550 cm.$^{-1}$ and show the absence of carbonyl absorption. The rather high hydroxyl frequency is further evidence for the carbinol structure since Coggeshall (7) has found a similar frequency for highly hindered phenols. Aromatic double-bond absorptions occur around 1500 and 1600 cm.$^{-1}$, but there is total absence of non-aromatic double-bond absorption. The presence of the mesityl, phenyl, and 1,2,4-trisubstituted phenyl groups is indicated by absorptions at 860, 706, and 810 cm.$^{-1}$, respectively.

Independent synthesis of 3,4-dimethoxyphenylmesitylphenylcarbinol. A solution of 9.0 g. of 3,4-dimethoxybenzophenone (8) in 75 ml. of ether was added over a period of 30 minutes to a reagent prepared from 28.5 g. of bromomesitylene and 2.2 g. of lithium in 75 ml. of ether. The mixture turned a slight brown and a precipitate began to form. The mixture was poured on ice, and the precipitate was washed with water. The product weighed 13.2 g. (96%), m.p. 201–202°. The pure carbinol melts at 202–203°. The mixture melting point with the product obtained above showed no depression.

Anal. Calc'd for $C_{24}H_{26}O_3$: C, 79.85; H, 7.23.
Found: C, 79.91; H, 7.39.

Reaction of 2-methoxy-5-methylphenyl mesityl ketone and phenyllithium. To a solution of phenyllithium, prepared from 7.1 g. of bromobenzene and 0.6 g. of lithium in 25 ml. of ether, was added over a period of 30 minutes a solution of 6 g. of the ketone (9) in 25 ml. of. ether. The mixture turned red-brown and became warm. When one-half of the ketone had been added a voluminous white precipitate began to form, the mixture becoming very viscous at the end of the addition. After being stirred for an additional 90 minutes at room temperature, the mixture was worked up as usual. Removal of the solvent left a very deep brown residue. Methanol was added and 4.4 g. (57% yield) of rust-colored crystals separated; m.p. 141–144° (corr.). Mesityl-2-methoxy-5-methylphenylphenylcarbinol separated from a mixture of benzene and methanol in light yellow plates; m.p. 149–149.5° (corr.).

Anal. Calc'd for $C_{24}H_{26}O_2$: C, 83.20; H, 7.56.
Found: C, 83.22; H, 7.61.

The infrared absorption spectrum of this compound is almost identical with that of the product from 3,4-dimethoxyphenyl mesityl ketone, discussed above.

Reaction of mesityl m-methoxyphenyl ketone and phenyllithium. A solution of 4.5 g. of the ketone (9) in 25 ml. of ether was added over a period of 20 minutes to the reagent prepared from 11.2 g. of bromobenzene and 1 g. of lithium in 50 ml. of ether. A brown color developed and the mixture refluxed gently. The usual procedures gave 8.7 g. of an amber oil which precipitated 0.45 g. (7.5%) of yellow crystals; m.p. 182–186° (corr.). The compound was recrystallized twice from high-boiling petroleum ether and again from a mixture of

benzene and methanol. It formed needles melting at 189.5–191° (corr.). It did not depress the melting point of a sample of mesityl 2-phenyl-5-methoxyphenyl ketone prepared from the same ketone by the action of phenylmagnesium bromide and found to melt at 190–192° (corr.)(9).

Arylation of duryl phenyl ketone with phenyllithium. The reaction was carried out in a manner similar to that employed in the addition of phenyllithium to the previous ketones. A solution of 18.5 g. of duryl phenyl ketone in 75 ml. of benzene was added over a period of 30 minutes to a solution of phenyllithium prepared from 2.1 g. of lithium and 23.6 g. of bromobenzene in 100 ml. of ether in a nitrogen atmosphere. The mixture was stirred mechanically at room temperature during the addition and for 2 additional hours. The solution turned red initially but began to darken with stirring. The mixture was decomposed in the usual manner and the organic layer evaporated to dryness. An oil remained which failed to deposit crystals from methanol, ethanol, or benzene. The oil was distilled *in vacuo* and the fraction of b.p. 220–230°/2 mm. collected. The crude duryl 2-biphenyl ketone was recrystallized from ethanol; m.p. 130–133°; yield 7.2 g. (28%). The pure ketone melted at 134–135°.

Anal. Calc'd for $C_{23}H_{22}O$: C, 87.86; H, 7.06.
Found: C, 87.88; H, 7.14.

Independent synthesis of duryl 2-biphenyl ketone: duryl o-methoxyphenyl ketone and phenylmagnesium bromide (9). A solution of 8.5 g. of duryl *o*-methoxyphenyl ketone[3] in 40 ml. of dry ether and 15 ml. of dry benzene was added over a period of 15 minutes to the reagent prepared from 1.55 g. of magnesium and 10 g. of bromobenzene in 50 ml. of ether. A noticeable reaction occurred and the color of the solution became successively blue, green, light brown, and finally blue again. After addition of the ketone, the mixture was stirred for an additional 90 minutes and then decomposed in an ice-hydrochloric acid mixture. The organic layer was washed with water three times, once with sodium bicarbonate, and again with water. Evaporation of the solvent left the duryl 2-biphenyl ketone as an oil. It was recrystallized from methanol, m.p. 133–134°; yield 3 g. A mixture melting point with the product obtained from duryl phenyl ketone and phenyllithium melted at 133–134°.

Arylation of duryl phenyl ketone with duryllithium. The reaction was carried out in accordance with the directions for the preparation of duryl 2-biphenyl ketone. To 20 g. of bromodurene dissolved in 200 ml. of ether was added, with stirring, 1.42 g. of lithium. Stirring was continued for 2 hours, after which much of the lithium remained unchanged. To the mixture was added 10 g. of duryl phenyl ketone over a period of 1 hour. A red-brown color resulted, and stirring was continued for 2 additional hours. After recrystallization from ethanol the product, duryl 2-durylphenyl ketone, melted at 191–192°. The yield was 6.8 g. (43%).

Anal. Calc'd for $C_{27}H_{30}O$: C, 87.52; H, 8.16.
Found: C, 87.85; H, 8.27.

Preparation of biphenylmesitylcarbinol. A solution of 10 g. of benzophenone in 75 ml. of ether was added to an ether solution of mesityllithium prepared from 2.8 g. of lithium and 40 g. of bromomesitylene. The formation of mesityllithium took place very slowly and the reaction was not complete when the ketone was added. The complex was decomposed without washing with dilute hydrochloric acid. The crude carbinol was recrystallized from ethanol; m.p. 88–90°; yield 11.2 g. (68%). The pure compound melted at 90–91°.

Anal. Calc'd for $C_{22}H_{22}O$: C, 87.38; H, 7.34.
Found: C, 87.33; H, 7.41.

Preparation of biphenyldurylcarbinol. A solution of 15 g. of benzophenone was added to a solution of duryllithium prepared from 1.42 g. of lithium and 20 g. of bromodurene dissolved in 200 ml. of absolute ether. The mixture was stirred for 3 hours and poured on ice. The product was washed three times with water, the organic layer dried over sodium sulfate,

[3] This ketone was prepared in an 89% yield from *o*-bromophenyl duryl ketone by refluxing for 14 hours in a 5 *N* solution of sodium methoxide in methanol (10).

the solvent removed, and the crude alcohol recrystallized from ethanol; m.p. 139–140°; yield 16 g. (62%).

Anal. Calc'd for $C_{22}H_{24}O$: C, 87.30; H, 7.64.

Found: C, 87.01; H, 7.72.

Reaction of 2,6-dimethoxyphenyl mesityl ketone with phenyllithium. Treatment of 2.5 g. of the ketone (11) with phenyllithium as described above yielded 3 g. of a light brown oil. It could not be induced to crystallize from the usual solvents.

Reaction of 2,2',4,4'-tetramethylbenzophenone and mesityllithium. Addition of a solution of 10 g. of the ketone (12) to mesityllithium prepared from 1.95 g. of lithium and 28 g. of bromomesitylene caused the solution to develop a brown color, which gradually changed to blue. The solution was stirred for an additional 90 minutes after the ketone was added. The reaction mixture was decomposed with ice. Usual procedures yielded 4.4 g. (30%) of white crystals which were recrystallized from methanol; m.p. 148° with development of a blue color.

Anal. Calc'd for $C_{26}H_{30}O$: C, 87.10; H, 8.43.

Found: C, 86.84; H, 8.28.

An attempt to prepare the methyl ether of the above carbinol failed. A deep blue solution resulted when pyridine was added to extract the hydrochloric acid. This behavior was found to be characteristic of this compound. The white carbinol turns red in hydrochloric acid and very dark red in sulfuric acid. When the solution is made basic with dilute sodium hydroxide a blue solution results. A blue compound (m.p. 172–173°) was isolated which had the same composition as the white carbinol.

Anal. Calc'd for $C_{26}H_{30}O$: C, 87.10; H, 8.43.

Found: C, 87.05; H, 8.59.

The white carbinol, 2,2',4,4'-tetramethylbiphenylmesitylcarbinol, was stable in pyridine and dilute sodium hydroxide. However, if a drop of hydrochloric acid was added to the carbinol in basic solution, a blue color resulted. When the solution was made acid a red color was obtained. This compound appears to behave as a true indicator and in acid or base has the characteristics of a dye.

SUMMARY

The action of phenyl-, mesityl-, and duryl-lithium with various diaryl ketones has been studied. Five triarylcarbinols were prepared in which one of the aryl groups is mesityl or duryl. Two hindered ketones containing methoxy groups were found to yield carbinols, whereas two others underwent arylation at an *ortho*-position.

URBANA, ILLINOIS

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE QUAKER OATS COMPANY AND NORTHWESTERN UNIVERSITY]

BASE-CATALYZED CONDENSATION OF α-HALOGENATED KETONES WITH β-KETO ESTERS

A. P. DUNLOP AND CHARLES D. HURD

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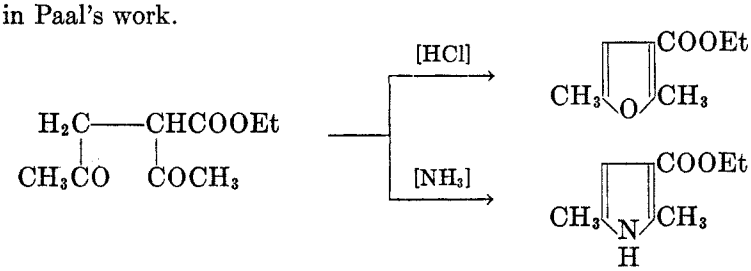
In the reaction of chloroacetone and other α-halo ketones with β-keto esters the mode of condensation is influenced by the nature of the condensing agent. Thus, C-alkylation of the ester is a well-established result under certain conditions, whereas the nature of the products in other instances has led to the postulation of O-alkylation as an intermediate step. It is the object of this paper to subject the existing evidence to critical examination and, for the reactions now regarded as O-alkylations, to present an alternative explanation particularly as it applies to the mechanism of formation of certain furan types.

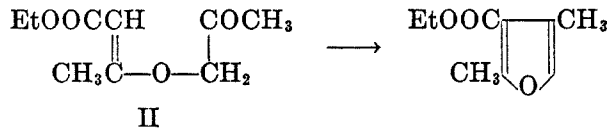
Paal (1) placed chloroacetone in reaction with ethyl sodioacetoacetate and obtained ethyl acetonylacetoacetate (I) from which a dimethylfuroic acid of m.p. 136° was obtained on treatment with hydrochloric acid. The structure claimed was 2,5-dimethyl-3-furoic acid, but no conclusive evidence to support it appeared until 1948 when Hurd and Wilkinson (2) obtained the same acid through an unequivocal synthesis starting with 2,5-dimethylfuran. The latter was converted into 2,5-dimethyl-3-furyl methyl ketone (by acetic anhydride, stannic chloride) which was then subjected to the haloform reaction, yielding 2,5-dimethyl-3-furoic acid, m.p. 135.4°.

It is certain from this evidence that C-alkylation of the acetoacetic ester occurred in Paal's work.



I

A similar C-alkylation explains the formation of 2,5-dimethyl-3-pyrrolecarboxylic acid by condensation of chloroacetone with acetoacetic ester in the presence of an excess of aqueous ammonia (3), but according to Feist (4) there is also formed a furan acid, melting at 122°. Feist believed this to be 2,4-dimethyl-3-furoic acid formed by way of the O-alkylation intermediate, ethyl 3-acetonyloxycrotonate (II), since he wrote "Es entsteht hierbei ein *O*-Acetonderivat des Ketonsäuresters." This step was in mind.

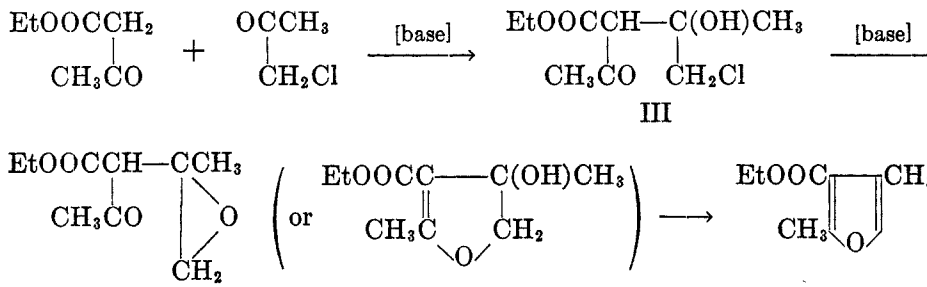


II

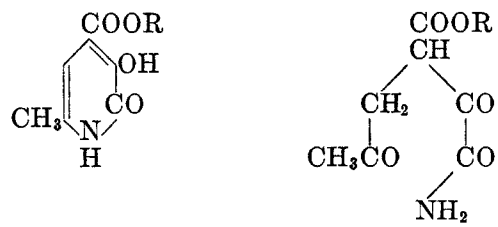
Feist's work proved neither the mechanism nor the 2,4-dimethyl structure, although the latter now seems unquestioned in view of the recent (2) proof of structure of the 2,5-isomer.

Chloroacetone, then, appears to condense with acetoacetic ester in two different ways depending upon the nature of the basic condensing medium. The published information can be summarized as follows. Sodium ethoxide (1, 2) produces, for the most part, the C-alkylation product, I, which on exposure to concentrated mineral acids is cyclized to 2,5-dimethyl-3-furoic acid. Aqueous ammonia (3, 4) also effects C-alkylation but, in addition, promotes condensation to a different intermediate, which is convertible to the 2,4-dimethyl isomer. Dry ammonia (2, 4) has been shown to bring about the latter result, as has aqueous sodium hydroxide (5). Actually, it is not improbable that reaction proceeds in both directions in each instance; that the ratio of the two intermediate products is influenced by the nature of the base and other experimental conditions. The published information, however, does not permit clarification of this point.

Although O-alkylation was postulated to explain the formation of 2,4-dimethyl-3-furoic acid, another explanation suggests itself, namely, an aldol-like condensation according to the steps:

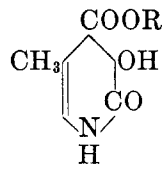


It is of interest to point out that Feist (4) suggested a related aldol-like process to explain products formed by interaction of chloroacetone, oxaloacetic ester, and aqueous ammonia. 5-Methyl-2,3-pyrroledicarboxylic ester was explained by C-alkylation, as was another product, IV, with V as the suggested intermediate.

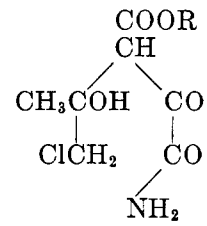


IV V

In view of his uncertainty regarding structure IV, however, he also proposed structure VI with VII as the intermediate. It is not clear why Feist did not suggest this type of intermediate (III) instead of O-alkylation (II) to account for his formation of 2,4-dimethyl-3-furoic acid.



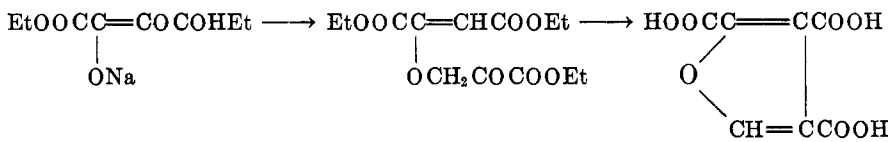
VI



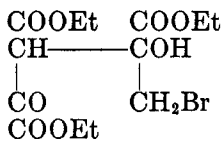
VII

Bromopyruvic ester, $BrCH_2COCOOR$, and chloroacetone, $ClCH_2COCH_3$, are closely related structurally, but apparently the two compounds respond differently towards the sodium salts of β-keto esters. If ethyl sodioöxaloacetate was C-alkylated by bromopyruvic ester (analogous to ethyl sodioacetoacetate and chloroacetone), then ring closure by hot hydrochloric acid should yield 2,3,5-furantricarboxylic acid. Sutter (6) believed he had effected this transformation. In any event, he obtained in 70% yield a compound of m.p. 79° which analyzed satisfactorily (C and H) for $C_{13}H_{18}O_8$ and changed into a furantricarboxylic acid by the action of mineral acids. This acid, said to be the 2,3,5-acid, melted at 273°.

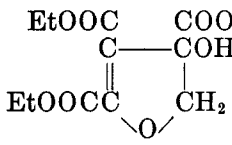
Reichstein and coworkers (7) showed that this was the 2,3,4-acid, not 2,3,5,- since it was also obtainable by decarboxylation of furantetracarboxylic acid. They postulated O-alkylation instead of C-alkylation:



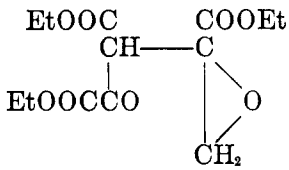
Let us assume instead that the aldol process is operative in the reaction with bromopyruvic ester. The initial adduct (VIII) would lose the elements of hydrogen bromide to form either IX or X, both of the empirical formula $C_{13}H_{18}O_8$



VIII



IX

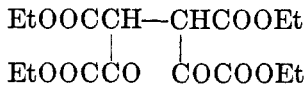


X

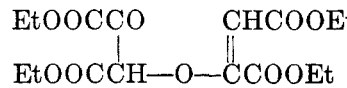
found by Sutter. Mineral acids would cause either of these structures to change into 2,3,4-furantricarboxylic ester (or acid), which was observed. Either structure (IX or X) explains the fact that ferric chloride gave a red color reaction. Of the two, we prefer IX, on the basis of the comparative ease of formation of a five-membered *versus* a three-membered ring.

There is another reaction which must be considered, namely, Sutter's treatment of ethyl sodioöxaloacetate with bromine to form a tetracarboxylic ester. Analysis (C, H) of the latter was satisfactory for $C_{16}H_{22}O_{10}$. The compound melted at 83° and gave no color reaction with ferric chloride. Sutter assigned structure XI and showed that on refluxing the ester with hydrochloric acid

cyclization, hydrolysis, and decarboxylation resulted to form the furantricarboxylic acid of m.p. 273°. Reichstein adopted structure XII, since he proved

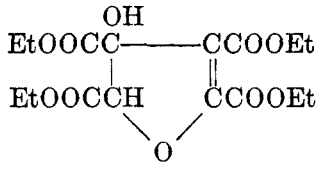


XI

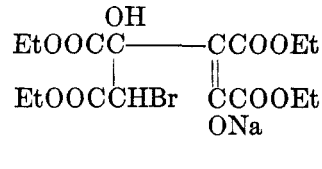


XII

that the latter was the 2,3,4-acid. His evidence was based on the isolation of furantetracarboxylic ester from XII (or XI) by treatment with concentrated sulfuric acid. Hydrolysis of this ester with boiling hydrochloric acid yielded furantetracarboxylic acid without any decarboxylation, but similar treatment of XII gave rise to Sutter's furantricarboxylic acid, m.p. 273°. Reichstein rationalized this decarboxylation as "ketonic hydrolysis" of the β-keto ester part of XII. Structure XI would have yielded the 2,3,5-isomer. XI and XII are both β-keto esters; hence both are unsatisfactory in explaining the non-reaction with ferric chloride. This observation would be explained if structure XIII was taken as the structure of Sutter's $C_{16}H_{22}O_{10}$ compound. Its formation is readily visualized by way of the intermediate aldol, XIV.



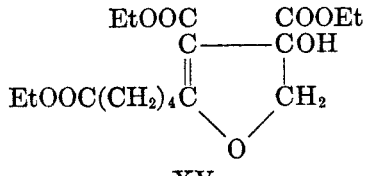
XIII



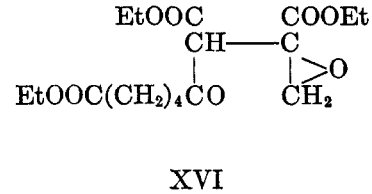
XIV

Archer and Pratt (8) also reported C-alkylation not to occur in the condensation of ethyl bromopyruvate and ethyl sodio-β-ketosuberate, since subsequent ring closure yielded 2-δ-carboxybutyl-3,4-furandicarboxylic acid. They accepted Reichstein's postulate of O-alkylation to explain their results:

With C-alkylation, Archer's compound would have been 5-δ-carboxybutyl-2,4-furandicarboxylic acid. Here again, no evidence precludes the possibility of an aldol type of intermediate (XV or XVI).



XV



XVI

There is other evidence also which strongly supports the aldol rather than the O-alkylation mechanism. Among other things, a suitable mechanism must account for facile cyclization of the intermediate, III or II, by a base to produce 2,4-dimethyl-3-furoic ester. That this is accomplished with great ease was demonstrated by Hurd and Wilkinson (2), who showed that mere passage of ammonia gas into an ether solution of chloroacetone and acetoacetic ester yielded a liquid reaction product boiling at 95–98° (14 mm.). This compound is ethyl 2,4-dimethyl-3-furoate—reported (9) to boil at 100–101° at 20 mm.—and not II, since it yields the furan acid on simple saponification. This result is readily explained if the aldol type of intermediate is assumed, but very difficult to reconcile with the O-alkylation intermediate. As a matter of fact it is unlikely that the latter, in basic medium, would cyclize to a furan under any conditions.

SUMMARY

Base-catalyzed reactions between α-halogenated ketones and β-keto esters which have been represented as O-alkylations are more probably aldol-type condensations. The existing evidence is examined critically.

CHICAGO, ILLINOIS
EVANSTON, ILLINOIS

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[CONTRIBUTION NO. 209 FROM THE RESEARCH LABORATORIES OF HOFFMANN-LA ROCHE INC.]

AROMATIZATION OF N-SUBSTITUTED PIPERIDINE COMPOUNDS

JOHN T. PLATI AND WILHELM WENNER

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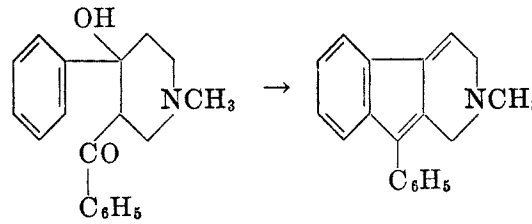
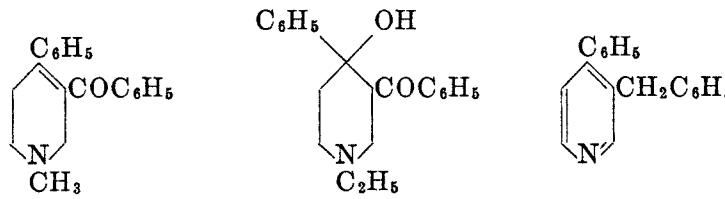
In a previous paper (1) a procedure was described by which 1-pyridindene derivatives could be obtained by the action of hydrobromic and sulfuric acid on several piperidine derivatives. In the special case of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I) the reaction yields 2-methyl-9-phenyl-2,3-dihydro-1-pyridindene (II). It was logical to initiate a study of other dehydrating agents in this reaction, and as a first approach an investigation of the action of acetic anhydride was undertaken.



I II

It was noted earlier (2) that 1-methyl-3-benzoyl-4-phenyl-4-acetoxypiperidine was obtained in excellent yield by the reaction of I with acetic anhydride at room temperature in the presence of a catalytic amount of sulfuric acid. The acetoxy base can be distilled without decomposition in the presence of a small amount of potassium carbonate.

The reaction with acetic anhydride took a different course when the temperature was raised to 90–100°. In this case a compound was isolated in about 15% yield, the analysis of which is in agreement with formula III.



III IV V

The position of the double bond was not rigidly established, but it is very likely that it is in the position indicated, since this position is associated with maximum conjugation.

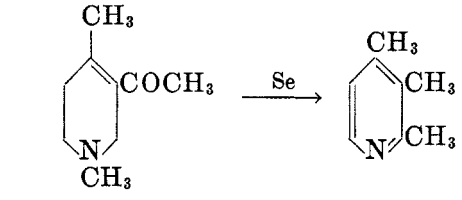
When, instead of isolating compound III, the reaction mixture was distilled under reduced pressure an unexpected reaction took place. A product of formula $C_{18}H_{15}N$, which can be isolated as an oxalate or hydrobromide, was obtained in about 30–35% yield. The neutral equivalent of the oxalate was abnormally low,

indicating a combination of the base and oxalic acid in the molecular ratio of 2:3 respectively. The free base on titration with hydrochloric acid showed the properties of a very weak base. It was suspected that the new compound was a pyridine derivative instead of a piperidine derivative. This assumption was supported by the finding that the corresponding N-ethyl derivative (IV) (3) under the same conditions gave the identical product as the N-methyl derivative (I). Obviously, then, the substituent on the nitrogen atom in the original piperidine bases must have been lost in the treatment with acetic anhydride. The unknown reaction product was hydrogenated catalytically, yielding a base which reacted with *p*-nitrobenzoyl chloride to give a *p*-nitrobenzoyl derivative. This finding indicated that a hydrogen atom was attached to the nitrogen in the hydrogenated product.

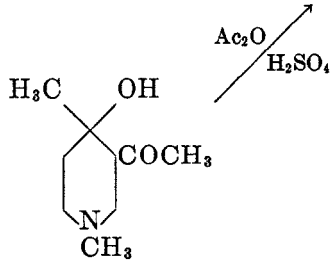
The unknown weak base was converted into the quaternary derivative with methyl *p*-toluenesulfonate, and the methyl *p*-toluenesulfonate was hydrogenated catalytically. A considerably stronger base than the original one resulted. It was possible to titrate this base with hydrochloric acid in the normal manner. From the analysis of the unknown weak base and from the properties just reported, it is possible to derive a preliminary formula containing a pyridine ring, two phenyls, a carbon, and two hydrogens.

The simple assumption that these fragments were fitted together as in V and that no change in original skeletal structure had occurred was not in agreement with the resistance of the substance to oxidation. It was largely unchanged after it had been boiled for 40 minutes with excess chromic oxide in acetic acid (56% recovered) or with excess potassium permanganate in pyridine for 9 hours (75% recovered).

In search for similar cases, the work of Prelog, Komzak, and Moor (4) came to our attention. These authors had subjected the unsaturated compound (VI) to the action of selenium and obtained 2,3,4-trimethylpyridine (VII).

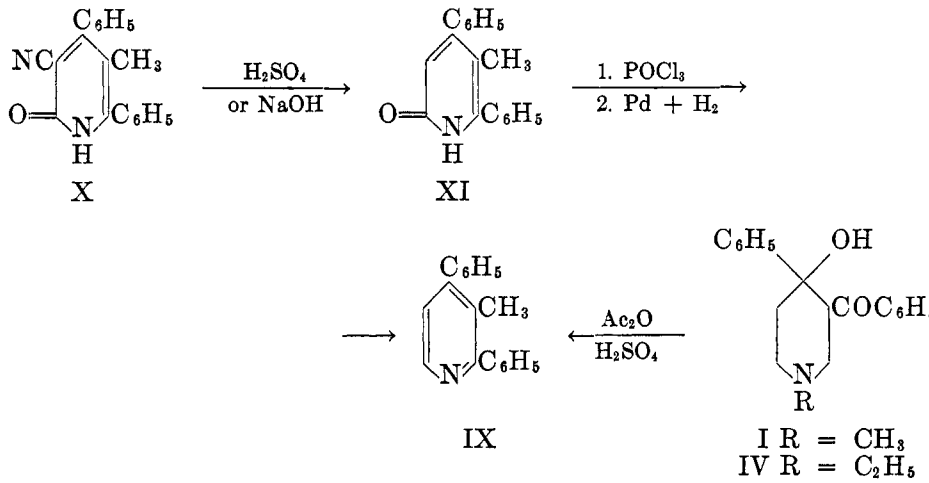


VI VII



VIII

These results and the difficulty of oxidation led us to suspect that our unknown pyridine derivative was in reality 2,4-diphenyl-3-methyl-pyridine (IX). To decide this question compound IX was synthesized by an unambiguous method. The starting material 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X) was synthesized according to the procedure of Basu (5) by the reaction of methyldibenzoylmethane and cyanoacetamide. Hydrolysis and decarboxylation with 80% sulfuric acid or aqueous alkali (6) gave the pyridone (XI), for which the melting point 228–229° was found instead of 263–264° as reported by Basu. When saponification was effected by aqueous alkali, 3-carboxy-4,6-diphenyl-5-methyl-2-pyridone could also be obtained. Treatment of XI with phosphorus oxychloride gave the chloro derivative which yielded the desired 2,4-diphenyl-3-methyl-pyridine (IX) on catalytic hydrogenation. This compound proved indeed to be identical with the weak base resulting from the acetic anhydride treatment of the original piperidine bases (I) and (IV).



It is important to point out a significant difference between the aromatizations in the case of Prelog's compound (VII) and our compound (IX). The Swiss workers started with a tetrahydropyridine derivative (VI), whereas the starting material for our investigation is the 4-hydroxypiperidine (I or IV). The Swiss workers utilized selenium and indicated that a dehydrogenation was involved, whereas in our case acetic anhydride and sulfuric acid were used.

It seemed likely that Prelog's compound (VII) could be obtained directly by starting with the corresponding 4-hydroxy compound (VIII), which Prelog and his group utilized as a starting material for the preparation of their tetrahydropyridine (VI). This was indeed found to be the case. Treatment with acetic anhydride and sulfuric acid was sufficient to bring about the desired aromatization.

From this discussion it may appear that an acid catalysis is responsible for the formation of the pyridine derivatives with the intermediate formation of unsaturated compounds. The situation, however, seems to be more complicated,

since it was found that when the unsaturated ketone (VI) was distilled slowly over a small amount of sulfuric acid without acetic anhydride the pyridine derivative (VII) could not be isolated. It may be possible that an acetoxy derivative is involved in the aromatization.

This new type of aromatization may prove useful in the preparation of certain pyridine derivatives.

EXPERIMENTAL

All melting points are uncorrected.

PART I. REACTION OF 1-METHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (I) WITH ACETIC ANHYDRIDE AND SULFURIC ACID

A. *1-Methyl-3-benzoyl-4-phenyl-1,2,5,6-tetrahydropyridine* (III). A mixture of 147 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I), 870 cc. of acetic anhydride, and 30 drops of concentrated sulfuric acid was placed on a steam-bath for 2.5 hours and shaken occasionally. The solvent was removed at the water pump in a bath which was gradually raised to 95°. To the residue 550 cc. of water and 500 cc. of ether were added, and the mixture was neutralized with about 140 g. of sodium carbonate below 30°. Three layers were obtained. The lowest layer was separated and discarded. To the remainder 140 cc. of water was added, the mixture was shaken, and the ether layer was separated. The ether layer was shaken with 70 cc. of 10% sodium carbonate and twice with 150 cc. of water, dried with sodium sulfate, and treated with an ethereal solution of oxalic acid until no further precipitate was obtained. Crystallization of the precipitate from 1700 cc. of ethanol gave 28 g. of the *oxalate* of 1-methyl-3-benzoyl-4-phenyl-1,2,5,6-tetrahydropyridine (III), m.p. 162–165°.

Anal. Calc'd for $C_{19}H_{19}NO \cdot C_2H_2O_4$: C, 68.65; H, 5.76.
Found: C, 68.59; H, 5.82.

Base. The base was obtained from a solution of the oxalate in dilute alcohol by treatment with alkali. After crystallization from dilute alcohol, the base melted at 95–96°.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.28; H, 6.90.
Found: C, 82.51; H, 6.75.

Hydrochloride. This compound was prepared by the passage of hydrogen chloride into a solution of the base in ether. It melted at 194–195°.

B. *2,4-Diphenyl-3-methylpyridine* (IX). A mixture of 500 g. of 1-methyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (I), 2500 cc. of acetic anhydride, and 87 drops of concentrated sulfuric acid was warmed on the steam-bath for 2.5 hours. The mixture was distilled first at the water pump and then at an oil pump provided with a large trap cooled with acetone and solid carbon dioxide. Evolution of some very volatile material occurred just before distillation of the main fraction. Caution should be exercised at this point, and the source of heat should be removed until the evolution has subsided. Continued distillation gave 244 g. of an oil boiling at 180–195° at 1.3 mm. The oil solidified on seeding with a previously prepared sample of 2,4-diphenyl-3-methylpyridine (IX).

Hydrobromide. The crude pyridine derivative was warmed to solution with 976 cc. of 48% hydrobromic acid, and the solution was poured into about 2 l. of water. The crystals of hydrobromide thus obtained weighed 180 g. and melted at 238–241°. The substance may be purified by crystallization from ethanol.

Anal. Calc'd for $C_{18}H_{15}N \cdot HBr$: C, 66.3; H, 4.9; Br, 42.5.
Found: C, 66.6; H, 4.5; Br, 24.5.

Oxalate. The crude base was dissolved in ether and treated with an ethereal solution of oxalic acid until no further precipitate was obtained. After crystallization from ethanol, the pure oxalate, m.p. 173–175°, was obtained.

Anal. Calc'd for $2\ C_{18}H_{15}N \cdot 3\ C_2H_2O_4$: C, 66.31; H, 4.77; N, 3.68; Neut. equiv., 127.
Found: C, 66.23; H, 4.97; N, 3.52; Neut. equiv., 129.

Base. The base can be obtained from the pure oxalate or hydrobromide by the action of alkali followed by distillation and crystallization from Skellysolve C or dilute alcohol. The pure substance melts at 60–61°. On electrometric titration with dilute hydrochloric acid no sharp point of inflection was noted.

Anal. Calc'd for $C_{18}H_{15}N$: C, 88.13; H, 6.16; N, 5.71.
Found: C, 87.84, H, 6.40; N, 5.47.

Hydrochloride. The hydrochloride melted over the range 219–226° after crystallization from alcohol-ether.

Anal. Calc'd for $C_{18}H_{15}N \cdot HCl$: C, 76.72; H, 5.72; Cl, 12.6.
Found: C, 76.97; H, 5.91; Cl, 12.6.

Methiodide. The methiodide was obtained when a solution of 10 g. of the base and 10 cc. of methyl iodide in 100 cc. of benzene was allowed to stand for 5 days. A yield of 6.9 g. was obtained. The compound melts at 221° with some preliminary softening at about 214°.

PART II. 2,4-DIPHENYL-3-METHYLPYRIDINE FROM THE REACTION OF 1-ETHYL-3-BENZOYL-4-HYDROXY-4-PHENYLPIPERIDINE (IV) WITH ACETIC ANHYDRIDE AND SULFURIC ACID

A mixture of 58 g. of 1-ethyl-3-benzoyl-4-hydroxy-4-phenylpiperidine (IV), 290 cc. of acetic anhydride, and 10 drops of sulfuric acid was treated as in Part I (B). At 185–200° and 0.9 mm., 23.5 g. of oil distilled over. On solution in ether and treatment with an ethereal solution of oxalic acid 21 g. of precipitate was obtained. After crystallization from ethanol, 14.2 g. of the oxalate of 2,4-diphenyl-3-methylpyridine was obtained, as indicated by the neutral equivalent of 132. A sample of the oxalate was converted into the base, m.p. 60°. The hydrobromide melted at 239–241°. The hydrochloride melted at 219–226°. Neither the base, the hydrobromide, nor the hydrochloride gave a depression in melting point when each was mixed with the corresponding substance from Part I (B).

PART III. OXIDATION OF 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

When 2 g. of 2,4-diphenyl-3-methylpyridine (IX) was refluxed for 40 minutes with 3 g. of chromium oxide in acetic acid, 1.69 g. (56%) of unchanged material was isolated as the oxalate. Heating of 1 g. of IX with 5 g. of potassium permanganate in boiling pyridine left the compound unchanged, 0.75 g. of starting material (75%) being recovered.

PART IV. HYDROGENATION EXPERIMENTS WITH 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

1-p-Nitrobenzoyl-2,4-diphenyl-3-methylpiperidine. A mixture of 1.23 g. of 2,4-diphenyl-3-methylpyridine, 0.20 g. of platinum oxide catalyst, 15 cc. of *N* hydrochloric acid, and 165 cc. of ethanol was hydrogenated at room temperature during a period of 1.5 hours and then at 55° for 5.5 hours. After removal of the catalyst and evaporation of the solvent, the residue was dissolved in 15 cc. of water and 25 cc. acetone. The mixture was made alkaline with 5 cc. of 10% sodium hydroxide and then treated alternately with *p*-nitrobenzoyl chloride and 10% sodium hydroxide. In this manner 3.0 g. of the chloride and 7 cc. of 10% sodium hydroxide were utilized for the reaction. The mixture was evaporated to dryness on the steam-bath, and the residue was extracted with dilute hydrochloric acid and ether. The ether solution was evaporated to dryness, and the residue was digested with Skellysolve B. In this manner 0.11 g. of the *p*-nitrobenzamide, m.p. 146–148°, was obtained. Crystallization from ethanol gave the pure product, m.p. 151–153°.

Anal. Calc'd for $C_{25}H_{24}N_2O_3$: C, 74.98; H, 6.04.
Found: C, 75.04; H, 5.93.

B. *1,3-Dimethyl-2,4-diphenyl-piperidine.* 1. *Quaternary salt.* A mixture of 24.5 g. of 2,4-diphenyl-3-methylpyridine and 18.6 g. of methyl *p*-toluenesulfonate was heated for 15 minutes at 160° and then dissolved in 160 cc. of ethanol.

2. *Hydrogenation.* The above solution was hydrogenated in the presence of 1.0 g. of platinum oxide catalyst at about 50 p.s.i. during about 2 hours at 50–70°. Very little hydrogen was absorbed, and it was necessary to add a fresh charge of catalyst on two separate

occasions in order to increase the rate of hydrogen absorption. Approximately 3.5 moles of hydrogen were absorbed during a total period of about 10 hours. After filtering the catalyst, the solution was treated with dilute alkali and allowed to crystallize overnight. In this manner 7.3 g. of almost pure 1,3-dimethyl-2,4-diphenylpiperidine was obtained. Crystallization from alcohol gave the pure product, m.p. 101–103°. On electrometric titration with standard acid a curve with a rather sharp point of inflection was obtained.

Anal. Calc'd for $C_{19}H_{23}N$: C, 85.99; H, 8.73; Neut. equiv., 265.

Found: C, 86.09; H, 9.06; Neut. equiv., 270.

The hydrochloride after crystallization from ethanol melted at 256–258°.

PART V. ALTERNATIVE SYNTHESIS OF 2,4-DIPHENYL-3-METHYLPYRIDINE (IX)

A. *3-Cyano-4,6-diphenyl-5-methyl-2-pyridone* (X). This compound was prepared essentially according to Basu (5) by refluxing 13.2 g. of methyldibenzoylmethane, 2.4 g. of piperidine, and 100 cc. of ethanol for about 12 hours. Yield 6.4 g., m.p. 295–298°.

B. *4,6-Diphenyl-5-methyl-2-pyridone* (XI). 1. *With sulfuric acid.* A mixture of 2.32 g. of the cyano compound (X), 9 cc. of water, and 18 cc. of sulfuric acid was refluxed for 1 hour. The mixture was poured into water and filtered. The precipitate was crystallized from ethanol to give 0.53 g. of 4,6-diphenyl-5-methyl-2-pyridone, m.p. 227–229°. Basu (5) reported a melting point of 263–264° for the same compound.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.7; H, 5.8; N, 5.4.

Found: C, 82.5; H, 6.2; N, 5.4.

2. *With alkali.* A mixture of 6.4 g. of 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X), 58 cc. of *N* sodium hydroxide, and 40 cc. of water was placed in an autoclave at 160° for 113 hours according to a previously published procedure (6). Acidification to *p*H 9.5 gave 4.7 g. of 4,6-diphenyl-5-methyl-2-pyridone, m.p. 226–227°. After crystallization from alcohol, it melted at 228–229°.

Anal. Calc'd for $C_{18}H_{15}NO$: C, 82.7; H, 5.8.

Found: C, 82.8; H, 5.8.

3. *3-Carboxy-4,6-diphenyl-5-methyl-2-pyridone.* A mixture of 1.46 g. of 3-cyano-4,6-diphenyl-5-methyl-2-pyridone (X), 25 cc. of water, and 13 cc. of *N* sodium hydroxide was heated in an autoclave at 160° during a period of about 42 hours. On addition of water 0.43 g. of crude 4,6-diphenyl-5-methyl-2-pyridone (X), m.p. 216–218°, was obtained. Acidification to *p*H 6.7 gave 0.10 g. of solid, m.p. 251–270°, whose identity was not established. Further acidification to *p*H 1.7 gave 0.80 g. of 3-carboxy-4,6-diphenyl-5-methyl-2-pyridone. The pure compound, m.p. 270–271°, was obtained by crystallization from methanol.

Anal. Calc'd for $C_{19}H_{15}NO_3$: C, 74.7; H, 4.9.

Found: C, 74.7; H, 4.6.

4. *2-Chloro-4,6-diphenyl-5-methylpyridine.* A mixture of 2.0 g. of 4,6-diphenyl-5-methyl-2-pyridone (XI) and about 5 cc. of phosphorus oxychloride was heated in a sealed tube at 200° for 2 hours. The mixture was poured into ice and neutralized with 10% sodium carbonate. The precipitate thus obtained was crystallized from ethanol. A yield of 1.6 g. of 2-chloro-4,6-diphenyl-5-methylpyridine, m.p. 92–93°, was obtained.

Anal. Calc'd for $C_{18}H_{14}ClN$: C, 77.28; H, 5.04.

Found: C, 76.84; H, 5.03.

5. *2,4-Diphenyl-3-methylpyridine* (IX). A mixture of 0.80 g. of 2-chloro-4,6-diphenyl-5-methylpyridine, 0.30 g. of palladium chloride, 2.0 g. Merck's activated charcoal, 20 cc. of *N* hydrochloric acid, and methanol to make a volume of 165 cc. was hydrogenated under a pressure of 120–190 cm. of mercury during 2 hours. The catalyst was filtered and the filtrate evaporated *in vacuo* to dryness. The residue was dissolved in water, treated with dilute alkali, and extracted with ether. After drying with sodium sulfate and evaporation of the ether, a solid residue was obtained. Crystallization from 4 cc. of Skellysolve B gave 0.45 g. of 2,4-diphenyl-3-methylpyridine (IX), m.p. 59–60°. No depression was obtained in the melting point when either the base or methiodide was mixed with the corresponding material from Part I (B). The hydrochloride and hydrobromide melted respectively at

218–223° and 236–238°, corresponding with the melting points of the hydrochloride and hydrobromide of 2,4-diphenyl-3-methylpyridine. The absorption spectrum of the base was practically identical with the base from Part I (B).

PART. VI EXPERIMENTS WITH 1,4-DIMETHYL-3-ACETYL-4-HYDROXYPIPERIDINE AND DERIVATIVES (VIII)

A. *2,3,4-Trimethylpyridine* (VII). A mixture of 36 g. of a mixture of the α and β stereoisomeric forms of 1,4-dimethyl-3-acetyl-4-hydroxypiperidine (VIII), 180 cc. of acetic anhydride, and 6 drops of sulfuric acid was heated on the steam-bath for 2.5 hours. Most of the excess acetic anhydride was distilled through a 12-plate column at about 10 mm. The residue was then distilled at ordinary pressure. A fraction, boiling at 174–178° and weighing 12.9 g., was collected. To an ether solution of this material a solution of picric acid in ether was added. In this manner 20.6 g. of picrate, m.p. 158–160°, was obtained. Crystallization from methanol gave 16.9 g. of the pure picrate of 2,3,4-trimethylpyridine (VII), m.p. 160–163°. The picrate was steam-distilled in the presence of 100 cc. of 50% potassium carbonate. The distillate was extracted with ether and the ether solution dried and distilled to give an oil boiling at 180–185°; $n^{24.7}_{D}$ 1.5127; d^{23}_{25} 0.952. The picrolonate after crystallization from methanol melted at 235–237°d. All of the above properties agree with those reported by Prelog, Komzak, and Moor (4).

B. *Distillation of 1,4-dimethyl-3-acetyl-1,2,5,6-tetrahydropyridine* (VI) *with sulfuric acid*. The tetrahydropyridine (VI) was prepared according to the method of Prelog and Komzak (7). A mixture of 9.73 g. of this material and 2 drops of sulfuric acid was distilled slowly at ordinary pressure. A fraction weighing 2.8 g. was collected below 100°. It had the strong odor of an amine. On continued distillation the temperature rose rapidly up to 270°. No material boiling in the range of 2,3,4-trimethylpyridine was noted.

Acknowledgment. We thank Dr. A. Steyermark for microanalyses and Mr. P. Bevilacqua for technical assistance.

SUMMARY

1-Alkyl-3-benzoyl-4-hydroxy-4-phenylpiperidines undergo rearrangement on treatment with acetic anhydride and sulfuric acid into 2,4-diphenyl-3-methylpyridine. The same type aromatization also occurs with 1,4-dimethyl-3-acetyl-4 hydroxypiperidine.

NUTLEY, N. J.

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[CONTRIBUTION FROM GULF RESEARCH & DEVELOPMENT COMPANY'S MULTIPLE FELLOWSHIP AT MELLON INSTITUTE]

THE INFLUENCE OF LOCATION OF SUBSTITUENT GROUPS ON THE VAPOR PRESSURE OF ALKYLATED PHENOLS

ROBERT S. BOWMAN AND DONALD R. STEVENS

Received April 24, 1950

During the preparation of a long series of *tert*-butylated phenols there were a few instances in which some uncertainty arose as to the exact position taken by the entering *tert*-butyl group. A certain degree of clarification was obtained by studying the correlation between the position occupied by an alkyl group on the phenol nucleus and the attendant effect on the vapor pressure of the alklyphenol; this effect appears to be associated with the degree of intermolecular interaction, known as hydrogen bonding. While the results of the correlations cannot provide final, irrefutable evidence, they do offer strong support for the assignment of structure.

Upon the addition of an alkyl group to a phenol, one always observes a rise in boiling point (or lowering of vapor pressure) because of the increase in molecular weight. It is evident, however, that without exception the boiling-point increase attending *ortho*-alkylation is significantly smaller than that associated with *meta*- or *para*-alkylation (see Table I). Hence an *ortho*-alkylated phenol characteristically boils at a lower temperature than its *meta* or *para* isomer. Furthermore, whereas the boiling-point differences between the *ortho* and *meta*, or ortho and *para*, isomers are quite large, there invariably is only a small difference, if any, in boiling point between the *meta* and *para* isomers. The introduction of an alkyl group in a *meta* or *para* position on the phenol nucleus effectively lowers the vapor pressure to a much greater extent than does the addition of the same alkyl group when *ortho* to the hydroxyl group, apparently because of the attenuated degree of hydrogen bonding in the *ortho*-alkylphenols.

That hydrogen bonding is intimately associated with the relatively high boiling points of phenols can be demonstrated by the observation that the non-hydrogen-bonding alkylphenyl ethers boil at considerably lower temperatures than their corresponding hydrogen-bonding isomeric alkylphenols. Examination of the Hirschfelder atom models of the various alkylphenols shows, however, than an *ortho*-alkyl group can partially hinder the formation of intermolecular hydrogen bonds by virtue of its close proximity to the hydroxyl group. Since this partial screening effect cannot occur in the *meta*- and *para*-alkylated phenols, these isomers undergo more complete hydrogen bonding with resultant relatively lower vapor pressures or higher boiling points. Hence the extent of intermolecular hydrogen bonding influences the vapor pressure of a compound, and one is therefore able to predict the order of boiling points within a given series of alkylphenols.

The infrared absorption studies of Coggeshall (1) have verified the postulation of hindered hydrogen bonding. He found that the hindering capacity of a given *ortho*-alkyl group is related to its size and bulk, and that complete interference

is manifested in an *o,o'*-dialkylphenol such as 2,6-di-*tert*-butyl-4-methylphenol where no intermolecular hydrogen bonds could be detected. The anticipated corollary, based upon vapor pressure effects, can be observed in Table III where the boiling-point differences between a series of *ortho*- and *para*-alkylated phenols can be seen to increase generally with the size and bulk of the alkyl group.

The series of *tert*-butylated phenols prepared and their boiling-point data are listed in Table II. All these compounds, except 2-*tert*-butylphenol and 3-methyl-4-*tert*-butylphenol, were synthesized by alkylating the starting phenol with isobutylene at atmospheric pressure and 70°, using five per cent by weight of concentrated sulfuric acid as the catalyst. In no instance was there any evidence for *meta*-alkylation or for the insertion of a *tert*-butyl group between two methyl groups, or between a methyl and a hydroxyl group placed *meta* to each other. For example, 3,5-dimethylphenol could not be butylated under these compara-

TABLE I

ALKYLATION *vs* BOILING-POINT INCREASE IN PHENOLS

NATURE OF ALKYL GROUP ADDED TO	BOILING POINT, °C./20 MM. AT POSITION			ATTENDANT INCREASE IN BOILING POINT, °C. AT POSITION		
	2	3	4	2	3	4
Phenol (85.0°)						
Methyl[b]	90.0	101.0	101.0	5.0	16.0	16.0
Ethyl[b]	101.5	114.5	115.0	16.0	29.5	30.0
n-Propyl[b]	122.0	127.0	128.0	37.0	42.0	43.0
Isopropyl[a]	106.0	120.0	120.0	27.0	35.0	38.0
n-Butyl[a]	123.0	138.0	138.0	38.0	53.0	53.0
sec-Butyl[a]	118.0	131.5	132.5	33.0	46.5	47.5
Isobutyl[a]	116.5	129.5	131.0	31.5	44.5	46.0
tert-Butyl[a]	113.0	129.5	130.0	28.0	44.5	45.0

[a] Data obtained in authors' laboratory.

[b] Pardee and Weinrich, *Ind. Eng. Chem.*, **36**, 595 (1944).

tively mild conditions, presumably because the active *ortho* and *para* positions are sufficiently hindered by the neighboring groups. Again, it is significant to note the complete conformity with the observation that *para* substitution is attended by the greater rise in boiling point. Also, the increases in boiling point become generally smaller as the number of alkyl groups on the parent phenol is increased. Figure 1 illustrates a characteristic division of the phenols into two broad groups; this is based on the graphing of the boiling-point increases accompanying *ortho*- and *para*-butylation. It is also apparent that the largest boiling-point increases occur when a 3- or 5-alkylphenol is butylated in the 4-position.

The observed "*ortho* effect" has been utilized in assigning the position taken by an entering *tert*-butyl group. For example, in the monobutylation of *o*-cresol, *m*-cresol, *o*-ethylphenol, *m*-ethylphenol, 2,3-dimethylphenol, and 2-*tert*-butyphenol, two isomers are formed in each instance. By noting and comparing the attendant boiling-point increases, the structures of the various products can be deduced

TABLE II

BOILING POINTS OF *tert*-BUTYLATED PHENOLS

ADDITION OF ONE *tert*-BUTYL GROUP TO	BOILING POINT, °C./20 MM.* POSITION OF ENTERING GROUP		ATTENDANT INCREASE IN BOILING POINT, °C./20 MM. POSITION OF ENTERING GROUP	
	2— or 6—	4—	2— or 6—	4—
Phenol (85°/20 mm.)	113.0	130.5	28.0	45.5
o-Cresol (90.0°/20 mm.)	118.0	132.0	28.0	42.0
m-Cresol (101.0°/20 mm.)	129.5	153.0	28.5	52.0
p-Cresol (101.0°/20 mm.)	126.0		25.0	
o-Ethylphenol (101.5°/20 mm.)	129.0	141.0	27.5	39.5
m-Ethylphenol (114.5°/20 mm.)	142.0		27.5	
p-Ethylphenol (115.0°/20 mm.)	137.0		25.0	
2,4-Dimethylphenol (105.0°/20 mm.)	131.0		25.0	
2,5-Dimethylphenol (105.0°/20 mm.)		151.0		46.0
2,6-Dimethylphenol (107.0°/20 mm.)		135.0	28.0	
2,3-Dimethylphenol (112.0°/20 mm.)	139.0	145.0	27.0	33.0
3,4-Dimethylphenol (122.0°/20 mm.)	143.0		21.0	
2-*tert*-Butylphenol (113.0°/20 mm.)		146.0		33.0
4-*tert*-Butylphenol (130.0°/20 mm.)	146.0		16.0	
2-Methyl-6-*tert*-butylphenol (118.0°/20 mm.)		149.0		31.0
2-Methyl-4-*tert*-butylphenol (132.0°/20 mm.)	149.0		17.0	
3-Methyl-6-*tert*-butylphenol (129.5°/20 mm.)		167.0		37.5
3-Methyl-4-*tert*-butylphenol (153.0°/20 mm.)	167.0		14.0	
4-Methyl-2-*tert*-butylphenol (126.0°/20 mm.)	147.0		21.0	
2,3-Dimethyl-6-*tert*-butylphenol (139.0°/20 mm.)		174.0		35.0
2,3-Dimethyl-4-*tert*-butylphenol	174.0		29.0	
2-Ethyl-6-*tert*-butylphenol (129.0°/20 mm.)		156.0		27.0
2-Ethyl-4-*tert*-butylphenol (141.0°/20 mm.)	156.0		15.0	
3-Ethyl-6-*tert*-butylphenol (142.0°/20 mm.)		174.0		32.0
4-Ethyl-2-*tert*-butylphenol (137.0°/20 mm.)	154.0		17.0	
2,4-Di-*tert*-butyphenol (146.0°/20 mm.)	158.0		12.0	

* Pardee and Weinrich, *Ind. Eng. Chem.*, **36**, 595 (1944).

TABLE III

BOILING-POINT DIFFERENCES IN *o*- AND *p*-ALKYLPHENOLS

ALKYLPHENOLS	DIFFERENCE IN B.P., °C. AT 20 MM.
o- and *p*-Methylphenols	11.0
o- and *p*-Ethylphenols	14.0
o- and *p*-Isopropylphenols	14.0
o- and *p*-*n*-Butylphenols	15.0
o- and *p*-*sec*-Butylphenols	14.5
o- and *p*-Isobutylphenols	14.5
o- and *p*-*tert*-Butylphenols	17.0

by analogy. Hence the *tert*-butyl-*o*-cresol (b.p. 118.0°/20 mm.) is 2-methyl-6-*tert*-butylphenol and the higher-boiling isomer (b.p. 132.0°/20 mm.) is the 2-methyl-4-

tert-butylphenol. These structures are further substantiated by the fact that the introduction of another *tert*-butyl group in 2-methyl-6-*tert*-butylphenol is accompanied by a greater increase in boiling point than is the introduction of a *tert*-butyl group in 2-methyl-4-*tert*-butylphenol; this is another indication that the 4-position is not occupied in the isomer assumed to be 2-methyl-6-*tert*-butylphenol.

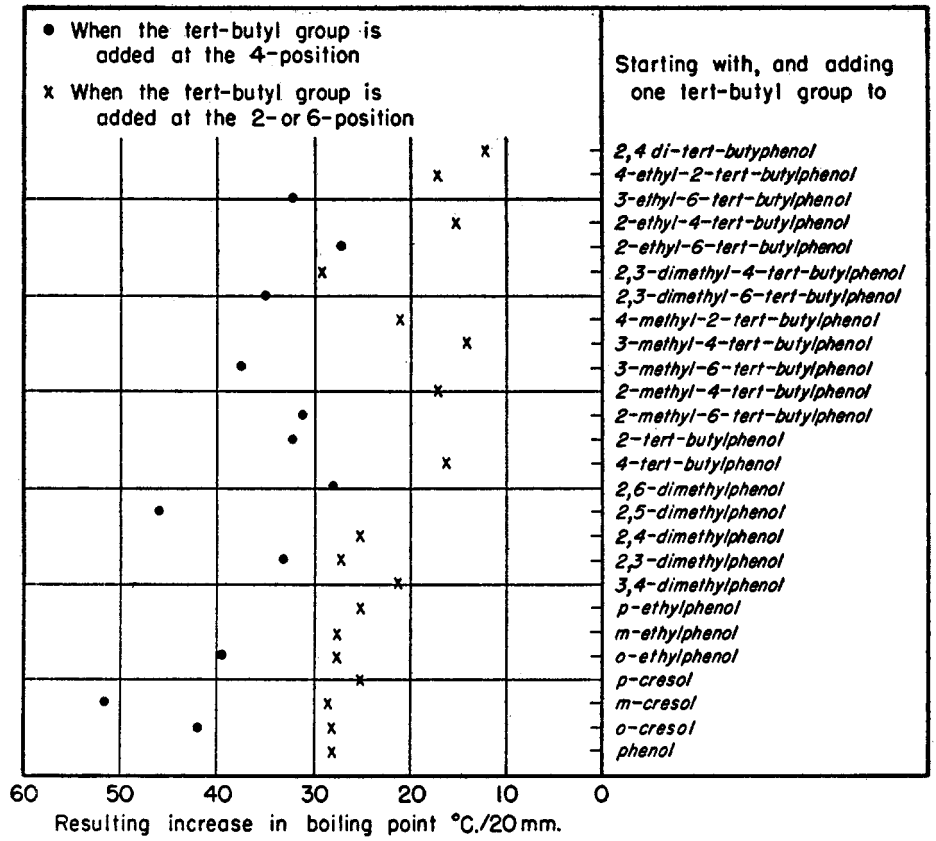

FIG. 1. Increase in boiling points attending substitution of *tert*-butyl groups in the 4-, and the 2- or 6-positions.

By the employment of similar reasoning, it is evident upon inspection of the data in Table II that the following designations can be made:

3-Methyl-*tert*-butylphenol (b.p. 129.5°/20 mm.) is 3-methyl-6-*tert*-butylphenol
3-Methyl-*tert*-butylphenol (b.p. 153.0°/29 mm.) is 3-methyl-4-*tert*-butylphenol
2-Ethyl-*tert*-butylphenol (b.p. 129.0°/20 mm.) is 2-ethyl-6-*tert*-butylphenol
2-Ethyl-*tert*-butylphenol (b.p. 141 0°/20 mm.) is 2-ethyl-4-*tert*-butylphenol
3-Ethyl-*tert*-butylphenol (b.p. 129.5°/20 mm.) is 3-ethyl-6-*tert*-butylphenol

(When the higher-boiling 3-ethyl-4-*tert*-butylphenol is prepared it probably will be found to boil in the neighborhood of 165°/20 mm.)

2,3-Dimethyl-*tert*-butylphenol (b.p. 139.0°/20 mm.) is 2,3-dimethyl-6-*tert*-butylphenol

2,3-Dimethyl-*tert*-butylphenol (b.p. 145.0°/20 mm.) is 2,3-dimethyl-4-*tert*-butylphenol

Di-*tert*-butylphenol (b.p. 146.0°/20 mm.) formed upon butylating 2-*tert*-butylphenol is 2,4-di-*tert*-butylphenol.

The assignment of a 6-position for the *tert*-butyl groups in both low-boiling *tert*-butyl-*o*-cresol and *tert*-butyl-*m*-cresol is also in accord with chemical evidence. Both of these isomers are less soluble in dilute alkali than their higher-boiling 4-*tert*-butyl isomers. Low alkali solubility is one of the characteristics of the hindered phenols, as shown by Stillson, Sawyer, and Hunt (2). In addition, the low-boiling 3-methyl-6-*tert*-butylphenol forms the urethan and phenoxyacetic acid derivatives at a noticeably slower rate than does the 3-methyl-4-*tert*-butylphenol, again indicating a steric hindrance effect attributable to the *ortho-tert*-butyl group in the 6-*tert*-butyl isomer.

SUMMARY

A general correlation, relating the effect of the location of an alkyl group upon the vapor pressure or boiling point of the alkylphenol, has been described. This correlation, explicable in terms of partial hindrance to intermolecular hydrogen bonding, affords support for the assignment of structures in certain *tert*-butylated phenols.

PITTSBURGH, PA.

REFERENCES

(1) COGGESHALL, *J. Am. Chem. Soc.*, **69**, 1620 (1947).
(2) STILLSON, SAWYER, AND HUNT, *J. Am. Chem. Soc.*, **67**, 303 (1945).

[CONTRIBUTION NO. 203 FROM THE DEPARTMENT OF ORGANIC CHEMISTRY, AND ENZYMOLOGY FORDHAM UNIVERSITY]

STUDIES ON THE CHEMISTRY OF HETEROCYCLICS. XI. FURTHER REACTIONS OF THENALDEHYDES.[1]

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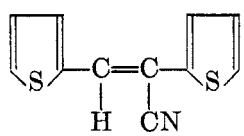
Received April 25, 1950

Hippuric acid and rhodanine have been shown in this laboratory to react readily with 2-thenaldehyde and some monosubstituted 2-thenaldehydes (1). These condensations are demonstrated here to be equally applicable to 3-thianaphthaldehyde and di- and tri-methylsubstituted thenaldehydes. In Table I are listed the products thus obtained.

The study of the effects of substitution of the thiophene nucleus on the ultraviolet absorption of the azlactones (1) was continued and also extended to the rhodanines prepared and to 2-methyl-4-(2-thenal)-5-oxazolone (2). From the spectra presented in Figures 1 and 2, and the data recorded in Table II it can be seen that, with the exception of 2-methyl-4-(2-thenal)-5-oxazolone which has only one peak, both the azlactones and the rhodanines exhibit two absorption peaks in the region 250–430 mμ. The di- and tri-methylsubstituted azlactones possess the lower absorption peak around 272 mμ which was found with the monosubstituted azlactones previously reported (1). Di- and tri-methylsubstitution of 2-phenyl-4-(2-thenal)-5-oxazolone causes a bathochromic shift of the major peak found at the longer wave lengths. This peak is present at shorter wave lengths in the azlactones derived from methylated 3- and 4-thenaldehydes. Furthermore, the shape of the curve of 2-phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone is flatter than those of the other azlactones and the intensity of the absorption at its major peak is considerably lower. The rhodanines display a similar bathochromic shift of their major peaks as a result of substitution of the thiophene ring. In addition the di- and tri-methylrhodanines show a plateau at the lower wave lengths.

α-Phenylcinnamonitrile has been prepared by condensing benzaldehyde and benzyl cyanide in the presence of sodium ethoxide (3). This method was utilized for obtaining a series of substituted α-phenylcinnamonitriles (4). 2-Thenaldehyde (5) and 2-thienylacetonitrile (1), which are easily accessible, when subjected to this procedure gave an 89% yield of α,β-di-(2-thienyl)acrylonitrile (I):

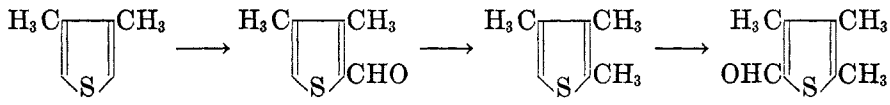


I

[1] This investigation was carried out under the auspices of the Office of Naval Research.

The reaction was successful if either benzaldehyde or benzyl cyanide was substituted for its thiophene analog, but the yields were lower than those obtained when both components in the condensation possessed a thiophene ring.

Two new thenaldehydes were prepared from 3,4-dimethylthiophene (II) by successive formylation and reduction. It is significant that while all the other



II

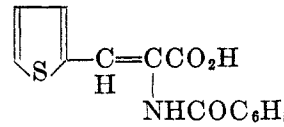
TABLE I

AZLACTONES AND RHODANINES PREPARED FROM SUBSTITUTED THENALDEHYDES

COMPOUND	YIELD, %	M.P., °C.	ANALYSES			
			Calc'd		Found	
			C	H	C	H
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone	54	195–196	67.84	4.59	67.78	4.38
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone	61	193.5–194.5	68.68	5.05	68.47	4.79
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone	75	205.2-206	67.84	4.59	67.94	4.36
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone	79	142.5–143.5	67.84	4.59	68.18	4.77
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone	18	101–102.5	68.68	5.05	68.87	4.95
2-Phenyl-4-(3-thianaphthal)-5-oxazolone	69	223–223.5	70.81	3.61	70.70	3.81
3,4-Dimethyl-2-thenalrhodanine	85	263–264	47.06	3.53	47.20	3.48
3,4,5-Trimethyl-2-thenalrhodanine	68	275–276	49.07	4.08	49.07	3.84
3-Thianaphthalrhodanine	90	240–241	51.98	2.52	51.90	2.43

thenaldehydes in this series (5, 6) were liquids at room temperature, the two described here are solids. They both exhibit typical aldehyde reactions in condensing with hippuric acid and rhodanine.

It has been shown (7) that veratralhippuric acid may be decarboxylated to the corresponding styrylamide by heating it in quinoline in the presence of copper chromite. In a similar manner α-benzamido-β-2-thienylacrylic acid (8) (III) was found to undergo decarboxylation, but excessive tar formation accompanied the reaction. When copper powder was substituted for copper chromite, a higher yield was obtained and the amount of tar formed was considerably diminished.



III

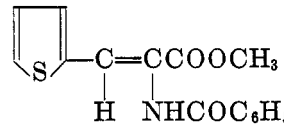
The susceptibility of thiophene azlactones to alcoholysis was found to parallel that of the benzene series. This was demonstrated by applying Nicolet's method (9) to 2-phenyl-4-(2-thenal)-5-oxazolone. With a methanol solution of sodium

TABLE II

ABSORPTION MAXIMA OF AZLACTONES AND RHODANINES

COMPOUND	mμ	ε × 10^{-3}	Log ε
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone	271–272	11.8	4.07
	411–414	35.2	4.55
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone	273	10.8	4.03
	429	37.6	4.57
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone	272	11.9	4.07
	421–422	39.1	4.59
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone	272	10.0	4.00
	390–391	34.1	4.53
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone	273	10.7	4.03
	387–388	17.3	4.24
2-Phenyl-4-(3-thianaphthal)-5-oxazolone	292	18.3	4.26
	411–412	31.3	4.50
2-Methyl-4-(2-thenal)-5-oxazolone	363	25.6	4.40
2-Thenalrhodanine	287–289	7.3	3.86
	397	34.1	4.53
5-Methyl-2-thenalrhodanine	294	7.5	3.87
	406–408	33.9	4.53
5-Ethyl-2-thenalrhodanine	291	8.0	3.90
	406–407	34.6	4.54
5-Propyl-2-thenalrhodanine	287	7.8	3.89
	407–408	35.1	4.55
3-Methyl-2-thenalrhodanine	292	5.6	3.75
	404–406	27.4	4.43
5-Chloro-2-thenalrhodanine	285	8.5	3.93
	401	33.9	4.53
5-Bromo-2-thenalrhodanine	287	9.3	3.97
	402	36.1	4.56
3-Thianaphthalrhodanine	286	9.3	3.97
	398	30.0	4.48
3,4-Dimethyl-2-thenalrhodanine	292	6.5	3.81
	408–409	33.6	4.52
3,4,5-Trimethyl-2-thenalrhodanine	298–306	7.1	3.85
	423	34.2	4.53

methoxide the azlactone was opened rapidly to the methyl ester (IV). Sodium ethoxide in ethanol acted as readily to produce the ethyl ester.



IV

The ease of hydrolysis of the azlactone ring of 2-methyl-4-(2-thenal)-5-oxazolone resembled that of its benzene analog (10). Refluxing with aqueous acetone was sufficient to effect ring opening to α-acetamido-β-2-thienylacrylic acid.

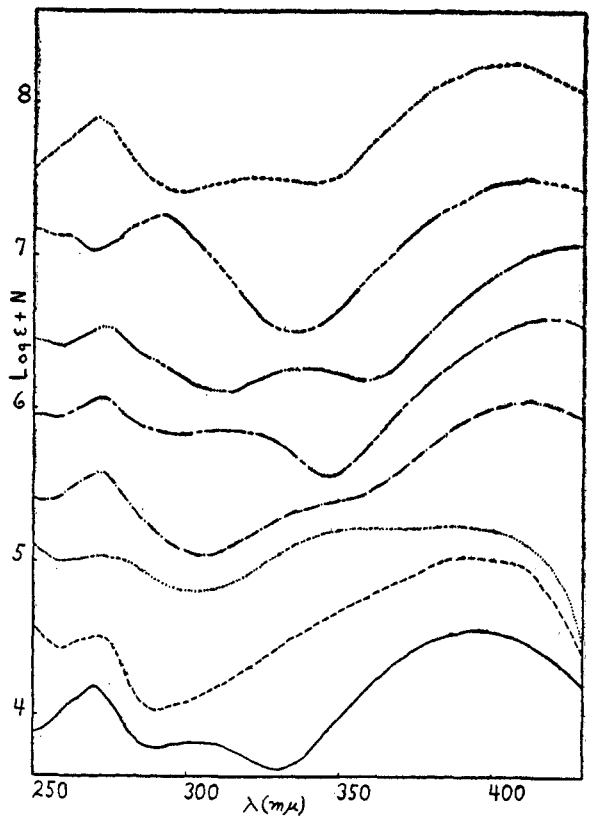


FIGURE 1. ULTRAVIOLET ABSORPTION CURVES OF AZLACTONES.

2-Phenyl-4-(2-thenal)-5-oxazolone ———	N = 0
2-Phenyl-4-(2,5-dimethyl-3-thenal)-5-oxazolone — — — —	N = 0.5
2-Phenyl-4-(2,3,5-trimethyl-4-thenal)-5-oxazolone.....	N = 1.0
2-Phenyl-4-(3,4-dimethyl-2-thenal)-5-oxazolone—.—.—.—.	N = 1.5
2-Phenyl-4-(4,5-dimethyl-2-thenal)-5-oxazolone—-—-—	N = 2.0
2-Phenyl-4-(3,4,5-trimethyl-2-thenal)-5-oxazolone—.....—.....	N = 2.5
2-Phenyl-4-(3-thianaphthal)-5-oxazolone—------—------	N = 3.0
2-Phenyl-4-(3-methyl-2-thenal)-5-oxazolone-----.....-----.....-----	N = 3.7

EXPERIMENTAL[2]

Azlactones and rhodanines. The procedure described previously for the preparation of other members of these series (1) was followed.

[2] The 3,4-dimethylthiophene used in these experiments was obtained through the courtesy of Dr. H. D. Hartough of the Socony-Vacuum Oil Company, Paulsboro, N. J. The analyses were performed by A. A. Sirotenko of this laboratory.

α,β-Di-(2-thienyl)acrylonitrile. 2-Thenaldehyde (5.0 g., 0.045 mole) and 5.5 g. (0.045 mole) of 2-thienylacetonitrile were dissolved in 68 cc. of ethanol contained in a 500-cc. round-bottom flask. One gram of sodium was dissolved in 90 cc. of ethanol and added to the above solution. Yellow crystals began to precipitate at once. The flask was fitted with a reflux condenser and heated over a low flame until the solution began to boil. After chill-

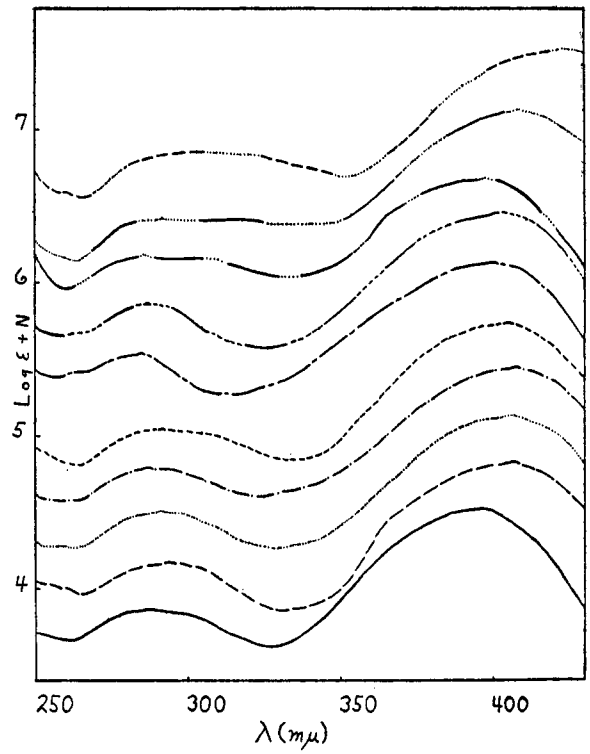


FIGURE 2. ULTRAVIOLET ABSORPTION SPECTRA OF RHODANINES.

2-Thenalrhodanine ———	N = 0
5-Methyl-2-thenalrhodanine — — — —	N = 0.3
5-Ethyl-2-thenalrhodanine.....	N = 0.6
5-Propyl-2-thenalrhodanine—.—.—.—.—.—.—.	N = 0.9
3-Methyl-2-thenalrhodanine----------	N = 1.3
5-Chloro-2-thenalrhodanine— - - - - - - - -	N = 1.6
5-Bromo-2-thenalrhodanine— - - - - - - - - - - - -	N = 1.9
3-Thianaphthalrhodanine—.....—.....—.....	N = 2.2
3,4-Dimethyl-2-thenalrhodanine—.....—	N = 2.6
3,4,5-Trimethyl-2-thenalrhodanine — — — — —.....	N = 3.0

ing in an ice-bath the contents of the flask were filtered, yielding 7.93 g. of yellow crystals. The filtrate was diluted with a little water and left in a refrigerator overnight. An additional 0.75 g. of product was thus obtained, giving a total yield of 8.68 g. (89%). After recrystallization from ethanol the m.p. was 129.5–130.5°.

Anal. Calc'd for $C_{11}H_7NS_2$: C, 60.82; H, 3.22.
Found: C, 60.83; H, 3.15.

α-Phenyl-β-(2-thienyl)acrylonitrile. Applying the above method a yield of 82% of yellow crystals was obtained, m.p. 89.5–90.5°, from 2-thenaldehyde and benzyl cyanide.

Anal. Calc'd for $C_{13}H_9NS$: C, 73.93; H, 4.26.

Found: C, 73.90; H, 4.04.

α-(2-Thienyl)-β-phenylacrylonitrile. Using the above procedure a yield of 77% of yellow crystals was obtained, m.p. 75.5–76.5°, from benzaldehyde and 2-thienylacetonitrile.

Anal. Calc'd for $C_{13}H_9NS$: C, 73.93; H, 4.26.

Found: C, 73.88; H, 4.13.

3,4-Dimethyl-2-thenaldehyde. The N-methylformanilide synthesis (5) was applied to 3,4-dimethylthiophene and gave an 83% yield. White needles were obtained from ethanol (Norit), m.p. 69–70°.

Anal. Calc'd for C_7H_8OS: C, 59.99; H, 5.71; M.W., 140.

Found: C, 59.82; H, 5.56; M.W., 156.

2,3,4-Trimethylthiophene. The Wolff-Kishner reduction was applied to 3,4-dimethyl-2-thenaldehyde as described for other members in these studies (6). The yield of the water-clear liquid was 81%, b.p. 47–49°/5 mm.; 162–165°/763 mm.; n_D^{20} 1.5213. Reference (11) lists b.p. 160–163° at normal pressure.

Anal. Calc'd for $C_7H_{10}S$: C, 66.67; H, 7.93.

Found: C, 66.33; H, 7.58.

3,4,5-Trimethyl-2-thenaldehyde. The N-methylformanilide synthesis (5) was applied to 2,3,4-trimethylthiophene. The yield of white needles after recrystallization from ethanol (Norit) was 79%, m.p. 46–47°; b.p. 116–117°/5 mm.

Anal. Calc'd for $C_8H_{10}OS$: C, 62.34; H, 6.49.

Found: C, 62.36; H, 6.34.

ω-Benzamido-2-vinylthiophene. α-Benzamido-β-2-thienylacrylic acid (8.2 g., 0.03 mole), 40 cc. of freshly distilled quinoline, and 1 g. of copper powder were heated in an oil-bath slowly to 180° and kept there for 20 minutes. The reaction mixture was cooled and decanted into dilute hydrochloric acid, whereupon a dirty yellow solid precipitated. The solid was filtered and washed successively with dilute hydrochloric acid and water. It was then boiled with dilute sodium carbonate solution for 15 minutes and filtered again. Upon recrystallization from aqueous ethanol (Norit) 1.2 g. of white plates was obtained which sintered at 135° and had m.p. 144.5–145.5°.

Anal. Calc'd for $C_{14}H_{11}NO_3S$: C, 68.12; H, 4.80.

Found: C, 67.83; H, 4.42.

Ethyl α-benzamido-β-(2-thienyl)acrylate. 2-Phenyl-4-(2-thenal)-5-oxazolone (3.48 g., 0.014 mole) was suspended in 14 cc. of benzene and 1.7 cc. of 1 *N* sodium ethoxide was added. The azlactone rapidly dissolved and the ester began to precipitate. After 3 minutes an excess of dilute hydrochloric acid was added and the mixture shaken. The white precipitate was filtered and washed with water. The yield after recrystallization from aqueous ethanol amounted to 3.55 g. (86%) of white needles, m.p. 177.5–178°.

Anal. Calc'd for $C_{16}H_{15}NO_3S$: C, 63.79; H, 4.98.

Found: C, 63.41; H, 4.59.

Methyl α-benzamido-β-(2-thienyl)acrylate. When the above procedure was repeated with 1 *N* sodium methoxide, the methyl ester was obtained in a yield of 75%, m.p. 185.5–186.5°.

Anal. Calc'd for $C_{15}H_{13}NO_3S$: C, 62.71; H, 4.52.

Found: C, 62.82; H, 4.23.

α-Acetamido-β-2-thienylacrylic acid. To a mixture of 328 cc. of acetone and 127 cc. of water was added 35.2 g. (0.18 mole) of 2-methyl-4-(2-thenal)-5-oxazolone. The mixture was refluxed for 4 hours and the acetone removed on the steam-bath. After addition of 290 cc. of water the solution was boiled for 5 minutes and filtered. The residue was again boiled with 250 cc. of water, filtered, and the combined filtrates left in a refrigerator overnight. The acid which had precipitated was filtered and dried *in vacuo* over P_2O_5 and KOH. After recrystallization from hot water (Norit) there was obtained 27.4 g. (71%) of white crystals, m.p. 227.5–228.5°d.

Anal. Calc'd for $C_9H_9NO_3S$: C, 51.18; H, 4.26.
Found: C, 51.13; H, 4.19.

Ultraviolet absorption spectra. The spectra were obtained with a Beckman quartz spectrophotometer, Model DU, using chloroform as the solvent for the azlactones and absolute alcohol for the rhodanines.

SUMMARY

1. Several azlactones and rhodanines were prepared from 3-thianaphthaldehyde and some di- and tri-methylsubstituted thenaldehydes and their ultraviolet absorption spectra were compared.

2. The condensation of aldehydes with arylacetonitriles was shown to take place in the thiophene series.

3. Two new thenaldehydes were synthesized from 3,4-dimethylthiophene by successive formylation and reduction.

4. The decarboxylation of α-benzamido-β-2-thienylacrylic acid to the corresponding styrylamide was effected by heating with quinoline and copper powder.

5. Alcoholysis of 2-phenyl-4-(2-thenal)-5-oxazolone proceeded readily with either methanol or ethanol.

6. Hydrolysis of 2-methyl-4-(2-thenal)-5-oxazolone was achieved in a 71% yield.

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[CONTRIBUTION FROM THE WEIZMANN INSTITUTE OF SCIENCE]

CONDENSATION REACTIONS OF 2,6-LUTIDINE AND AN ESTROGENIC 2,6-DISTYRYLPYRIDINE DERIVATIVE

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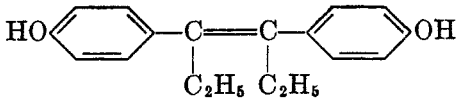
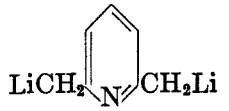
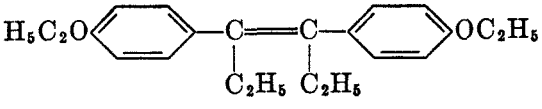
I. In the studies on synthetic estrogens [for a review, see (1)], no attention appears to have been paid to the possibility of introducing heterocyclic radicals in suitable positions into the active molecule of stilbestrol (I). In connection with other experiments, the reaction of the dilithium derivative (II) of 2,6-lutidine with *p*-ethoxypropiophenone (2, 3, 4) (as a model experiment, the reaction of 2,6-lutidine with 1 mole of benzaldehyde was investigated; see Experimental Part), and conversely the condensation by means of acetic anhydride,



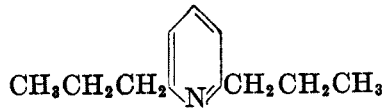
I



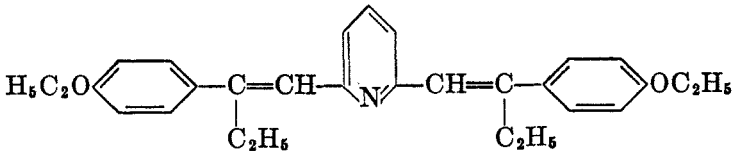
II



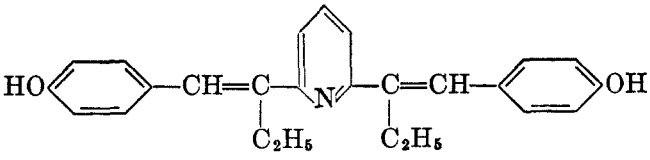
Ia



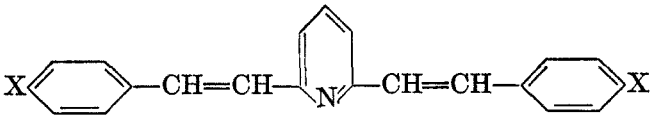
III



IV



V

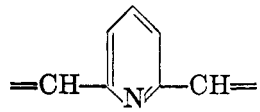


VI, X = OH
VII, X = CN

[1] Part of a thesis presented by S. Pinchas to the Hebrew University in partial fulfilment of the requirements for the degree of Ph.D.

of 2,6-dipropylpyridine (III) with *p*-hydroxybenzaldehyde, was studied. In the former instance, IV, in the latter, V was formed. It is interesting that V showed no estrogenic activity, while IV is—very slightly, yet distinctly—active. Its activity is 33 mouse units per gram.[2] Stilbestrol diethyl ether (Ia) is 125 times less active than I (5).

The interposition, in stilbestrol, of the group



does not destroy its activity. Compound IV appears as a higher vinylog of stilbestrol; however, a shift of the ethyl groups in IV gives a completely inactive

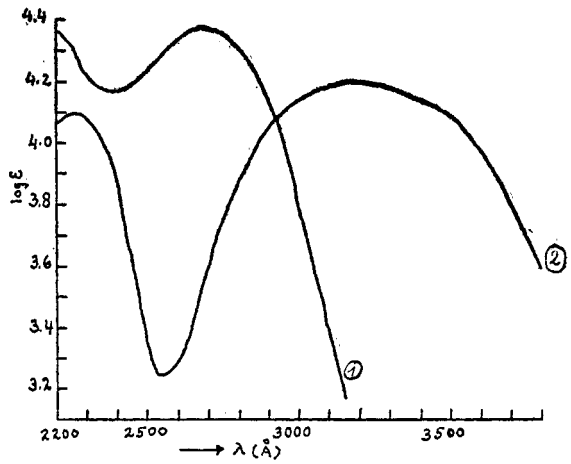


FIG. 1. Ultraviolet absorption (in alcoholic solution) of (1) 2,6-di-(4′-ethoxy-α-ethylstyryl)pyridine (IV) and of (2) 2,6-di-(*p*-hydroxystyryl)pyridine (VI).

substance, as in V. IV corresponds in type to the equally active 3-(*p*-hydroxyphenyl)-4-propyl-7-hydroxycoumarin (6) and to the cinnolines recently described by Kornfeld (7).

2,6-Dipropylpyridine was obtained from II and ethyl bromide, in analogy to Wibaut and Beets' synthesis of β-(2-pyridyl)propionaldehyde acetal (8). Its ability to condense with *p*-hydroxybenzaldehyde is considerably greater than that of 2,6-lutidine, to judge from the relatively good yield of V (see below).

The absorption spectrum of IV is significantly different from that of 2,6-di-(*p*-hydroxystyryl)pyridine (VI) (Fig. 1). This difference cannot be ascribed to the presence of the *p*-ethoxy groups in IV; it must be connected with the ethyl groups and recalls the difference in ultraviolet absorption between stilbene and α, β-dialkylstilbenes (9, 9a, 10, 10a).

[2]For the biological evaluation, we are indebted to Prof. B. Zondek, Hadassah Hospital, Jerusalem.

II. In the presence of acetic anhydride as condensing agent, *p*-hydroxybenzaldehyde (which is converted into its acetyl derivative) undergoes condensation with 2,6-lutidine to VI only with difficulty; the best yield obtained was 23%. The slowness of the reaction expresses itself in contradistinction with other benzaldehydes (11), in the formation of considerable quantities of *p*-acetoxybenzaldiacetate which is no longer capable of easy condensation. Also in the reaction with malonic acid (12), *p*-hydroxybenzaldehyde gives the smallest yield of all aldehydes investigated. As in the case of benzaldehyde (13), the second molecule of the aldehyde reacts more easily than the first: even if a molar ratio of the two components is used, the distyryl compound prevails in the product.

III. In connection with these experiments, 2,6-di-(*p*-cyanostyryl)pyridine (VII) was synthesized. For its preparation, two possibilities were envisaged: the reduction of the easily available 2,6-di-(*p*-nitrostyryl)pyridine to the corresponding diamino compound and subsequent replacement of the amino groups, or the condensation of 2,6-lutidine with *p*-cyanobenzaldehyde. The first method failed, as the replacement of the amino groups by nitrile radicals gave a most unsatisfactory yield. Also an attempt to condense *p*-aminobenzaldehyde (in form of its sulfate) with 2,6-lutidine, met with no success. As to the second method, it was to be expected that *p*-cyanobenzaldehyde would behave like *p*-nitrobenzaldehyde, in view of the general similarity between the NO_2 and the CN groups. This prediction is borne out by the facts. The two aldehydes resemble each other also in that respect, that they are not converted into the benzaldiacetates under the influence of boiling acetic anhydride [for *p*-nitrobenzaldehyde, see Shaw and Wagstaff (11)].

Difficulties were encountered in the preparation of *p*-cyanobenzaldehyde. Neither the oxidation of *p*-cyanobenzyl alcohol nor that of *p*-cyanobenzyl chloride (with cupric nitrate) (14) nor the Sandmeyer reaction of *p*-aminobenzaldehyde gave satisfactory yields (15). The method of choice was the oxidation of *p*-tolunitrile with chromic acid anhydride in presence of acetic anhydride, and subsequent hydrolysis of the *p*-cyanobenzaldiacetate obtained. However, even in this method, the desired aldehyde was always accompanied by *p*-carbamidobenzaldehyde (16); the methods of its isolation and transformation into the *p*-cyano compound are described in the Experimental Part. Surprisingly, the presence of traces of *p*-carbamidobenzaldehyde has an adverse effect on the reaction of 2,6-lutidine with the *p*-cyano derivative.

EXPERIMENTAL

2,6-Di-(4'-ethoxy-α-ethylstyryl)pyridine (IV). In a slow current of nitrogen, and with stirring, a solution of bromobenzene (63 g., 0.4 mole) in ether (100 cc.) was quickly added to a suspension of lithium turnings (5.5 g., 0.8 atom) in the same solvent (150 cc.). In an exothermic reaction, practically all the lithium disappeared within two hours. The addition of 2,6-lutidine (16 g., 0.15 mole) in ether (50 cc.) caused a renewed exothermic reaction, and the solution turned dark red. After one hour, 4-ethoxypropiophenone (54 g., 0.30 mole, b.p. 140–145°/3 mm.) (17) was slowly added and the reaction product hydrolyzed by careful addition of water (100 cc.) and dilute hydrochloric acid (300 cc.). The top layer was dried

and concentrated in the vacuum of the suction pump, and the residue subjected to fractionation under 0.1 mm. pressure. The fraction (20 g.) boiling at 120–160° was re-distilled; b.p. 110°/0.22 mm.; b.p. 125°/0.2 mm. It formed a slightly yellowish, viscous oil, which gave a hygroscopic and very unstable hydrochloride. Yield, 30% of theory.

Anal. Calc'd for $C_{29}H_{33}NO_2$: C, 81.5; H, 7.7.

Found: C, 82.0; H, 7.8.

2,6-Dipropylpyridine. A solution of dilithio-2,6-lutidine was prepared, as above, from lithium (11 g., 1.6 atoms) and bromobenzene (125 g., 0.8 mole) in ether (500 cc.) with 2,6-lutidine (32 g., 0.3 mole). Upon slow addition of ethyl bromide (75 g., 0.7 mole), dissolved in ether (100 cc.), the solution began to boil and the color disappeared. After addition of 300 cc. of water, the ethereal layer was separated and the aqueous layer extracted with fresh ether (50 cc.). The reaction product showed, after repeated fractionation, the b.p. 54–56°/4 mm.; it was an almost colorless, mobile oil, insoluble in water, but soluble in acids, and had a characteristic, not at all lutidine-like odor. Yield, 28 g.

Anal. Calc'd for $C_{11}H_{17}N$: C, 81.0; H, 10.4; N, 8.6.

Found: C, 81.5; H, 10.9; N, 8.7.

2,6-Di-(4'-hydroxy-β-ethylstyryl)pyridine (*V*). A mixture of 2,6-dipropylpyridine (4.5 g., 0.028 mole), *p*-hydroxybenzaldehyde (10.0 g., 0.08 mole) and acetic anhydride (23 cc., 0.25 mole) was refluxed for thirty hours and poured into an excess of water. The reaction product which precipitated as a dark resin, was triturated with concentrated hydrochloric acid and thus converted (hydrolysis of the acetoxy to hydroxy groups) into the *hydrochloride* which crystallized from the solution. It was filtered and recrystallized repeatedly from nitrobenzene and glacial acetic acid and finally from 75% acetic acid. Yellow, prismatic crystals of m.p. 282°; yield, 5 g. The substance is insoluble in water and hydrocarbons, but dissolves in pyridine, aqueous alkali and alcohol.

Anal. Calc'd for $C_{25}H_{26}ClNO_2$: C, 73.6; H, 6.4.

Found: C, 73.0; H, 6.3.

The *free base* was prepared by addition of aqueous ammonia to the solution of the hydrochloride in dilute acetic acid; from a mixture of acetic acid and water (6:1), its *dihydrate* crystallized as a yellow, microcrystalline powder, m.p. 146°. It is very soluble in alcohols, acetone, acetic acid and its esters, insoluble in water and hydrocarbon solvents. The analysis was none too satisfactory, but the *picrate* of the base was well-defined and homogeneous; it formed orange-red crystals of m.p. 236°.

Anal. Calc'd for $C_{25}H_{25}NO_2 \cdot 2H_2O$: C, 73.7; H, 7.1; N, 3.4.

Found: C, 74.3; H, 6.2; N, 3.7.

2-Methyl-6-(2'-phenyl-2'-hydroxyethyl)pyridine. To a solution of phenyllithium (from 0.5 g. of lithium turnings and 5 g. of bromobenzene in 50 cc. of ether), there was added 2.8 cc. of 2,6-lutidine and, after some standing, 2.7 g. of benzaldehyde in ethereal solution. The reaction product was decomposed with a solution of ammonium chloride (5 g.) in water (100 cc.) and purified by repeated distillation *in vacuo*; b.p. 133°/0.01 mm.; yield, 2 g.

Anal. Calc'd for $C_{14}H_{15}NO$: C, 78.8; H, 7.0; N, 6.6.

Found: C, 79.2; H, 7.6; N, 6.8.

2,6-Di-(p-acetoxystyryl)pyridine. A mixture of 2,6-lutidine (27 g.; 0.25 mole), *p*-hydroxybenzaldehyde (92 g.; 0.75 mole), and acetic anhydride (250 cc.; 2.7 moles) was refluxed for twenty-one hours at 150–160° (bath temperature). The reaction mixture was poured into water (1.5 l.) and kept, with occasional shaking, until the excess acetic anhydride was completely hydrolyzed. The brown solid product was filtered, washed with water and recrystallized repeatedly from ethyl alcohol. Thus, 23 g. of colorless prismatic needles of m.p. 183° was obtained; their solution exhibited a violet fluorescence.

Anal. Calc'd for $C_{25}H_{21}NO_4$: C, 75.2; H, 5.3; N, 3.5.

Found: C, 75.2; H, 5.7; N, 3.5.

Concentration of the alcoholic mother liquors gave 37 g. of crystals of m.p. 96°, which were identified as *p*-acetoxybenzaldiacetate (18).

Without condensing agent, no reaction took place in boiling toluene (four hours) or at

120–130° without solvent (six hours). Increase of the amount of acetic anhydride used, reduces the yield, and more *p*-acetoxybenzaldiacetate is formed, which does not condense easily, if at all, with 2,6-lutidine. Even under conditions, which stoichiometrically favor the formation of 2-methyl-6-(*p*-acetoxystyryl)pyridine, the di-(*p*-acetoxystyryl) compound is formed predominantly.

2,6-Di-(p-hydroxystyryl)pyridine (VI). A mixture of the preceding substance (1.5 g.) and of 0.75 *N* alcoholic potassium hydroxide (15 cc.) was refluxed for ninety minutes and the reaction product precipitated from the clear solution as a voluminous powder by a current of carbon dioxide. It was precipitated as the *hydrochloride hydrate* from aqueous sodium hydroxide solution by dilute hydrochloric acid and recrystallized from water (250 cc.). Long yellow needles, which melted above 300° under carbonization, and were slightly soluble in boiling alcohol, easily in pyridine.

Anal. Calc'd for $C_{21}H_{13}ClNO_2 \cdot H_2O$: C, 68.1; H, 5.4; N, 3.8.
Found: C, 68.1; H, 5.5; N, 3.7.

Hydrate formation of such styryl-pyridine derivatives has been observed in a number of instances (13, 19, 20).

The *free base* was obtained from the hydrochloride hydrate, when its solution in 10% aqueous sodium hydroxide solution was acidified with 50% acetic acid. From butyl or ethyl alcohol, light yellow, small needles, m.p. 254° (decomp.). The solution of the base in pyridine, cyclohexanone, acetic acid and alcohols show strong fluorescence; the base is insoluble in hydrocarbon solvents and water.

Anal. Calc'd for $C_{21}H_{17}NO_2$: C, 80.0; H, 5.4; N, 4.4.
Found: C, 80.0; N, 5.5; N, 4.4.

2-Methyl-6-(p-hydroxystyryl)pyridine. A mixture of lutidine (2.2 g.), *p-acetoxy*benzaldehyde (3.6 g.) (b.p. 160–170°/22 mm.) (21), acetic anhydride (5 cc.) and glacial acetic acid (5 cc.) was refluxed for ten hours in a slow current of nitrogen. The dark resin so obtained was washed with water and extracted with 50 cc. of ethyl alcohol. This left 0.8 g. of 2,6-di(*p*-acetoxystyryl)pyridine undissolved. The alcoholic solution was concentrated and the residue hydrolyzed with an excess of concentrated hydrochloric acid. The solution so obtained was brought to dryness *in vacuo*, and the residue dissolved in 10% aqueous sodium hydroxide solution and precipitated by neutralisation. Repeated crystallization from methanol, butyl acetate and aqueous methanol gave colorless needles of m.p. 232° (decomp.), which are soluble in acetic acid and most other organic solvents and fluoresce in solution.

Anal. Calc'd for $C_{14}H_{13}NO$: C, 79.6; H, 6.2; N, 6.6.
Found: C, 80.0; H, 6.4; N, 6.6.

Acetyl derivative, prepared with acetic anhydride and a drop of concentrated sulfuric acid, from very little of dilute alcohol shiny, colorless leaflets of m.p. 95°.

Anal. Calc'd for $C_{16}H_{15}NO_2$: C, 75.9; H, 5.9; N, 5.5.
Found: C, 75.6; H, 6.3; N, 6.1.

2,6-Di-(p-cyanostyryl)pyridine (VII) and 2-methyl-6-(p-cyanostyryl)pridine. A mixture of *p*-cyanobenzaldehyde (4.0 g.), 2,6-lutidine (1.7 cc.) and acetic anhydride (13 cc.) was refluxed for ten hours and diluted with water (200 cc.). After the excess acetic anhydride had undergone hydrolysis, a brown solid remained, which was filtered, washed with water and dissolved in boiling alcohol (75 cc.) in the presence of charcoal. From the filtered solution, 2,6-di-(*p*-cyanostyryl)pyridine crystallized upon cooling (yield, 1.5 g., 25%). Repeated recrystallization from 80% alcohol and glacial acetic acid gave the compound in long, almost colorless prismatic needles of m.p. 175–176°. Its solution in alcohol or benzene shows an intense violet fluorescence.

Anal. Calc'd for $C_{23}H_{15}N_3$: C, 82.9; H, 4.5; N, 12.6.
Found: C, 83.3; H, 4.5; N, 12.5.

The alcoholic mother liquor was cautiously diluted with aqueous ammonia, until turbidity appeared; upon standing, 2-methyl-6-(*p*-cyanostyryl)pryidine crystallized. Repeated recrystallization from 70% alcohol gave colorless prismatic needles of m.p. 131°, in a yield of 0.7 g.

Anal. Calc'd for $C_{15}H_{12}N_2$: C, 81.8; H, 5.5; N, 12.7.
Found: C, 82.2; H, 5.6; N, 12.7.

p-Cyanobenzaldehyde. (a) *p-Carbamidobenzaldehyde.* To a mixture of *p*-tolunitrile (38 g.) (22), glacial acetic acid (450 cc.) and acetic anhydride (450 cc.) which was cooled in an ice-salt mixture, concentrated sulfuric acid (67 cc.) was added slowly with vigorous agitation, so that the temperature did not exceed 25°. The solution was then cooled to 5°, and in the course of ninety minutes, finely ground chromic acid anhydride (72 g.) was added at a temperature of 5–8°. Thirty minutes after the addition, the temperature began to rise slowly. When it reached 10°, the stirring was interrupted and the reaction mixture left overnight. It was then poured out onto 2 kg. of ice, and water (2 l.) was added. The fine colorless precipitate so obtained was washed with water. (From the mother liquors, a small quantity of *p*-cyanobenzaldehyde could be secured by extraction with benzene, hydrolysis and conversion into the bisulfite compound.) The solid was suspended in 2% sodium carbonate solution (400 cc.), filtered, washed, dried (28 g.) and refluxed for thirty minutes with a mixture of concentrated sulfuric acid (7 cc.), ethyl alcohol (75 cc.) and water (100 cc.). From the filtered solution, a mixture of *p*-cyanobenzaldehyde (long white needles of m.p. 92–93°) and an oil separated on standing. The solid was separated and the mother liquor (containing the oil) diluted with an equal volume of water. Thereby, the oil was induced to crystallize: 7 g. of *p*-carbamidobenzaldehyde (14%), m.p. 75–76°. A second small crop of *p*-cyanobenzaldehyde was obtained by concentration of the mother liquor; total yield, 6.3 g. (15%). *p*-Carbamidobenzaldehyde crystallized from dilute alcohol or petroleum ether in colorless needles, m.p. 75–76°.

Anal. Calc'd for $C_8H_7NO_2$: N, 9.4. Found: N, 9.4.

(b) *p-Carbamidobenzaldiacetate.* A mixture of *p*-carbamidobenzaldehyde (2 g.), acetic anhydride (10 cc.) and one drop of conc'd sulfuric acid was refluxed for thirty minutes, and diluted with water (100 cc.). The crystals which separated upon standing, were recrystallized from dilute alcohol or petroleum ether, m.p. 118°.

Anal. Calc'd for $C_{12}H_{13}NO_5$: C, 55.2; H, 5.4; N, 5.6; acetyl, 34.0.
Found: C, 55.8; H, 5.2; N, 5.3; acetyl, 32.0.

(c) *p-Cyanobenzaldehyde.* A mixture of the preceding substance (64 g.) and thionyl chloride (100 cc.) was refluxed for two hours aud the excess thionyl chloride distilled off. To the remaining red oil, alcohol (200 cc.), water (200 cc.), and dilute sulfuric acid (40 cc.) was added and the mixture refluxed again for one hour. The filtered solution was diluted with an equal volume of water and cooled at 0°, whereupon *p*-cyanobenzaldehyde (25 g.) crystallized. A small second crop secured by concentration of the mother liquor, brought the yield to 85%.

2,6-Di-(p-nitrostyryl)pyridine and 2-methyl-6-(p-nitrostyryl)pyridine. A mixture of *p*-nitrobenzaldehyde (30.2 g.), 2,6-lutidine (11.2 cc.) and acetic anhydride (60 cc.) was refluxed for six hours and after addition of 2,6-lutidine (5.6 cc.) for further eight hours, and then poured into water (500 cc.). The crystals of the di-nitrostyryl compound which precipitated, were separated from the aqueous mother liquor and some adherent oil; from pyridine (intense green fluorescence), shiny yellow leaflets, m.p. 258° (decomp.); yield, 31% (23). The filtrate was further diluted, and deposited, upon standing, a 50% yield of 2-methyl-6-(*p*-nitrostyryl) pyridine, from water or 50% alcohol, yellow needles, m.p. 135° (24), from 80% alcohol, needles of m.p. 96°. The latter substance is converted into 2,6-di-(*p*-nitrostyryl)pyridine only with difficulty.

2,6-Di-(p-aminostyryl)pyridine. A mixture of 2,6-di-(*p*-nitrostyryl)pyridine (12.5 g.), tin (20 g.) and 10% hydrochloric acid (300 cc.) was gently refluxed until the metal had disappeared completely. The *stannous chloride double salt* of the desired diamine, which precipitated, was collected, washed with water and alcohol and dried (22.0 g.); it was soluble in acetone (as in other solvents, with red color) and crystallized from hydrochloric acid in orange prisms.

The salt was triturated with a mixture of 180 cc. of alcohol and 20 cc. of 33% aqueous sodium hydroxide solution. Filtration and extraction of the solid with boiling alcohol (100 cc.)

gave two extracts, which were combined. The alcohol was removed by distillation and the residue triturated with water, filtered and dried; m.p. 230°; yield, quantitative. Royer's method (25) which used as reducing agent hydrogen and Raney nickel, gave only 49% yield. The base is soluble in pyridine and dilute acids, sparingly soluble in benzene and acetone.

Anal. Calc'd for $C_{21}H_{19}N_3$: C, 80.5; H, 6.1; N, 13.4.

Found: C, 79.9; H, 6.5; N, 13.2.

The transformation of the diamino into the dicyano compound failed.

SUMMARY

1. In the presence of acetic anhydride, *p*-hydroxybenzaldehyde and 2,6-lutidine condense to 2-methyl-6-(*p*-hydroxystyryl)pyridine and 2,6-di-(*p*-hydroxystyryl)pyridine (VI). The same behavior is shown by *p*-nitro- and *p*-cyanobenzaldehyde. The preparation of the latter aldehyde is described in detail.

2. 2,6-Di-(*p*-nitrostyryl)pyridine can be reduced to the diamino compound; the conversion of the latter into 2,6-di-(*p*-cyanostyryl)pyridine failed.

3. The dilithio-compound of 2,6-lutidine (II) gives with ethyl bromide 2,6-dipropylpyridine, and the latter with *p*-hydroxybenzaldehyde 2,6-di-(4′-hydroxy-β-ethylstyryl)pyridine (V).

4. The dilithio-compound (II) gives, with *p*-ethoxypropiophenone, 2,6-di-(4′-ethoxy-α-ethylstyryl)pyridine (IV). IV, a "vinylog" of stilbestrol, has estrogenic activity, V has not.

REHOVOTH, ISRAEL

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[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

AMINES DERIVED FROM 3,3-DIPHENYL-2-BUTANONE AND 2,2-DIPHENYLCYCLOHEXANONE

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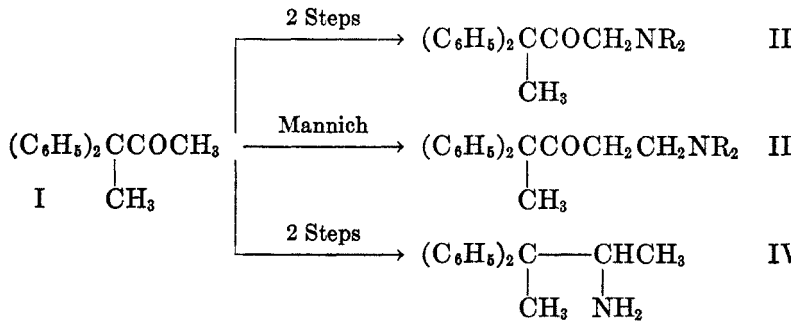
An important feature of the potent analgesic, methadon, seems to be the quaternary carbon atom to which are attached two phenyl groups, a carbonyl group, and a basic side chain. In order to determine whether arrangement of these essential groups in a different way around the quaternary carbon atom would still result in analgesic activity, the following derivatives of 3,3-diphenyl-2-butanone (I) (1) were prepared:



In Table I are listed the derivatives of types II and III which were prepared. In every case, however, the analgesic activity was of a low order.

A similar modification was employed in the preparation of analogous derivatives of 2,2-diphenylcyclohexanone (V) (2):

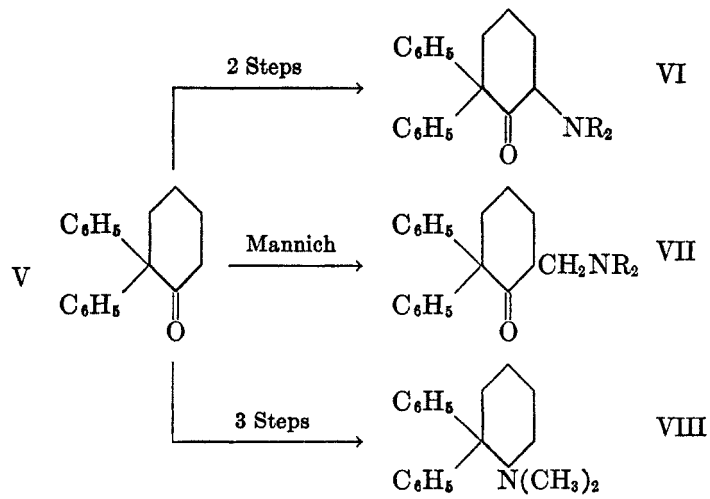


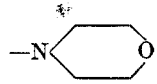
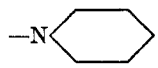
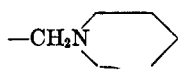
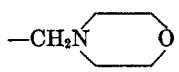
Table II lists the derivatives of types VI and VII which were prepared.[1] Here too, even though the basic residue is attached to the quaternary carbon atom through the cyclohexane ring, the analgesic activity in every case was of a low order. The cyclohexanone derivative VI ($-NR_2$ = piperidino) showed strong local anesthetic activity but proved to be too irritating for practical purposes.

The two amines IV and VIII were also prepared through the corresponding ketoximes. These likewise showed no interesting pharmacological properties.

TABLE I

1-DIALKYLAMINO-3,3-DIPHENYL-2-BUTANONES (II) AND 1-DIALKYLAMINO-4,4-DIPHENYL-3-PENTANONES (III)

$(C_6H_5)_2C(CH_3)COCH_2X$

X[a]	M.P.,[b] °C.	YIELD, %	FORMULA	ANALYSES, %					
				Calc'd			Found		
				C	H	N	C	H	N
$-N(CH_3)_2$	238–239	70[c]	$C_{18}H_{22}ClNO$	71.15	7.30	4.61	71.42	7.48	4.55
	219–221	75[c]	$C_{20}H_{24}ClNO_2$	69.45	6.99	4.05	69.67	6.88	3.81
	194–196	59[c]	$C_{21}H_{26}ClNO$	73.34	7.62	4.07	73.30	7.44	3.95
$-CH_2N(CH_3)_2$	170–171	33[d]	$C_{19}H_{24}ClNO$	71.83	7.61	4.41	71.56	7.56	4.41
$-CH_2N(C_2H_5)_2$	112–113	1[d]	$C_{21}H_{28}ClNO$	72.91	8.15	4.04	72.54	8.17	4.06
	188–189	36[d,e]	$C_{22}H_{28}ClNO$	73.85	7.88	3.91	73.68	7.70	4.01
	177–178	17[d]	$C_{21}H_{26}ClNO_2$	70.08	7.28	3.90	70.28	7.17	3.94

[a] All compounds reported as hydrochlorides. [b] Uncorrected. [c] Based on bromoketone. [d] Based on ketone. [e] Prepared in refluxing isoamyl alcohol.

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EXPERIMENTAL

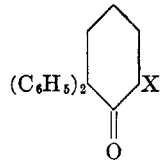
3,3-Diphenyl-2-butanone (I) was prepared according to the procedure outlined by Meerwein (1). Since experimental details are lacking in this case, the following procedure is

[1] Burger, Bennet, Turnbull, and Dinwiddie (Abstracts of Papers, A.C.S. Meeting, Philadelphia, April, 1950, p. 13K) have recently indicated the preparation of cyclohexanone derivatives of the identical type.

given. Fifty-six grams of 1,1-dimethyl-2,2-diphenylethylene glycol (1) was added with stirring to 300 cc. of concentrated sulfuric acid cooled in an ice-bath, keeping the temperature below 5°. After standing at room temperature for two hours the red solution was poured into ice-water and diluted to a volume of three liters. After refrigeration overnight, the yellow solidified product was filtered, taken up in ether, washed with bicarbonate solution,

TABLE II

6-DIALKYLAMINO- (VI) AND 6-DIALKYLAMINOMETHYL-2,2-DIPHENYLCYLOHEXANONES (VII):



X[a]	M.P.,[b] °C.	YIELD, %	FORMULA	ANALYSES, %					
				Calc'd			Found		
				C	H	N	C	H	N
—$N(C_2H_5)_2$[e]	186–187	1[c]	$C_{23}H_{32}ClNO_2$[f]	70.86	8.27	3.59	71.43	7.61	3.69
—N⟨⟩	200–201	68[c]	$C_{24}H_{32}ClNO_2$[f]	71.70	8.02	3.48	71.48	8.21	3.51
—N⟨⟩[h]	187–191	81[c]	$C_{23}H_{30}ClNO_2$[f]	71.20	7.79	3.61	71.10	7.56	3.89
—N⟨O⟩	238–239	78[c]	$C_{22}H_{26}ClNO_2$	71.04	7.04	3.76	71.14	6.87	3.76
—$CH_2N(CH_3)_2$[e,g]	165–166	27[d]	$C_{22}H_{30}ClNO_2$[f]	70.29	8.04	3.72	69.45	8.05	3.87
—$CH_2N(C_2H_5)_2$	158–159	31[d]	$C_{24}H_{34}ClNO_2$[f]	71.29	8.48	3.46	70.98	8.56	3.53
—CH_2N⟨⟩	229–230	30[d]	$C_{24}H_{30}ClNO$	75.07	7.87	3.64	75.07	7.91	3.70
—CH_2N⟨O⟩	173–174	8[d]	$C_{23}H_{28}ClNO_2$	71.57	7.31	3.63	71.78	7.37	3.66

[a,b,c,d] See corresponding footnotes for Table I. [e] Not obtained analytically pure. [f] Contains one molecule of methanol of crystallization. [g] Free base: needles from Skellysolve B, m.p. 106–107°. *Anal.* Calc'd for $C_{21}H_{25}NO$: C, 82.04; H, 8.20; N, 4.56. Found: C, 82.09; H, 8.07; N, 4.59. [h] Free base: flat prisms from Skellysolve B, m.p. 111–113°. *Anal.* Calc'd for $C_{22}H_{25}NO$: C, 82.71; H, 7.87; N, 4.38. Found: C, 82.98; H, 7.76; N, 4.36.

and dried. After removal of the ether, the residue was distilled *in vacuo*. There was obtained 38 g. (73% yield) of ketone I, b.p. 101–103°/0.3 mm., m.p. 40–41°.

2,2-Diphenylcyclohexanone (V) was also prepared according to the method of Meerwein (2). Cyclopentanone was treated with anhydrous hydrogen cyanide and the resulting cyanohydrin hydrolyzed in an 85% over-all yield to 1-hydroxycyclopentanecarboxylic acid. Direct esterification with methanol gave the corresponding methyl ester in an 80% yield. Treatment of this hydroxy ester with excess phenylmagnesium bromide gave the corre-

sponding glycol in yields varying from 94 to 98% in three runs (Meerwein reported a 60% yield). However, the quantitative yield reported by Meerwein for the pinacol rearrangement of this glycol could be duplicated only when the sulfuric acid was diluted with ether according to the following procedure.

A solution of 77 g. of the glycol in 350 cc. of ether was added dropwise with stirring to 380 cc. of concentrated sulfuric acid, keeping the temperature below 5°. After standing for two hours at room temperature the solution was poured into ice and diluted to a volume of four liters. The product was filtered, washed well with water and pentane, and dried. There was obtained 71.5 g. (99% yield) of ketone V, m.p. 93–96°. One recrystallization from Skellysolve B gave large prisms, m.p. 97–99°.

3,3-Diphenyl-2-butanone oxime was prepared in the usual manner from ketone I in 87% yield, m.p. 149–151° (long flat prisms from methanol).

Anal. Calc'd for $C_{16}H_{17}NO$: C, 80.30; H, 7.16.
Found: C, 80.70; H, 7.26.

1,1-Diphenyl-2-aminobutane (IV). Preliminary attempts to reduce the above oxime in ethanolic hydrogen chloride solution with 20% palladium-charcoal catalyst at low pressure failed. Hydrogenation was finally accomplished in ethanolic ammonia with Raney nickel catalyst (5 g. for 10 g. of oxime) activated with chloroplatinic acid, at 75° and 1000 pounds hydrogen pressure for eight hours. The product, obtained in only 40% yield, was isolated as the *hydrochloride*, m.p. 224–225° (from isopropanol).

Anal. Calc'd for $C_{16}H_{20}ClN$: C, 73.42; H, 7.78; N, 5.35.
Found: C, 72.95; H, 7.92; N, 5.36.

2,2-Diphenylcyclohexanone oxime could not be prepared in good yield by the usual dilute alkali procedure. However, refluxing 8.6 g. of ketone V with 8.6 g. of hydroxylamine hydrochloride in a solution of 43 cc. of pyridine in 43 cc. of dry ethanol gave, after removal of solvents and recrystallization from 95% ethanol, 7 g. (77% yield) of the oxime (long needles), m.p. 203–204°.

Anal. Calc'd for $C_{18}H_{19}NO$: N, 5.28. Found: N, 5.23.

2,2-Diphenylcyclohexylamine. A solution of 7.4 g. of the above oxime in 100 cc. of dry methanol was treated with 5 cc. of liquid ammonia. Three grams of Raney nickel and 0.03 g. of chloroplatinic acid hexahydrate was added and the mixture was hydrogenated at 75° and 1400 pounds pressure for one hour. The product, isolated as the *hydrochloride*, weighed 6 g. (75% yield), m.p. 267–268° (from isopropanol-ether).

Anal. Calc'd for $C_{18}H_{22}ClN$: N, 4.86. Found: N, 4.94.

A sample was converted to the free *base*: colorless platelets from Skellysolve B, m.p. 91–92°.

Anal. Calc'd for $C_{18}H_{21}N$: C, 86.00; H, 8.42; N, 5.57.
Found: C, 86.17; H, 8.47; N, 5.40.

N,N-Dimethyl-2,2-diphenylcyclohexylamine (VIII). A solution of 1.4 g. of 2,2-diphenylcyclohexylamine (free base) in 7 cc. of 90% formic acid was refluxed with 0.33 g. of paraformaldehyde for four hours. Removal of the solvent *in vacuo* and isolation of the product as the *hydrochloride* gave 1.3 g., m.p. 231–235°. Recrystallization from ethanol-ether gave m.p. 235–236°.

Anal. Calc'd for $C_{20}H_{26}ClN$: C, 76.04; H, 8.29; N, 4.43.
Found: C, 75.86; H, 8.59; N, 4.16.

1-Bromo-3,3-diphenyl-2-butanone. To a solution of 22.4 g. (0.1 mole) of ketone I in 250 cc. of dry ether at 25° was added, dropwise with stirring over a period of 2½ hours, a solution of 16 g. of bromine in 125 cc. of chloroform. The temperature rose to 30° during the addition. The mixture was stirred for another hour and poured into ice-water. After washing to neutrality, the ether and chloroform were distilled and the residue was distilled *in vacuo*. There was obtained 26 g. (86% yield) of colorless product, b.p. 164–165°/0.8 mm., n_D^{25} 1.5980. This bromoketone could not be crystallized.

Anal. Calc'd for $C_{16}H_{15}BrO$: C, 63.38; H, 4.99.
Found: C, 65.47; H, 5.36.

As indicated by the analytical results this bromo compound is not pure. However, it was used successfully without further purification.

6-Bromo-2,2-diphenylcyclohexanone. The bromination of cyclohexanone V was carried out in essentially the same manner as indicated above for the bromination of butanone I. From 20 g. of ketone V in 250 cc. of dry ether and 25 cc. of chloroform, treated with 12.8 g. of bromine in 100 cc. of chloroform, was obtained 26 g. (98% yield) of product, m.p. 112–115°. Recrystallization from Skellysolve B for analysis gave colorless, slender needles, m.p. 114–115°.

Anal. Calc'd for $C_{18}H_{17}BrO$: C, 65.69; H, 5.21.
Found: C, 65.89; H, 4.95.

Preparation of 1-dialkylamino-3,3-diphenyl-2-butanones (II). *Piperidino derivative.* A solution of 6.6 g. of 1-bromo-3,3-diphenyl-2-butanone in 60 cc. of dry ether was treated with 3.72 g. of piperidine. The precipitation of piperidine hydrobromide began almost at once and the mixture warmed perceptibly. After standing overnight at room temperature, the piperidine hydrobromide was filtered and washed with ether. The combined washings and filtrate were shaken with 60 cc. of 2 *N* sodium hydroxide and washed with four 60-cc. portions of water. The ether was then extracted with two 60-cc. portions of 10% hydrochloric acid. The combined acid extracts were made alkaline with excess sodium hydroxide. The precipitated oil was taken up in ether, washed, and dried over magnesium sulfate. Treatment of the filtered ether solution with ethereal hydrogen chloride precipitated 4.4 g. (59% yield) of *1-piperidino-3,3-diphenyl-2-butanone hydrochloride*, m.p. 194–196°. Recrystallization from isopropanol-ether did not raise the melting point. The dimethylamino and morpholino derivatives (Table I) were prepared in a similar manner.

Preparation of 6-dialkylamino-2,2-diphenylcyclohexanones (VI). *Morpholino derivative.* The bromine atom in the cyclohexanone derivative proved to be less reactive than that in the bromobutanone. Reactions with the secondary amines were carried out in refluxing toluene. A solution of 8.6 g. of 6-bromo-2,2-diphenylcyclohexanone in 30 cc. of dry toluene was refluxed and stirred with 6.5 g. of morpholine for five hours. The morpholine hydrobromide was filtered and the filtrate was worked up as described in the immediately preceding procedure. There was obtained 7.6 g. (78% yield) of product which on recrystallization from isopropanol gave 5.1 g. of fine needles, m.p. 238–239°. Further details on this compound and on other members of the same series are given in Table II. As can be seen, the yield of the diethylamino derivative was very low. The dimethylamino derivative could not be prepared even when the reaction was carried out under pressure in a closed system. The first three compounds in Table II were recrystallized from a methanol-ether mixture and contained one molecule of methanol of crystallization.

Preparation of 1-dialkylamino-4,4-diphenyl-3-pentanones (III). *Dimethylamino derivative.* A solution of 8.96 g. (0.04 mole) of 3,3-diphenyl-2-butanone (I) in 40 cc. of dry ethanol was refluxed for 12 hours with 16.4 g. of dimethylamine hydrochloride, 3.0 g. of paraformaldehyde, and 0.2 cc. of concentrated hydrochloric acid. The reaction mixture was treated with dilute hydrochloric acid and ether and separated. The acidic extract was made basic with 20% sodium hydroxide and the oil which separated was taken up in ether and washed with water to neutrality. Drying of the ether solution (magnesium sulfate) and treatment with ethereal hydrogen chloride gave 4.2 g. (33% yield) of colorless crystalline powder, m.p. 170–171° (rapid heating). Recrystallization from methanol-ether resulted in no change, although the rate of heating of the bath affected the melting point appreciably. Further details, as well as data on other compounds of this series, are given in Table I. The piperidino derivative could not be prepared in this manner, but a higher-boiling solvent, isoamyl alcohol, was necessary. The procedure used in this case was essentially that described below for the cyclohexanone derivatives.

Preparation of 6-dialkylaminomethyl-2,2-diphenylcyclohexanones (VII). *Dimethylamino derivative.* A mixture of 5 g. (0.02 mole) of 2,2-diphenylcyclohexanone, 2.4 g. of dimethylamine hydrochloride, 1.6 g. of paraformaldehyde, and 30 cc. of isoamyl alcohol was refluxed for ten minutes. Then a further 1.6 g. of paraformaldehyde was added in small portions over a

period of 30 minutes with continued refluxing. After addition was complete, 0.2 cc. of concentrated hydrochloric acid was added and refluxing was continued for another five minutes. The cooled solution was extracted with three 50-cc. portions of water. The combined aqueous extracts were made alkaline with 20% sodium hydroxide and the precipitated basic oil was converted to the *hydrochloride* in the usual manner. There was obtained 1.9 g. (27% yeild) of product, m.p. 161–166°, which on recrystallization from methanol-ether gave fine colorless needles, m.p. 165–166°, containing one molecule of methanol of crystallization. The last two compounds in Table II were recrystallized from isopropanol which did not appear in the product. The rate of heating of these Mannich compounds affected their melting points appreciably. The reported melting points were taken with rapid heating.

SUMMARY

A number of amines derived from 3,3-diphenyl-2-butanone and from 2,2-diphenylcyclohexanone have been prepared as possible analgesics related to methadon.

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[CONTRIBUTION FROM THE ORGANIC RESEARCH DEPARTMENT, ABBOTT LABORATORIES]

1-PHENYL-2-TETRALONE AND 1-PHENYL-2-NAPHTHYLAMINE

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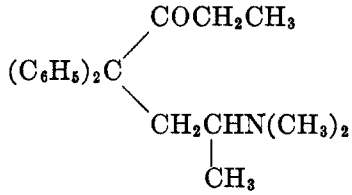
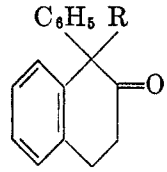
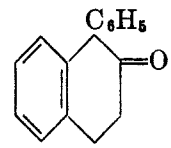
In the structure of the potent analgesic methadon, ring-closure between the propionyl and one of the phenyl groups would result in the β-tetralone structure I (R = 2-dimethylaminopropyl). In the present work attempted synthesis of this type led to the preparation of 1-phenyl-2-tetralone (II) by perbenzoic acid oxidation of 1-phenyl-3,4-dihydronaphthalene.





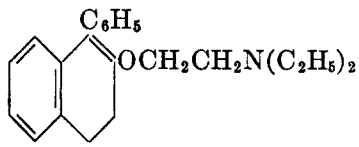
I



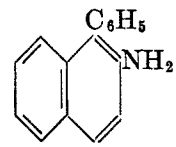
II

Unlike previously reported (1) alkylations of β-tetralones, alkylation of II with diethylaminoethyl chloride, using sodamide as a condensing agent resulted in O-alkylation to give the enol ether III isolated as the acid oxalate, m.p. 155–156°.

Further anomalous behavior in this series was encountered when attempts were made to hydrogenate (in acid solution) the oxime of 1-phenyl-2-tetralone (II) to the corresponding 1-phenyl-1,2,3,4-tetrahydro-2-naphthylamine. Instead of reduction, dehydroisomerization occurred and the sole product isolated was 1-phenyl-2-naphthylamine (IV).



III



IV

The identity of this compound was established by conversion to a diacetylimino derivative and by other properties described in the experimental section. The same product was obtained from the oxime of II by acid treatment in the absence of catalytic reducing conditions as well as by catalytic dehydrogenation. Similar transformations of cyclic oximes have already been noted. The most recent report (2) seems to be that of the acid-catalyzed dehydroisomerization of several substituted thiophanone oximes to the corresponding aminothiophenes. However, the tendency for this type of reaction to take place appears to be unpredictable. In the present work, unsubstituted β-tetralone oxime could not be converted to β-naphthylamine either under the conditions used for the conversion of the oxime of II or by the procedure of Cheney and Piening (2).

EXPERIMENTAL

1-Phenyl-2-tetralone (II). The perbenzoic acid oxidation was an adaptation of the method of English and Cavaglieri (3). To a solution of 24 g. (0.116 mole) of 1-phenyl-3,4-dihydronaphthalene (4) in 200 cc. of chloroform cooled to −10° was added dropwise with stirring a solution of 17.4 g. (0.126 mole) of perbenzoic acid (5) (determined iodometrically) in 485 cc. of chloroform. The temperature was not allowed to rise above −4° and after addition was complete, the mixture was kept in the ice-bath for 2½ hours. Iodometric titration of a sample indicated nearly complete consumption of the perbenzoic acid. The solution was then washed with excess 2 *N* sodium hydroxide and water, and dried over magnesium sulfate. Distillation of the chloroform *in vacuo* gave 27 g. of a viscous oil which could not be crystallized. This oil was then refluxed for 3½ hours with 200 cc. of 30% sulfuric acid, taken up in ether, washed with bicarbonate, and dried. Distillation of the ether gave 26 g. of the viscous oil which still could not be crystallized. It was then fractionally distilled *in vacuo* through a nine-inch helix-packed column. There was obtained 18 g., b.p. 141–142°/0.5 mm. Redistillation of a sample for analysis gave b.p. 156–158°/1 mm., n_D^{24} 1.6089.

Anal. Calc'd for $C_{16}H_{14}O$: C, 86.45; H, 6.34.
Found: C, 86.06; H, 6.30.

Phenylhydrazone, prepared from the ketone in the usual manner, m.p. 146–147.5° (from ethanol-methanol mixture).

Anal. Calc'd for $C_{22}H_{20}N_2$: N, 8.96. Found: N, 9.09.

During the distillation of the phenyltetralone, a solid material came over in the first fraction. Crystallization from 95% ethanol gave a small amount of a compound, m.p. 124–125.5°.

Anal. Calc'd for $C_{16}H_{14}O_2$: C, 80.64; H, 5.91.
Found: C, 80.35, 80.25; H, 5.67, 5.81.

This corresponds to a structure containing one more oxygen atom than the 1-phenyl-2-tetralone. This by-product is very likely one of the two possible isomeric lactones formed by further oxidative rearrangement of ketone (6). Since insufficient material was at hand, the compound was not investigated further.

1-Phenyl-2-tetralone oxime. A mixture of 10 g. of 1-phenyl-2-tetralone, 25 g. of hydroxylamine hydrochloride, 100 cc. of 10% sodium hydroxide, 150 cc. of water, and 200 cc. of 95% ethanol was heated to boiling for ten minutes. Cooling in ice gave 7 g. of crude oxime. Recrystallization from 200 cc. of hot alcohol by the addition of 10 cc. of hot water gave 5 g., m.p. 184–185°.

Anal. Calc'd for $C_{16}H_{15}NO$: C, 80.98; H, 6.37; N, 5.90.
Found: C, 81.01; H, 6.35; N, 5.96.

1-Phenyl-2-naphthylamine (IV) *A. By dehydroisomerization.* A solution of 6 g. of 1-phenyl-2-tetralone oxime in 200 cc. of absolute ethanol containing 2.8 g. of hydrogen chloride was treated with 0.6 g. of 20% palladium on charcoal and shaken with hydrogen at 35 pounds pressure and 55° for 36 hours. No hydrogen uptake was observed. The catalyst was filtered and the filtrate was concentrated *in vacuo* to 25 cc. This solution was treated with 200 cc. of water and 20 cc. of concentrated hydrochloric acid, heated to boiling and filtered from a small amount of insoluble oil. Cooling in ice and filtering gave 4.0 g. of crystalline powder, m.p. 235–236° (dec.). Recrystallization of a sample from ethanol-ether resulted in no change of melting-point.

Anal. Calc'd for $C_{16}H_{14}ClN$: N, 5.48. Found: N, 5.26.

Conversion to the free *base* gave small prisms (from Skellysolve B), m.p. 93–94°.

Anal. Calc'd for $C_{16}H_{13}N$: C, 87.64; H, 5.97; N, 6.39.
Found: C, 87.91; H, 5.90; N, 6.17.

This product could be diazotized and coupled with β-naphthol; with lithium aluminum hydride at 100° in the quantitative apparatus (7) it showed 1.94 active hydrogen atoms per mole of compound. (It is interesting to note that with the Grignard reagent, CH_3MgI, only one active hydrogen atom reacted under the same conditions.)

When the oxime (0.5 g.) was treated in the absence of catalyzed hydrogen with 100 cc. of dry alcohol containing 0.25 g. of hydrogen chloride for 65 hours at 40°, 0.27 g. of 1-phenyl-2-naphthylamine hydrochloride, m.p. 235–236° (dec.), was obtained. It formed a free base identical in every way with that reported above.

B. By catalytic dehydrogenation. A solution of 1.0 g. of the above oxime in 40 cc. of *p*-cymene was refluxed with 0.5 g. of 20% palladium on charcoal for four hours. The catalyst was filtered and the *p*-cymene was removed *in vacuo*. Working up of the residue in the usual way gave a very small amount of a hydrochloride which on conversion to the free base melted at 92–94° after recrystallization from Skellysolve B. When mixed with a sample of 1-phenyl-2-naphthylamine prepared by procedure A, it gave no melting point depression.

1-Phenyl-2-diacetyliminonaphthalene. The naphthylamine (V) (free-base) (0.6 g.) was refluxed for three hours with 7 cc. of acetic anhydride. The excess anhydride was decomposed with water and the residual solid (0.57 g., m.p. 98–102°) was recrystallized several times from Skellysolve B to give fine white needles, m.p. 105–107°.

Anal. Calc'd for $C_{20}H_{17}NO_2$: C, 79.18; H, 5.65; N, 4.62.

Found: C, 79.40; H, 5.85; N, 4.89.

Alkylation of 1-Phenyl-2-tetralone. A solution of 5 g. of 1-phenyl-2-tetralone and 3.9 g. of freshly distilled diethylaminoethyl chloride in 50 cc. of dry toluene was treated with stirring, in a nitrogen atmosphere, with a suspension of sodamide (prepared from 1.13 g. of sodium with liquid ammonia) in 30 cc. of dry toluene. The temperature was maintained below 35° during the addition. Then it was raised to 90° and maintained between 90° and 92° for five hours with continued stirring. After refluxing finally for one hour, the reaction mixture was cooled and extracted with excess dilute hydrochloric acid (1:5). The aqueous solution was then extracted with ether and made alkaline with excess 20% sodium hydroxide. The oil which separated was taken up in ether, washed, and dried over magnesium sulfate. Filtration and distillation of the ether gave 5.1 g. of an orange oil which could not be crystallized. However 6.5 g. of crude oxalate was obtained in solid form. Recrystallization from 40 cc. of absolute ethanol gave 4.0 g. of small shiny leaflets, m.p. 155–156°. Further recrystallizations for analysis did not improve the melting point.

Anal. Calc'd for $C_{22}H_{27}NO \cdot H_2C_2O_4$: C, 70.04; H, 7.10; N, 3.40.

Found: C, 69.93; H, 6.99; N, 3.52.

This product was not stable in warm dilute aqueous acid but decomposed to give a neutral substance; and no water insoluble basic material remained on prolonged heating.

Acknowledgment. Grateful acknowledgment is made to Mr. E. F. Shelberg, head of the Abbott Microanalytical Laboratory, for the elementary analyses.

SUMMARY

1-Phenyl-2-tetralone has been prepared and its alkylation has been attempted. 1-Phenyl-2-tetralone oxime has been found to undergo acid-catalyzed dehydroisomerization to 1-phenyl-2-naphthylamine.

NORTH CHICAGO, ILLINOIS

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF IOWA STATE COLLEGE]

SILICON-CONTAINING AZO DYES

S. V. SUNTHANKAR AND HENRY GILMAN

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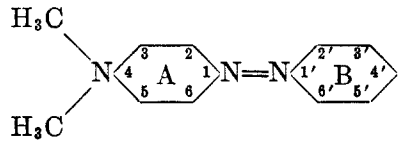
The relation between chemical constitution and the carcinogenic action of the azo dyes has not been as extensively investigated as in the case of polynuclear hydrocarbons. However, from the studies of the carcinogenic action of *p*-aminoazobenzene and its derivatives, it was found that methyl groups greatly enhance the potency of the parent azo dye, provided these groups occupy certain positions. For example, 4-N,N-dimethylaminoazobenzene (I) and its 2′-, 3′-, and 4′-methyl derivatives as well as 2-methyl- and 2,2′-dimethyl derivatives were found to possess carcinogenic potency (1). It was, therefore, thought to be of



I

interest to study the carcinogenic action of some trimethylsilyl and triphenylsilyl derivatives of (I), to compare the effect of an R_3Si group with a methyl group from the point of view of carcinogenic potency of the respective azo dyes. The second purpose was to examine the substantivity of these dyes for textile fibers, in order to find out if the substitution of the R_3Si group has any favorable effect on their substantivity. We, therefore, have synthesized several silicon-containing azo dyes, which are reported in this paper.

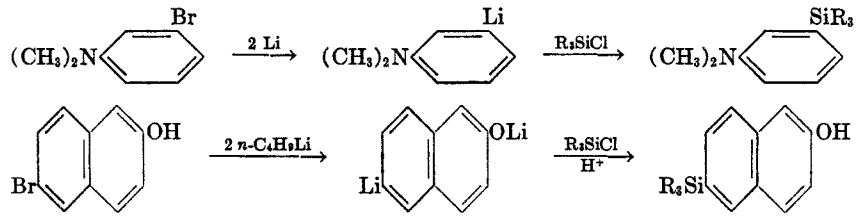
The only silicon-containing azo compound reported in the literature is 4,4′-bis(triethylsilyl)azobenzene, obtained by the reduction of 4-nitrophenyltriethylsilane with zinc and sodium hydroxide (2).

The preparation of the trimethylsilyl and triphenylsilyl derivatives of (I) met with certain difficulties. For example, attempts to prepare derivatives of (I) with an R_3Si group in the benzene ring B have not been successful. The reaction of organolithium derivatives of aniline with the appropriate chlorosilanes yielded polymeric products rather than the trimethylsilyl- and triphenylsilylaniline required for coupling with dimethylaniline. Furthermore, the reduction of *p*-nitrophenyltrimethylsilane with hydrogen under pressure using Raney nickel as a catalyst is reported to give only a low over-all yield of the corresponding amine.[1] Therefore, our preliminary study was restricted to the preparation of dyes having an R_3Si- substituent in the benzene ring A.

The silicon-containing azo dyes were prepared by coupling organosilicon compounds with selected diazonium salts. The organosilicon compounds were synthesized by the action of trimethylsilyl chloride and triphenylsilyl chloride

[1] Unpublished studies by Dr. R. A. Benkeser.

on the organolithium derivatives of dimethylaniline and 2-naphthol (3). The lithium compounds of dimethylaniline were prepared by the direct action of lithium on the corresponding bromodimethylanilines (4) and those of 2-naphthol



were obtained by the halogen-metal interconversion reaction of *n*-butyllithium with the bromonaphthols (5).

A notable difference was observed in the behavior of *ortho*-, *meta*-, and *para*-substituted dimethylanilines toward diazonium salts. *p*-Trimethylsilyl- and *p*-triphenylsilyl-dimethylaniline coupled readily with the *p*-nitrobenzenediazonium salt; but the dye isolated in both cases was N,N-dimethyl-4-(*p*-nitrophenylazo)aniline in about 80% yield. The latter is evidently formed by the replacement of trimethylsilyl and triphenylsilyl groups by the diazonium cation, during the diazo-coupling reaction. Several examples of the replacement of substituents in the diazo-coupling reaction have been recorded in the literature. The earliest ones are the replacement of the carboxyl group during diazo-coupling with 2-hydroxy-1-naphthoic acid and *p*-hydroxybenzoic acid (6). Later, it was observed that halogen and sulfonyl groups in the 1-position of 2-naphthol are also replaced by the diazonium ion (7). Similarly, organolead groups (R_3Pb-) have been found to be replaced by the diazonium cation (8). During our work we have observed that bromine or the carboxyl group *para* to the tertiary amino group in *p*-bromodimethylaniline and *p*-dimethylaminobenzoic acid, respectively, is replaced to some extent.

Next, in order to study empirically the comparative ease of replacement of different substituents, a few competitive coupling reactions were carried out. First, only one equivalent of *p*-nitrobenzenediazonium salt was allowed to react competitively with one equivalent of dimethylaniline and one of *p*-triphenylsilyldimethylaniline in acetic acid solution. From the reaction mixture the products isolated were N,N-dimethyl-4-(*p*-nitrophenylazo)aniline (70%) and *p*-triphenylsilyldimethylaniline (90%). This indicates that the diazonium cation replaces a proton in preference to the triphenylsilyl group. When the reaction was repeated in dilute sodium hydroxide-acetone mixture as a solvent, the same two compounds were isolated, but the yield of the dye was 50%. Similar competitive coupling reactions, when carried out in acetic acid with mixtures of the same silicon compound and each of *p*-dimethylaminobenzoic acid and *p*-bromodimethylaniline separately, gave no conclusive results. Some tarry products were isolated from the reaction mixtures and the separation of the constituents was not possible. The *p*-nitrobenzenediazonium salt, therefore, was allowed to react separately with *p*-bromodimethylaniline and *p*-dimethylaminobenzoic acid.

TABLE I

SILICON-CONTAINING AZO DYES

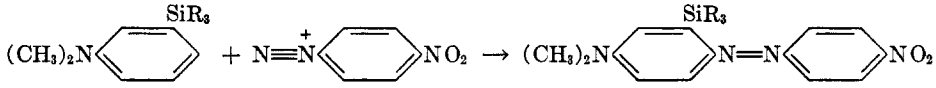
NO.	AMINE DIAZOTIZED	TIME OF COUPLING REACTION, HR.[a]	COLOR OF DYE	M.P., °C., (Uncorr.)	YIELD, %	FORMULA	ANALYSIS			
							Si, %		N(Cl or S[b]), %	
							Calc'd	Found	Calc'd	Found
	COUPLER: *m*-TRIMETHYLSILYLDIMETHYLANILINE									
1	Aniline[c]	1	Orange	110	60	$C_{17}H_{23}N_3Si$[e]	9.43	9.24	14.13	
2	*p*-Nitroaniline	1	Red-violet	192	95	$C_{17}H_{22}N_4O_2Si$[e]	8.19	7.98	16.38	16.70
3	2,4-Dinitroaniline[d]	2	Blue-violet	238–240	36	$C_{17}H_{21}N_5O_4Si$	7.23	6.94	18.09	
4	2-Chloro-4-nitroaniline[c]	0.5	Blue-violet	205–206	77	$C_{17}H_{21}ClN_4O_2Si$	7.44	7.45	9.43^{Cl}	9.39
5	2,6-Dichloro-4-nitroaniline[d]	1	Blue-violet	146	66	$C_{17}H_{20}Cl_2N_4O_2Si$	6.98	7.23	17.28^{Cl}	17.55
6	2,4-Dinitro-6-chloroaniline[d]	3	Blue-violet	158	35	$C_{17}H_{20}ClN_5O_4Si$	6.65	6.73	16.63	17.02
7	2-Trifluoromethyl-4-nitroaniline[d]	1.5	Blue-violet	223–224	83	$C_{18}H_{21}F_3N_4O_2Si$[e]	—	—	13.66	13.90
8	2-Methylsulfonyl-4-nitroaniline[d]	2	Blue-violet	243–244	69	$C_{18}H_{24}N_4O_4SSi$	6.67	6.47	7.62^{S}	7.61
9	2,4-Bis(methylsulfonyl)aniline[d]	1.5	Deep red	217–218	51	$C_{19}H_{27}N_3O_4S_2Si$	6.18	5.93	9.27	9.53
10	2-Hydroxy-4-nitroaniline[d]	10	Blue-violet	225–226	14	$C_{17}H_{22}N_4O_3Si$	7.82	8.11	15.64	
11	Sulfanilic acid[f]	1	Orange	251 d.	87	$C_{17}H_{23}N_3O_3SSi$	7.43	7.21	8.49^{S}	8.53
12	Metanilic acid[f]	1	Red-brown	240–241 d.	70	$C_{17}H_{23}N_3O_3SSi$	7.43	7.10	8.49^{S}	8.26
13	Sulfanilamide	1	Red-brown	213	75	$C_{17}H_{24}N_4O_2SSi$	7.45	7.71	8.51^{S}	8.54
14	Anthranilic acid[c]	9	Red	242 d.	53	$C_{18}H_{23}N_3O_2Si$[g]	8.21	7.98	12.31	12.60
15	*p*-Aminobenzoic acid[c]	2	Orange	240–241 d.	65	$C_{18}H_{23}N_3O_2Si$[h]	8.21	8.14	12.31	12.33
	COUPLER: *m*-TRIPHENYLSILYLDIMETHYLANILINE									
16	Aniline	2	Orange	193–194	50	$C_{32}H_{29}N_3Si$	5.8	6.07	8.70	
17	*p*-Nitroaniline	1	Brown-red	205–206	95	$C_{32}H_{28}N_4O_2Si$	5.31	5.28	10.62	10.64
18	2,4-Dinitroaniline[i]	1	Blue-violet	213–214	44	$C_{32}H_{27}N_5O_4Si$	4.88	4.88	12.21	11.92
19	2-Chloro-4-nitroaniline	2	Blue-violet	233–234	65	$C_{32}H_{27}ClN_4O_2Si$	4.98	5.22	9.96	10.26
20	2,6-Dichloro-4-nitroaniline	1	Garnet	230–231	53	$C_{32}H_{26}Cl_2N_4O_2Si$	4.69	4.92	9.38	9.71
21	2-Methylsulfonyl-4-nitroaniline[i]	3	Blue-violet	263	37	$C_{33}H_{30}N_4O_4SSi$	4.62	4.84	9.24	9.37
22	2,4-Bis(methylsulfonyl)aniline	3	Red-brown	235–236	20	$C_{34}H_{33}N_3O_4S_2Si$	4.38	4.51	6.57	6.81

23	Sulfanilic acid	2	Maroon	253–254 d.	85	$C_{32}H_{29}N_3O_3SSi$	4.97	4.65	7.46[N] 5.68[S]	7.23 5.41
24	Metanilic acid	2	Maroon	260 d.	80	$C_{32}H_{29}N_3O_3SSi$	4.97	4.75	5.68[S]	5.35
25	Sulfanilamide	2	Scarlet	224	90	$C_{32}H_{30}N_4O_2SSi$	4.98	5.21	7.47	7.28
26	Anthranilic acid	10	Red	254–255	10	$C_{33}H_{29}N_3O_2Si$	5.32	5.17	7.98	7.62
27	*p*-Aminobenzoic acid	2	Orange-red	274–275	70	$C_{33}H_{29}N_3O_2Si$	5.32	5.12	7.98	8.17
	NAPHTHOL AZO DYES									
	COUPLER: 6-TRIMETHYLSILYL-2-NAPHTHOL									
28	*p*-Nitroaniline	1	Orange-red	234–235	83	$C_{19}H_{19}N_3O_3Si$	7.68	7.48	11.51	11.38
29	Benzidine[j] (disazo dye)	2	Violet	314–315	70	$C_{38}H_{38}N_4O_2Si_2$	8.78	8.48	8.78	8.57
30	*o*-Dianisidine[i] (disazo dye)	2	Violet-blue	291–292	62	$C_{40}H_{42}N_4O_4Si_2$	8.41	8.70		
	COUPLER: 6-TRIPHENYLSILYL-2-NAPHTHOL									
31	*p*-Nitroaniline	2	Orange-red	316–317 d.	75	$C_{34}H_{25}N_3O_3Si$	5.08	5.31	7.62	7.61
32	Sulfanilamide	2	Orange-red	312–313	50	$C_{34}H_{27}N_3O_3SSi$	4.78	4.92	7.18	7.32
33	Benzidine[j] (disazo dye)	2	Violet	359–360	90	$C_{68}H_{50}N_4O_2Si_2$	5.54	5.46	5.54	5.50
34	*o*-Dianisidine[i] (disazo dye)	2	Blue	340	60	$C_{70}H_{54}N_4O_4Si_2$	5.23	5.27	5.23	5.52

[a] The times selected for many of these reactions were arbitrary and in slow coupling, the reactions were carried out for several hours at room temperature. [b] The figures in this column stand for the N%, unless otherwise indicated by superscript for chlorine or sulfur. [c] Diazotized by the method (A). [d] Diazotized by the method (B). [e] Final purification of the dye was done by the chromatographic method. [f] Crystallized from acetone. [g] Crystallized from chloroform. [h] Diazotized according to the procedure given by Fierz-David and Blangey (19). [i] Crystallized from benzene. [j] Crystallized from chlorobenzene.

The yields of the azo dye, N,N-dimethyl-4-(*p*-nitrophenylazo)aniline, obtained by the partial replacement of bromine and the carboxyl group during coupling, were 18% and 54%, respectively. From the yields of the azo dye, obtained under similar conditions, the ease of replacement of the substituents seems to decrease in the order H > SiR_3 > COOH > Br. It will be noted that, due to the similar electronegativities of hydrogen and silicon, both are displaced by the diazonium cation with relative ease.

m-Trimethylsilyl- and *m*-triphenylsilyl-dimethylaniline, however, showed normal behavior towards diazonium salts and gave a series of azo dyes in very good yields. The color of the dyes, obtained from these two compounds and the respec-



II

tive diazonium salts, was of almost the same tone but a comparison of the visual color of some of these dyes with that of unsubstituted dyes shows that the substitution of trimethylsilyl and triphenylsilyl groups in the azo dyes has a general bathochromic effect on the color. However, the exact effect can not be judged unless determined by spectroscopic methods. In general, the trimethylsilyl derivative coupled more readily than the triphenylsilyl compound, and this may be attributed to steric effects. A notable difference was observed in their reaction with certain diazonium salts containing functional groups in the *o*-position to the diazo group. For example, the diazonium sulfates obtained from 2-hydroxy-4-nitroaniline, 2,4-dinitro-6-chloroaniline, and 2-trifluoromethyl-4-nitroaniline coupled readily with the trimethylsilyl compound but failed to react with the triphenylsilyl derivative, even though the reaction was carried out for a prolonged time.

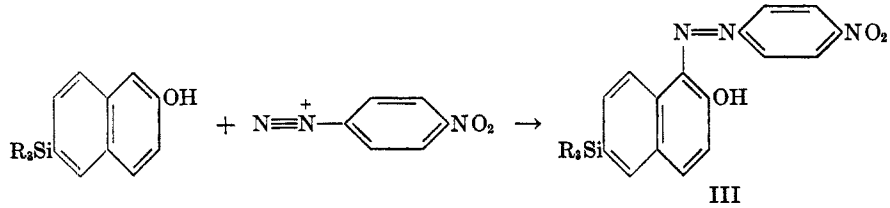
Since the diazonium ion is an electrophilic reagent, its cationoid reactivity will be increased by electron-attracting (−E) and decreased by electron-releasing (+E) substituents in the molecule. The nitro and trifluoromethyl groups are strongly electron-attracting and therefore, 2,4-dinitro-6-chlorobenzenediazonium ions and 2-trifluoromethyl-4-nitrobenzenediazonium ions should be very reactive. It seems, therefore, that their failure to couple with the triphenylsilyl compound may be due to the steric effect between the triphenylsilyl, and nitro and trifluoromethyl groups respectively, which happen to be in the *ortho* positions to the azo linkage being formed. The general low reactivity of 2-hydroxy-4-nitrobenzenediazonium ions may be due to both the +E effect of the hydroxyl group and the steric effect. Moreover, the diazonium salt obtained from 2-hydroxy-4-nitroaniline when added to water forms an internal diazo oxide, which couples with difficulty. It is also likely that the triphenysilyl group has more deactivating effect on the *ortho* position than has the trimethylsilyl group. The difference in reactivity due to the steric effect is also observed in the reaction of diazonium salts from anthranilic acid and *p*-aminobenzoic acid. The diazonium salt from anthranilic acid coupled with both the compounds but gave low yields, especially with the triphenylsilyl compound; whereas the dyes from *p*-aminobenzoic acid were obtained in good yields. That the steric effects, however, are not the only

considerations will be observed from the reaction of the diazonium salts from 2-methylsulfonyl-4-nitroaniline and 2,4-bis(methylsulfonyl)aniline with both the silicon compounds. In both cases, the bulky methylsulfonyl group which is in the *o*-position to the diazo group would be expected to offer more steric hindrance. Perhaps the activation of the diazonium cation may be increased considerably by the (−E) effect of the methylsulfone group. A comparison of the reactivity of the diazonium salts from 2-methylsulfonyl-4-nitroaniline and 2-trifluoromethyl-4-nitroaniline also reveals that the activation due to the substituent effect of methylsulfonyl group is, probably, more than that of the trifluoromethyl group, assuming the steric effect is the same in both cases.

o-Trimethylsilyl- and *o*-triphenylsilyl-dimethylaniline did not couple with the *p*-nitrobenzenediazonium salt even though the reaction was carried out for several hours. It has been reported that dimethylaniline substituted with the nitro- (9), methyl (10), and chloro- (11) groups in the *ortho*-position does not show any tendency to couple with the diazonium salt. We have found that *o*-bromodimethylaniline also fails to react with the diazonium salt. There are several other observations reported in the literature which show that *ortho*-substituted dimethylaniline is much less reactive than dimethylaniline in electrophilic substitutions. For example, *o*-nitrodimethylaniline, N,N-dimethyl-*o*-toluidine, and *o*-N,N-dimethylamino-*p*-xylene do not form *p*-nitroso derivatives by the action of nitrous acid (12). *o*-Chlorodimethylaniline is similarly indifferent to aqueous nitrous acid (9). The low reactivity of the above amines is also exhibited by the difficulty of their reactions with benzaldehyde and formaldehyde (12).

A rational interpretation of this general inactivity of *ortho*-substituted dimethylaniline can be given by taking into account its resonance interaction. The *o*-substituents in dimethylaniline crowd the tertiary amino group to a serious extent in the planar arrangement and thus disturb the planarity between the tertiary amino group and the benzene ring. This increases the energies of the contributing polar structures and diminishes their resonance interaction. Consequently the *p*-position, which is activated mainly by the resonance effect of the amino group, becomes less reactive towards electrophilic reagents.

Silicon-containing naphthols also showed a similar behavior toward *p*-nitrobenzenediazonium chloride. 1-Trimethylsilyl-2-naphthol, when reacted with *p*-nitrobenzenediazonium chloride, gave the azo dye 1-(*p*-nitrophenylazo)-2-naphthol. Since in 2-naphthol, the carbon in the 1-position is the only center of attack for the diazonium ion, the coupling takes place with the elimination of the trimethylsilyl group. 6-Trimethylsilyl- and 6-triphenylsilyl-2-naphthol, however, coupled with the different diazonium compounds and gave silicon-containing



III

dyes in good yields. Only the dyes from sulfanilic acid could not be obtained in pure form due to their high solubilities in water. 3-Trimethylsilyl- and 3-triphenylsilyl-2-methoxynaphthalene, however, did not couple with *p*-nitrobenzenediazonium chloride, although 2-methoxynapthhalene has been reported to couple with *p*-nitrobenzenediazonium chloride (13).

Action of acid-cleaving agents on the azo dyes. The action of acid-cleaving agents on the azo dyes was studied with a double purpose, first, to study the stability of the carbon-silicon bond in the azo dyes and, second, to remove the R_3Si-group to establish the structural position of the azo linkages.

It has been found that hydrogen chloride in acetic acid is a convenient reagent for the cleavage of organosilicon compounds (14). However the azo dyes (II, $R=CH_3$) and (II, $R=C_6H_5$) were unaffected when dry hydrogen chloride gas was bubbled through their refluxing acetic acid solutions for a long period. The dye (II, $R=C_6H_5$), being a tetraaryl silane derivative, would be expected to be much less susceptible to the acid cleavage since it has been observed that the tetraarylsilanes are much more resistant to acid cleavage than the trialkylarylsilanes (14); but the resistance of the dye (II, $R=CH_3$), containing the trimethylsilyl group, to acid cleavage warrants some discussion. The acid cleavage of organosilicon compounds involves a nucleophilic displacement on silicon by Cl^- accompanied by an electrophilic attack by proton on carbon and rupture of the C-Si bond. The acid cleavage of the C-Si bond should, therefore, be considerably influenced by the substituents in the aromatic ring. From the studies of the hydrogen chloride cleavage of organosilicon compounds, the order of the ease of cleavage of the groups is *p*-anisyl > *p*-dimethylaminophenyl > *p*-tolyl > *p*-chlorophenyl (14). Interestingly, this order is in essential agreement with the σ-constants of the substituents in the benzene ring (15). Since in the dye (II, $R=CH_3$) there are two groups having opposite effects, and since it is more resistant to the acid cleavage than *m*-trimethylsilyldimethylaniline, it is probable that the *p*-nitrobenzeneazo group has a more pronounced electronic effect than the *m*-dimethylamino group of σ-value (−0.211) (15). Furthermore, the azo linkage is *ortho* to the C-Si bond and therefore, steric effects may play a major role in the deactivation of the *ortho*-position.

Both the dyes (II, $R=CH_3$ and $R=C_6H_5$), however, were quite susceptible to acidic reducing agents. By the action of tin, or stannous chloride, and hydrochloric acid reduction of the azo linkage to amino groups and simultaneous cleavage of the C-Si bond took place. For structure proof, the dye (II, $R=CH_3$) was reduced with tin and hydrochloric acid. *p*-Aminodimethylaniline, obtained as one of the products, indicated that the azo linkage in the dye is *para* to the tertiary amino group and *ortho* to the trimethylsilyl group.

In the case of the naphthol azo dyes, the dye (III, $R=CH_3$) was cleaved smoothly by passing hydrogen chloride into its refluxing acetic acid solution. The product obtained was 1-(*p*-nitrophenylazo)-2-naphthol, indicating that the coupling takes place in the 1-position of the naphthalene ring. The dye (III, $R=C_6H_5$), however, was unaffected by this reagent, even though 6-triphenylsilyl-2-naphthol was cleaved smoothly by dry hydrogen chloride in acetic acid.

This gives further support to the assumption of the stabilization of the C-Si bond by the *p*-nitrobenzeneazo group.

The carcinogenic action and the dyeing properties of the dyes will be reported elsewhere.

EXPERIMENTAL

o-Triphenylsilyldimethylaniline. To a solution of 21 g. (0.071 mole) of triphenylchlorosilane dissolved in 100 ml. of ether was added 0.075 mole of *o*-dimethylaminophenyllithium [prepared from 20 g. (0.1 mole) of *o*-bromodimethylaniline and 1.8 g. (0.26 g.-atom) of lithium in 90% yield]. The reaction was instantaneous and Color Test I (16) was negative after the addition of the organolithium compound. The mixture was hydrolyzed by pouring into water. The ethereal layer was separated and dried over sodium sulfate. Ether was removed and the residue (18 g.) of m.p. 80–90°, which was contaminated with some oily compound, was purified by crystallization from ethanol; the yield of the pure compound was 10 g. (39%); m.p. 95.5°.

Anal. Calc'd for $C_{26}H_{25}NSi$: N, 3.69; Si, 7.39.

Found: N, 4.00 Si, 7.33.

The *meta*- and the *para*-isomers were prepared in a similar manner (17, 18).

m-Trimethylsilyldimethylaniline. To 16 g. (0.148 mole) of trimethylchlorosilane in 50 ml. of ether was added an ethereal solution of 0.14 mole of *m*-dimethylaminophenyllithium [prepared from carefully purified *m*-bromodimethylaniline (30 g., 0.15 mole) and lithium (2.3 g., 0.33 g.-atom) in 92% yield]. The reaction was prompt and Color Test I was negative just after the addition of the organolithium compound. The mixture was hydrolyzed and worked up in the customary manner. The yield of the crude product was 21 g. (77%). The liquid was purified by distillation under reduced pressure, b.p. 86–87° (1.0 mm.). The yield of pure *m*-trimethylsilyldimethylaniline was 14 g. (52%); d_4^{20} 0.9124; n_D^{20} 1.5257; MR_D 64.91 (calc'd MR_D 64.99).

Anal. Calc'd for $C_{11}H_{19}NSi$: Si, 14.51. Found: Si, 14.23.

o-Trimethylsilyldimethylaniline. This compound was prepared as in the previous case. The yield was 45%. It boiled at 65–65.5° (1.0 mm.); d_4^{20} 0.9324; n_D^{20} 1.5080; MR_D 62.16 (Calc'd MR_D: 64.99). The product, however, did not analyze correctly for silicon; probably it forms an azeotrope.

Anal. Calc'd for $C_{11}H_{19}NSi$: Si, 14.51. Found: Si, 11.65.

The *para*-isomer was prepared in a similar way (14).

PREPARATION OF THE AZO DYES

The diazotizations of the amines and their coupling reactions with the silanes were carried out by the customary procedures. The following are typical examples:

Diazotization of the amines. The amines containing one functional group were diazotized by the usual procedure, using hydrochloric acid and sodium nitrite (19). The aniline derivatives containing more than one negative group were diazotized by the nitrosyl sulfuric acid method (20).

Method (A). *p*-Nitroaniline (1.4 g., 0.01 mole) was added to 3 ml. of conc'd hydrochloric acid and 3 ml. of water. The mixture was warmed to 70° and then cooled to 0°, by keeping in ice. Three ml. of hydrochloric acid and 3 ml. of water were added. The mixture was stirred occasionally. A 20% solution of 0.7 g. (0.011 mole) of sodium nitrite was added and the mixture was kept in ice for 15–20 minutes. The diazonium salt solution was diluted by adding 10 g. of ice. Excess of nitrous acid was destroyed by adding urea and the resulting solution was used for coupling.

Method (B). 2,4-Dinitroaniline (1.83 g., 0.01 mole) was added to 20 ml. of glacial acetic acid and the mixture was heated to 70°, then cooled by keeping in ice. The amine acetate which separated was added as a slurry to a nitrosyl sulfuric acid solution. In order to

prepare the latter, 0.8 g. (0.011 mole) of sodium nitrite was added to 5.5 ml. of conc'd sulfuric acid (*d*, 1.84) and the mixture was heated to 70 ° and then cooled to 10°. During the addition of the amine acetate to nitrosylsulfuric acid, the temperature of the mixture was not allowed to rise above 15°. The diazonium salt was kept in ice for 30 minutes, with occasional stirring. Fifteen grams of ice were added. The excess of nitrous acid was destroyed by adding urea. The diazonium salt solution was added to the solution of the coupler through a filter paper.

N,N-Dimethyl-4-(p-nitrophenylazo)-3-(trimethylsilyl)aniline. To a solution of 1.93 g. (0.01 mole) of *m*-trimethylsilyldimethylaniline in 50 ml. of glacial acetic acid was added a filtered solution of 0.01 mole of *p*-nitrobenzenediazonium chloride and the mixture was stirred for half an hour, keeping the temperature of the reaction mixture below 10°. Sodium acetate was added to neutralize the mineral acid and to hasten the coupling reaction. After stirring for about 15 minutes more, the brown-red dye was collected; 3.25 g. (95%), m.p. 188–190°. The dye was crystallized from alcohol; the pure product melted at 192°.

1-(p-Nitrophenylazo)-6-trimethylsilyl-2-naphthol. To a solution of 3 g. (0.014 mole) of 6-trimethylsilyl-2-naphthol in 100 ml. of ethanol and 10 ml. of 20% sodium hydroxide was added an aqueous solution of *p*-nitrobenzenediazonium chloride, prepared from 2.1 g. (0.015 mole) of *p*-nitroaniline, and the mixture was stirred for 2 hours. The red-orange product (2.5 g., m.p. 234–235°) was collected and crystallized from acetic acid to give a pure dye melting at 235°. From the filtrate, 1.0 g. of the product was recovered making the total yield 70%.

Purification of the dyes. In most of the cases, the dyes separated from the coupling reactions in pure crystalline form. The dyes were further purified by crystallization from ethanol. Acetic acid was also found to be a suitable solvent for crystallization. In certain cases, however, the dyes had to be finally purified by chromatographic methods. The chromatographic separations were done by a usual procedure on a column of alumina (Fisher Adsorption Alumina, 80–200 mesh), using chloroform as a solvent. The dyes adsorbed on the alumina column were eluted by using chloroform containing 2–5% of methanol.

Coupling reaction of p-nitrobenzenediazonium acetate with p-triphenylsilyldimethylaniline. To an ice-cold solution of *p*-triphenylsilyldimethylaniline (3 g., 0.008 mole) in 100 ml. of glacial acetic acid and 50 ml. of acetone was added dropwise a filtered aqueous solution of 0.008 mole of *p*-nitrobenzenediazonium acetate. The reaction mixture was stirred for two hours, keeping the temperature below 10°. A thick garnet-colored precipitate, which separated, weighed 2 g. (92.5%), m.p. 160–172°. It was crystallized twice from acetic acid; the pure product, 1.7 g. (78.6%) had a m.p. and a mixed m.p. with N,N-dimethyl-4-(*p*-nitrophenylazo)aniline of 230–231°. From the acetic acid filtrate was recovered triphenylsilanol, 1.6 g. (72.7%), m.p. 135–140°. On crystallization from petroleum ether (b.p. 80–100°), its m.p. and mixed m.p. with triphenylsilanol was 152–153°.

The coupling reaction of *p*-nitrobenzenediazonium acetate with *p*-trimethylsilyldimethylaniline, carried out in a similar way, gave the dye, N,N-dimethyl-4-(*p*-nitrophenylazo)aniline, in about 80% yield.

Competitive coupling reaction of p-nitrobenzenediazonium acetate with dimethylaniline and p-triphenylsilyldimethylaniline. To a solution of 2.5 g. (0.0066 mole) of *p*-triphenylsilyldimethylaniline and 0.81 g. (0.0066 mole) of dimethylaniline in 100 ml. of ethanol, 50 ml. of acetic acid, and 100 ml. of acetone, was added dropwise a filtered solution of *p*-nitrobenzenediazonium acetate, prepared from 0.92 g. (0.0066 mole) of *p*-nitroaniline. The mixture was stirred for 3 hours, at 0–5°. The red-brown product was collected (3.5 g.). It was extracted with petroleum ether (b.p., 80–100°). The dye, insoluble in the petroleum ether, weighed 1.2 g. (70%) and melted at 225–230°. On crystallization from glacial acetic acid, it melted at 230–231°. The m.p. was not depressed when the compound was mixed with N,N-dimethyl-4-(*p*-nitrophenylazo)aniline. The weight of silicon compound recovered was 2.21 g. (88.5%). On crystallization from petroleum ether (b.p., 80–100°), it melted at 146–147°. The mixed m.p. with *p*-triphenylsilyldimethylaniline was 146–147°.

CLEAVAGE REACTIONS

Acid cleavage of m-trimethylsilyldimethylaniline. Dry hydrogen chloride gas was passed into a stirred, refluxing solution of 1.00 g. (0.0052 mole) of the silicon compound in 15 ml. of glacial acetic acid, for 24 hours. On cooling, the reaction mixture was neutralized with a saturated aqueous solution of sodium carbonate. The resulting mixture was extracted with ether. From the ether, 0.5 g. (80%) of dimethylaniline was recovered. It was identified by preparing its picrate of m.p. 159–161°; the mixed m.p. with the picrate of dimethylaniline was 160–161°. The dyes (II, R = CH_3 and R = C_6H_5), when treated in a similar manner with dry hydrogen chloride gas in glacial acetic acid, were unaffected and in both cases, the original dyes were recovered in more than 50% yields.

Acid cleavage of the azo dye (III, R = CH_3). Dry hydrogen chloride gas was passed into a refluxing solution of 1.00 g. of the azo dye (III, R = CH_3), in 100 ml. of glacial acetic acid for 18 hours. After 15 hours, the color of the solution changed from orange-red to brown-red. The reaction was continued for three hours more. The mixture was cooled and the crystalline azo dye was collected, 0.6 g. (75%), m.p., 249–250°, which was not depressed when the compound was mixed with 1-(*p*-nitrophenylazo)-2-naphthol. The dye (III, R = C_6H_5), when treated in a similar manner with dry hydrogen chloride gas, was unaffected.

Reductive cleavage of the azo dye (II, R = CH_3). The azo dye, 1.00 g., was heated on a steam-bath with 50 ml. of conc'd hydrochloric acid and 0.5 g. of tin powder. The dye was reduced slowly and the mixture became colorless after about one hour. The mixture was diluted with 200 ml. of water and filtered. The filtrate was made basic by adding solid sodium carbonate and the basic mixture was extracted with ether. The brown liquid obtained from ether was heated on a steam-bath with 5 ml. of acetic anhydride for 3 hours. The reaction product was poured into 200 ml. of water and the resulting solution was filtered to separate *p*-nitroacetanilide. The filtrate was neutralized with sodium bicarbonate. No precipitate separated. Therefore, the water from the filtrate was removed by slow evaporation, by blowing air over it at room temperature. The residue was extracted with ether. On removing ether, 0.2 g. of a colorless product was obtained, m.p. 80–90°. It was crystallized from water. The pure crystalline product melted at 129–130°. A mixed melting point of the compound with *p*-dimethylaminoacetanilide was 129–130°.

SUMMARY

1. The preparation of *o*-, and *m*-trimethylsilyl- and *o*-triphenylsilyl-dimethylanilines has been reported.

2. The *p*-nitrobenzenediazonium salt was found to couple with *p*-trimethylsilyl- and *p*-triphenylsilyl-dimethylaniline, and 1-trimethylsilyl-2-naphthol with the replacement of the R_3Si-group.

3. From the competitive coupling reaction and the replacement reactions, the ease of replacement of the substituents, during diazo-coupling, was found to decrease in the order: H > R_3Si > COOH > Br.

4. Several silicon-containing azo dyes have been synthesized by coupling *m*-trimethylsilyl- and *m*-triphenylsilyl-dimethylaniline, and 6-trimethylsilyl- and 6-triphenylsilyl-2-naphthol with selected diazonium salts, and their properties have been described.

5. The failure of *m*-triphenylsilyldimethylaniline to couple with certain diazonium salts from *ortho*-substituted aniline derivatives, such as 2,4-dinitro-6-chloro-, 2-hydroxy-4-nitro-, and 2-trifluoromethyl-4-nitro- has been attributed to the steric and substituent effects of the triphenysilyl group.

6. In the cleavage studies of the dyes with dry hydrogen chloride in glacial

acetic acid, it has been observed that the *p*-nitrobenzeneazo group stabilizes the carbon-silicon bond.

7. Reduction of two of the dyes with tin and hydrochloric acid was found to cleave the C-Si bond, and also to reduce the azo linkage to the corresponding amino products.

AMES, IOWA

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[CONTRIBUTION FROM THE KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE COLLEGE]

THE REACTION OF 1,2-EPOXY-2-METHYLPROPANE WITH AKLYLMAGNESIUM BROMIDES

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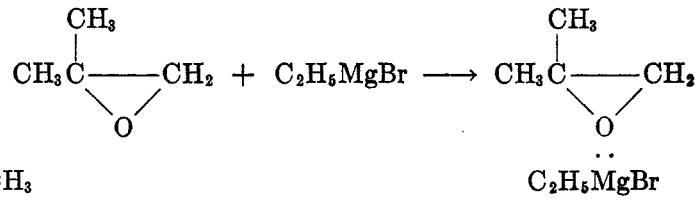
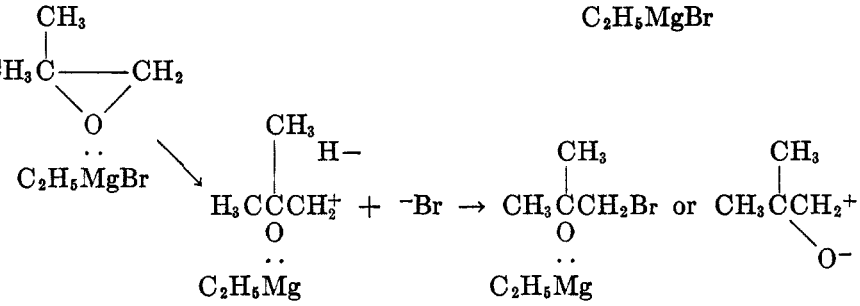
Olefin oxides have been found to react with both the alkylmagnesium and magnesium halide bonds of the Grignard reagent (1–4). A similarity also is marked in the formation of by-product carbonyl compounds. 1,2-epoxyethane, 1,2-epoxypropane, and 2,3-epoxybutane from ethanal (3), propanone (2), and 2-butanone (4) respectively. Rearrangement of the positive-negative fragment to form the carbonyl derivative takes place readily in alkaline media, (Grignard reagent). The shift of the hydrogen through the protonized double bond is therefore considered probable.

The reaction of 1,2-epoxy-2-methylpropane with an alkylmagnesium bromide may likewise involve either the alkylmagnesium bond (5) or the magnesium-bromide bond or both. The positive-negative fragment $CH_3\overset{\displaystyle O^-}{\overset{|}{C}}CH_2^+$ (with CH_3 below the C), which would result from the reaction of the magnesium-bromine bond, can not undergo a simple rearrangement by shifting a hydrogen from the oxygenated carbon to the positive end carbon as in the case of the fragment from 1,2-epoxypropane. However the shift of negative oxygen gives the fragment $CH_3\overset{\displaystyle +}{\overset{|}{C}}CH_2O^-$ (with CH_3 below the C) which may in turn undergo rearrangement by hydrogen shift to form 2-methylpropanal. Failure to isolate the 2-bromo-2-methyl-1-propanol from the reaction products and the formation of 2-methylpropanal from 1-bromo-2-methyl-2-propanol indicates that the fragment $CH_3\overset{\displaystyle +}{\overset{|}{C}}CH_2O^-$ (with CH_3 below the C) is not formed by the opening of the alternate carbon oxygen bond of the epoxide.

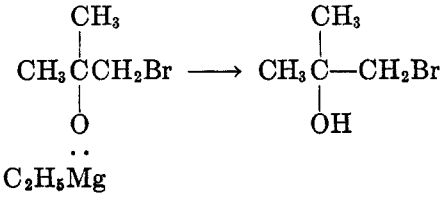
Henry (6) assumed that 2-methylpropanal was an intermediate in the formation of 3-methyl-2-butanol from 1,2-epoxy-2-methylpropane but proposed no mechanism for its formation.

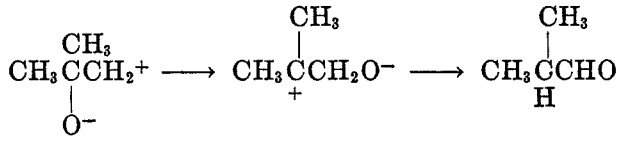
The addition of 1,2-epoxy-2-methylpropane to molecular equivalents of ethylmagnesium bromide or *n*-propylmagnesium bromide shows no apparent reaction of the alkyl-magnesium bond. The secondary alcohol, 2-methyl-3-pentanol or 2-methyl-3-hexanol, was in each case the principal product. A slightly smaller yield of the bromohydrin, 1-bromo-2-methyl-2-propanol was formed. There was also some reduction of 2-methylpropanal as evidenced by the positive identification, in each case of 2-methyl-1-propanol.

1. 

2. 

(It is obvious that the ring could be opened by $MgBr_2$ also).

3. 

4. 

When an excess of 1,2-epoxy-2-methylpropane (2 moles) was added to ethylmagnesium bromide or *n*-propylmagnesium bromide there was a marked *increase* in the yield of bromohydrin, and a marked *decrease* in the yield of secondary alcohol as compared with yields when molecular equivalents were used (Table I). Most of that portion of the 2-methylpropanal which was formed by rearrangement (equation 4) which did not react to form secondary alcohol was recovered as the trimer $C_{12}H_{24}O_3$ (7). The small amount of Grignard reagent available to react with 2-methylpropanal was decreased by the excess of 1,2-epoxy-2-methylpropane which apparently reacted with the alkylmagnesium bond.

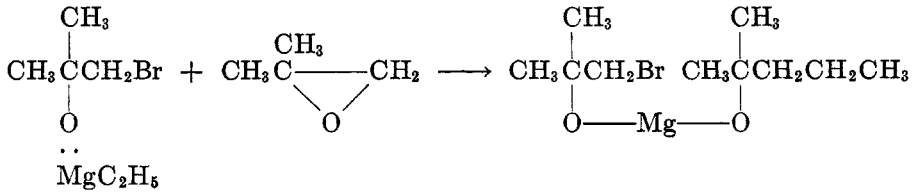
5. 

TABLE I

PERCENTAGE YIELDS OF ALCOHOLS FROM 1,2-EPOXY-2-METHYLPROPANE AND GRIGNARD REAGENTS FROM ETHYL BROMIDE OR *n*-PROPYL BROMIDE

GRIGNARD REAGENT FROM	1 $CH_3C(CH_3)(O)CH_2$ + 1 RMgBr		2 $CH_3C(CH_3)(O)CH_2$ + 1 RMgBr			
	1 Bromo-2-methyl-2-propanol	Secondary alcohol	1 Bromo-2-methyl-2-propanol	Secondary alcohol	Tertiary alcohol	Polymer
Ethyl bromide	28.3	2-Methyl-3-pentanol 42.2	51.2	2-Methyl-3-pentanol 13.2	2-Methyl-2-pentanol 17.9	$(C_4H_8O)_3$ 14
n-Propyl bromide	30.5	2-Methyl-3-hexanol 39.4	57.2	2-Methyl-3-hexanol 12.8	2-Methyl-2-hexanol 15.2	$(C_4H_8O)_3$ 28

TABLE II

PERCENTAGE YIELDS OF ALCOHOLS FROM 1,2-EPOXY-2-METHYLPROPANE AND TWO MOLES OF GRIGNARD REAGENT OR ONE MOLE OF DIALKYLMAGNESIUM

REAGENT FROM	$CH_3C(CH_3)(O)CH_2$ + 2RMgBr		$CH_3C(CH_3)(O)CH_2$ + R_2Mg
	1-Bromo-2-methyl-2-propanol	Secondary alcohols	Tertiary alcohol
Methyl bromide	40.2	2-Methyl-3-butanol 40.8	2-Methyl-2-butanol —[a]
Ethyl bromide	40.4	2-Methyl-3-pentanol 51.4	2-Methyl-2-pentanol 35.0
n-Propyl bromide	23.0	2-Methyl-3-hexanol 44.5	2-Methyl-2-hexanol 25.5
sec-Propyl bromide	60.0	2,4-Dimethyl-3-pentanol 21.5	
n-Butyl bromide	41.0	2-Methyl-3-heptanol 20.1	2-Methyl-2-heptanol 11.5
tert-Butyl bromide	56.0	2,2,4-Trimethyl-3-pentanol 0.0	2,4,4-Trimethyl-2-pentanol 6.0

[a] The percentage yield was not determined.

Dialkylmagnesium resulting from the Schlenk equilibrium could also react directly with 1,2-epoxy-2-methylpropane to give intermediates which would yield, upon hydrolysis, 2-methyl-2-pentanol or 2-methyl-2-hexanol.

When 1,2-epoxy-2-methylpropane is added to an excess of ethylmagnesium bromide or *n*-propylmagnesium bromide (2 moles) there is a definite increase

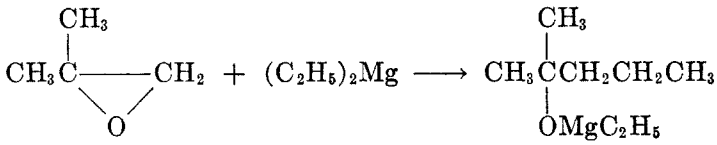
in the yields of secondary alcohol over those obtained when the reactants are used in molecular equivalents (Table II). This indicates a more efficient production of 2-methylpropanal (reactions 2 and 4) and a more complete conversion into the secondary alcohol. The yields of 1-bromo-2-methyl-2-propanol were definitely increased in the presence of excess ethylmagnesium bromide and decreased in the presence of excess *n*-propylmagnesium bromide.

Since the best yields of secondary alcohols were obtained in these simple cases the epoxide was reacted with methylmagnesium bromide, *sec*-propylmagnesium bromide, *n*-butylmagnesium, and *tert*-butylmagnesium bromide under the same conditions.

Methylmagnesium bromide gave a yield of 1-bromo-2-methyl-2-propanol approximately equal to that given by ethylmagnesium bromide but the yield of secondary alcohol was somewhat smaller. The increased yield of 1-bromo-2-methyl-2-propanol resulting from the reaction between *sec*-propylmagnesium bromide indicates that secondary alkyls favor the formation of bromohydrin at the expense of 2-methylpropanal and alcohol.

A large yield of 1-bromo-2-methyl-2-propanol was also formed when *tert*-butylmagnesium bromide was used. In this case, the absence of secondary alcohol was attributed to the lack of ability of the *tert*-butylmagnesium bromide to react with 2-methylpropanal. The aldehyde was isolated as the trimer.

The addition of a mole of 1,2-epoxy-2-methylpropane to a mole of diethylmagnesium leads to the rupture of the ethylmagnesium bond and the formation of an intermediate which gives upon hydrolysis 2-methyl-2-pentanol (5).

6. 

The reaction is quite slow and the yield of tertiary alcohol is small even when it is allowed to proceed until the Michler ketone test is negative (6 days). The time required to bring the reaction between di-*tert*-butylmagnesium and 1,2-epoxy-2-methylpropane to completion was from 30 to 40 days.

There was no evidence of the formation of 2-methylpropanal or its trimer in any of the reactions between dialkylmagnesium and 1,2-epoxy-2-methylpropane.

The 1-bromo-2-methyl-2-propanol which was formed in all reactions of 1,2-epoxy-2-methylpropane with Grignard reagents was prepared in quanity by adding 1,2-epoxy-2-methylpropane to a solution of magnesium bromide in ether. It was also synthesized from bromoacetone and methylmagnesium bromide (8). The identity of the compounds was proved by the melting points of the 3,5-dinitrobenzoates.

Attempts to prepare pure dibromo-di-*tert*-butoxymagnesium by dropping diethylmagnesium into 1-bromo-2-methyl-2-propanol gave precipitates which contained less bromine and more magnesium than the calculated amounts. Hydrolysis gave 1-bromo-2-methyl-2-propanol, 2-methylpropanal and its trimer, and

some 2-methyl-1-propanol. When the reaction mixture was refluxed overnight and then hydrolyzed the only product isolated was the trimer of 2-methylpropanal.

Two experiments with ethylmagnesium bromide and 1,2-epoxy-2-methylpropane were performed under conditions which would provide an excess of the epoxide. When one mole of the Grignard reagent was dropped into one mole of the epoxide the products were: 1-bromo-2-methyl-2-propanol, 2-methyl-3-pentanol, and the trimer of 2-methylpropanal. A small amount of distillate came over at the boiling point of 2-methyl-2-pentanol, but it was not pure enough to be identified by its 3,5-dinitrobenzoate. When one mole of ethylmagnesium bromide was dropped into two moles of 1,2-epoxy-2-methylpropane the products were: 1-bromo-2-methyl-2-propanol, 2-methyl-1-propanol, 2-methyl-2-pentanol, and the trimer of 2-methylpropanal. The small fraction which came over at the boiling temperature of 2-methyl-3-pentanol was not pure enough to give a sharp-melting 3,5-dinitrobenzoate.

EXPERIMENTAL

Reactions of Grignard reagents with 1,2-epoxy-2-methylpropane. In the preparation of Grignard reagents and the reactions of these with 1,2-epoxy-2-methylpropane, the same techniques were used and the same precautions observed as in the study of 1,2-epoxypropane (2).

After the yield of 1-bromo-2-methyl-2-propanol had been determined by decomposition and titration, the ether solution was distilled at atmospheric pressure through a Fenske-type column to a temperature above the boiling point of 1,2-epoxy-2-methylpropane, and beyond that point at reduced pressure. In all cases a sufficient amount of 2-methylpropanal was isolated for identification by a mixed melting point (120°) of its 2,4-dinitrophenylhydrazone. The yield of 1,2-epoxy-2-methylpropane approximated in each case the yield of 1-bromo-2-methyl-2-propanol. In those reactions where two molecular equivalents of 1,2-epoxy-2-methylpropane reacted with one of Grignard reagent a small amount of 2-methyl-1-propanol was isolated and identified by its boiling point (106–108°) and the mixed melting point determination of its 3,5-dinitrobenzoate.

In these same reactions and in the reaction between one-half molecular equivalent of 1,2-epoxy-2-methylpropane and one of *tert*-butylmagnesium bromide the trimer of 2-methylpropanal was isolated. This was identified (7) by its boiling point (127° at 17 mm.), its refractive index (n_D^{30} 1.4370), and its depolymerization when treated with sulfuric acid.

Reactions of 1,2-epoxy-2-methylpropane with the dialkylmagnesiums. In the preparation of the dialkylmagnesium solutions the mixture was allowed to stand from 3 to 5 days before the dioxane precipitate was separated from the dialkylmagnesium by centrifuging. The concentration was determined by titrating with standard acid. In the preparation of dimethylmagnesium the dioxane precipitate was not centrifuged. The ether solution was decanted from the precipitate, and the latter was washed by shaking with ether and decanting. The dimethylmagnesium content of the combined ether solutions was not determined.

The reaction was carried out in the same manner and in the same apparatus as were the reactions with Grignard reagents except that refluxing with sodium hydroxide was omitted. Distillation of the dried ether solution gave no evidence of the presence of 2-methylpropanal or its trimer. Distillation of the tertiary alcohols was at reduced pressures.

Preparation of 1-bromo-2-methyl-2-propanol. One mole of 1,2-epoxy-2-methylpropane in 500 ml. of ether was slowly added to one mole of $MgBr_2$ in 500 ml. of ether (2). After standing one hour the solution was poured on cracked ice and the basic salts were dissolved in dilute hydrochloric acid. The ether layer was shaken with 5% sodium bicarbonate, washed with water, and dried over sodium sulfate. Distillation gave 1-bromo-2-methyl-2-propanol (56

g.), which was identified by its physical properties and the melting point of the 3,5-dinitrobenzoate as the same compound which was prepared from bromoacetone and methylmagnesium bromide (8).

The preparation of dibromodi-tert-butoxymagnesium. Two molecular equivalents of 1,2-epoxy-2-methylpropane in ether was slowly added to one mole of an ether solution of magnesium bromide. The precipitate was washed with anhydrous ether, centrifuged, and brought to constant weight in a vacuum desiccator.

Anal. Calc'd for $C_8H_{16}Br_2MgO_2$: Mg, 7.31; Br, 48.87.
Found: Mg, 7.67; Br, 42.3.

TABLE III

IDENTIFICATION OF ALCOHOLS

ALCOHOL	DERIVATIVE	M.P., °C.	NITROGEN	
			Calc'd	Found
1-Bromo-2-methyl-2-propanol (8) B.p.$_{16mm}$49.5°; n_D^{20} 1.4710	3,5-dinitrobenzoate	120	8.04	8.11
2-Methyl-3-butanol (9) B.p.$_{745mm}$110–112°; n_D^{20} 1.3973	3,5-dinitrobenzoate	163	9.93	10.13
2-Methyl-2-butanol (10) B.p.$_{740mm}$102°; n_D^{20} 1.4020	3,5-dinitrobenzoate	116 (11)		
2-Methyl-3-pentanol (12) B.p.$_{740mm}$127–128°; n_D^{20} 1.4168	3,5-dinitrobenzoate	85 (11)		
	3-nitrophthalate	150.5 (12		
2-Methyl-2-pentanol (11) B.p.$_{740mm}$117–118°; n_D^{20} 1.4125	3,5-dinitrobenzoate	72 (11)		
2-Methyl-3-hexanol (14) B.p.$_{740mm}$142–145°; n_D^{20} 1.4178	3,5-dinitrobenzoate	59–60	9.80	9.60
	acid phthalate	59–60 (9)		
2-Methyl-2-hexanol (15) B.p.$_{740mm}$139–140°; n_D^{20} 1.4175	3,5-dinitrobenzoate	53–54°	9.03	9.10
	phenylurethan	44–45 (16)		
2,4-Dimethyl-3-pentanol (12) B.p.$_{740mm}$137–138°; n_D^{20} 1.4250	3,5-dinitrobenzoate	75	9.03	9.27
	phenylurethan	94–94.5 (17)		
2-Methyl-3-heptanol (12) B.p.$_{740mm}$165–167°; n_D^{20} 1.4259	3,0-dinitrobenzoate	53–54	8.64	8.44
	acid phthalate	47–48 (9)		
2-Methyl-2-heptanol (18) B.p.$_{15mm}$65°; n_D^{20} 1.4248	3,5-dinitrobenzoate	43–44	8.64	8.40
2,2,4-Trimethyl-3-pentanol (18) B.p.$_{15mm}$55°; n_D^{20} 1.4038				

One molecular equivalent of diethylmagnesium in ether was added to two equivalents of 1-bromo-2-methyl-2-propanol in an equal volume of ether. After centrifuging and removing ether in a vacuum, the precipitate was analyzed.

Anal. Calc'd for $C_8H_{16}Br_2MgO_2$: Mg, 7.31; Br, 48.78.
Found: Mg, 9.4; Br. 42.9.

In one experiment the reaction mixture was hydrolyzed immediately after the addition of the diethylmagnesium. Distillation of the dried ether layer gave 1-bromo-2-methyl-2-propanol as the main product. Small amounts of the trimer of 2-methylpropanal, and 2-methyl-1-propanol were also identified.

In another experiment the reaction mixture was refluxed overnight and then hydrolyzed. The dried ether layer gave upon distillation only the trimer of 2-methylpropanal.

Addition of ethylmagnesium bromide to 1,2-epoxy-2-methylpropane. One mole of 1,2-epoxy-2-methylpropane in an equal volume of anhydrous ether was cooled with salt and ice. One

mole of ethylmagnesium bromide was added slowly. The reaction mixture was stirred for two hours and allowed to stand overnight at room temperature. It was decomposed with ammonium bromide and the ether portion dried with sodium sulfate. The 1-bromo-2-methyl-2-propanol was decomposed and the distillation carried out as when the addition was made in the usual (reverse) manner. The following mole-% yields were obtained:

1-Bromo-2-methyl-2-propanol	27.3%
2-Methyl-3-pentanol	13.8%
Trimer of 2-methylpropanal	5.0%

About 5 ml. came over near the boiling point of 2-methyl-2-pentanol (116–121°) but a sharpmelting 3,5-dinitrobenzoate was not obtained.

When one mole of ethylmagnesium bromide was slowly added to a cooled ether solution of two moles of 1,2-epoxy-2-methylpropane and the reaction mixture treated as above the following yields were obtained:

2-Bromo-2-methyl-2-propanol	33.1%
2-Methyl-2-pentanol	8.5%
2-Methyl-1-propanol	6.0%
Trimer of 2-methylpropanal	16.0%

About 6 ml. which came over at 126–130° did not give a sharp melting 3,5-dinitrobenzoate of 2-methyl-3-pentanol.

Identification of alcohols. The boiling points and refractive indices were checked against those cited in the literature as were the melting points of known solid derivatives. (Table III). In those cases where the 3,5-dinitrobenzoates were not given in the literature these were prepared, analyzed, and checked by mixed melting points against those of alcohols prepared by methods cited in the literature.

SUMMARY

The addition of one or one-half molecular-equivalent of 1,2-epoxy-2-methylpropane to one equivalent of alkylmagnesium bromide leads to the opening of the oxirane ring and the reaction of the magnesium-bromine bond. The products formed are: 1-bromo-2-methyl-2-propanol, 2-methyl-1-propanal, and the secondary alcohol resulting from the reaction of 2-methylpropanal and excess Grignard reagent. When the Grignard reagent does not react with 2-methylpropanal, the trimer of the aldehyde is formed. When equimolecular quantities of reactants were used there was some reduction of the aldehyde to 2-methyl-1-propanol.

The addition of two molecular equivalents of 1,2-epoxy-2-methylpropane to one of ethylmagnesium bromide or of propylmagnesium bromide leads to the reaction of the magnesium-bromine bond with the formation of 1-bromo-2-methyl-2-propanol, 2-methylpropanal, and a relatively small yield of 2-methyl-3-pentanol or 2-methyl-3-hexanol. The trimer of 2-methylpropanal is formed in quantity. There is at the same time reaction of the alkylmagnesium bond with the formation of 2-methyl-2-pentanol or 2-methyl-2-hexanol.

EAST LANSING, MICHIGAN

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[CONTRIBUTION FROM THE AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

DERIVATIVES OF α,β-DIAMINO KETONES

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Certain α,β-diamino ketones had been found to possess mild avian antimalarial activity.[1] It seemed possible that conversion of these α,β-diamino ketones to more soluble derivatives might increase the interest in them for various types of pharmacological screen testing. Previous investigations in this laboratory have indicated that the carbonyl group in the α,β-diamino ketones is not readily reduced to a secondary alcohol function[2] (1). Other studies have shown the addition of Grignard reagents to such ketones results in the formation of the tertiary alcohols in low yields (2, 3, 4). It has been postulated (3) that the low reactivity of the carbonyl group in the α,β-diamino ketones results from the steric effects of the *alpha* and *beta* amino groups. It thus seemed reasonable that the new and versatile reducing agent (5), lithium aluminum hydride, might be especially well suited for the reduction of these sterically hindered ketones. The fact that these compounds are readily reduced by this reagent indicates that the steric requirement of lithium aluminum hydride in such hydrogenations is considerably less than that of the surface active catalysts, and less than that of aluminum isopropoxide. The mechanism of such related hydrogenations has been investigated and discussed by Trevoy and Brown (6).

α,β-Bis-dimethylaminobenzylacetone was prepared in fair yield by the reaction of α,β-dibromobenzylacetone with dimethylamine. The other α,β-diamino ketones used in these studies were selected as representative types from the lists of such compounds which have been reported previously (7). The α,β-diamino alcohols which were prepared are described in Table I. In several cases two isomeric products, presumably different racemic mixtures, were isolated from these reaction mixtures. The benzoyl and acetyl derivatives of some of these alcohols are listed in Table II.

One of the diamino alcohols, 3,4-dimorpholino-4-phenyl-2-butanol (IA) was

[1] For the antimalarial activities of the various amino ketones and derivatives that have been reported in the early papers in these series see, *A Survey of Antimalarial Drugs, 1941–1945*, Vol. I and II, F. Y. Wiselogle, editor, Edwards Brothers, Ann Arbor, Michigan, 1946.

[2] Many unsuccessful attempts have been made in this laboratory during the past eight years to reduce these α,β-diamino ketones to α,β-diamino secondary alcohols. α,β-Dimorpholinobenzylacetone could not be reduced using platinum oxide and 50 p.s.i. of hydrogen in absolute alcohol alone, or in an ethanol solution containing two molar equivalents of hydrogen chloride. Palladium on barium sulfate or on charcoal was not effective in reducing this compound, or α,β-ditetrahydroisoquinolinobenzylacetone, in absolute ethanol in the presence, or absence, of hydrogen chloride. α,β-Dimorpholinobenzylacetone was unchanged after shaking with hydrogen at 55° and 1500 p.s.i. in the presence of Raney nickel catalyst for four hours. This diamino ketone, as well as the related α,β-dimorpholinobenzylacetophenone, was unchanged by aluminum isopropoxide using the usual method to provide for the removal of acetone as it is formed during the reaction. Attempts to reduce these ketones with sodium and ethanol resulted in decomposition reactions.

chlorinated to yield 1-phenyl-1,2-dimorpholino-3-chlorobutane which reacted with morpholine to produce 1-phenyl-1,2,3-trimorpholinobutane. Another triamine, 1-phenyl-1,2-dimorpholino-3-aminobutane was obtained by reducing the oxime of α,β-dimorpholinobenzylacetone. The benzamide of this latter triamine was also prepared.

TABLE I

PHYSICAL AND ANALYTICAL DATA FOR DIAMINO ALCOHOLS

$C_6H_5CHCHCHR$
| | | |
N N OH
/\ /\

	M.P., °C.	No.	YIELD, %	Formula	PERCENTAGE COMPOSITION Carbon Calc'd	Carbon Found	Hydrogen Calc'd	Hydrogen Found	Nitrogen Calc'd	Nitrogen Found
4-Phenyl-2-butanol										
3,4-Dimorpholino	(IA)	173–175	99	$C_{18}H_{28}N_2O_3$	67.47	67.70	8.81	8.90	—	—
	(IB)	138–140				67.57		8.85		
3,4-Dipiperidino	(II)	90–93	84	$C_{20}H_{32}N_2O$	75.90	75.73	10.19	10.05	8.85	8.89
3,4-Bis-[dimethylamino]	(III)	50–52[a]	87	$C_{14}H_{24}N_2O$	71.14	71.15	10.24	9.95	11.86	11.90
3,4-Di-[*p*-methoxy-N-methylbenzylamino]	(IV)	oily product								
3-Morpholino-4-tetrahydroquinolino	(V)	130–131	81	$C_{23}H_{30}N_2O_2$	75.37	75.46	8.26	8.32	—	—
1,3-Diphenyl-1-propanol										
2,3-Dimorpholino	(VIA)	159–160	75	$C_{23}H_{30}N_2O_3$	72.22	72.25	7.91	7.62	7.33	7.28
	(VIB)	104–105								7.28
2-Morpholino-3-tetrahydroquinolino	(VIIA)	182–183	80	$C_{28}H_{32}N_2O_2$	78.47	78.77	7.53	7.74	—	—
	(VIIB)	163–164				78.39		7.23		

[a] B.p. 127–130° (0.20 mm.).

EXPERIMENTAL[3]

α,β-Bis-[dimethylamino]benzylacetone. A mixture of 153.0 g. (0.50 mole) of α,β-dibromobenzylacetone (8) and 800 ml. of dry ether was cooled to −12°. To this mixture was added, with rapid stirring, 100 g. (2.22 moles) of cold anhydrous dimethylamine. The reaction mixture was stirred for five hours while the temperature was held between −2 and −5°. The mixture was allowed to stand an additional 24 hours at 0°. The precipitated dimethylamine hydrobromide was removed and the filtrate washed with five 50-ml. portions of water. From the dried, concentrated solution was obtained a total of 53.2 g. (45.5% yield) of the desired

[3] Microanalyses for carbon, hydrogen, and nitrogen are by the Clark Microanalytical Laboratory, Urbana, Ill., arranged for through the courtesy of the Smith, Kline, and French Laboratories, Philadelphia, Pa.

product, m.p. 97–99°. Recrystallization from 90% methanol gave a pale-yellow crystalline product, m.p. 98–99.5°.

Anal. Calc'd for $C_{14}H_{22}N_2O$: C, 71.75; H, 9.47; N, 11.96.

Found: C, 71.45; H, 9.49; N, 11.66.

Reduction of diamino ketones with lithium aluminum hydride. Three different procedures were used to reduce these various diamino ketones. The first of the following procedures was applied to the more soluble diamino ketones while the other two were used with the less soluble substances. See Table I. Procedures A and B are similar to those described by Nystrom and Brown (5) but more reaction time was required.

Procedure A. To a solution of 0.05 mole of lithium aluminum hydride in 250 ml. of dry ether was added slowly (five hours) with stirring a solution of 0.1 mole of the diamino ke-

TABLE II

PHYSICAL AND ANALYTICAL DATA FOR DERIVATIVES OF THE DIAMINO ALCOHOLS

$C_6H_5CHCHCHR$
| | |
N N OCOR
/\ /\

	M.P., °C.	YIELD, %	FORMULA	PERCENTAGE COMPOSITION					
				Carbon		Hydrogen		Nitrogen	
				Calc'd	Found	Calc'd	Found	Calc'd	Found
BENZOATES OF:									
(IA)	167–169	80	$C_{25}H_{32}N_2O_4$	70.73	70.61	7.60	7.53	6.60	6.60
(IB)	148–150	75							6.48
(II)	119–120	60	$C_{27}H_{36}N_2O_2$	77.11	77.47	8.63	8.38	6.66	6.92
(III)	91–92	80	$C_{21}H_{28}N_2O_2$	74.08	73.80	8.29	8.15	8.23	8.15
(IV)	98–100	5	$C_{35}H_{40}N_2O_4$	—	—	—	—	5.07	5.12
(VIB)	153–155	50	$C_{30}H_{34}N_2O_4$	74.05	73.98	7.04	7.23	5.76	5.71
ACETATES OF:									
(IA)	142–143	81	$C_{20}H_{30}N_2O_4$	66.22	66.48	8.34	8.55	7.73	7.68
(IB)	101–102	60			66.16		8.17	—	—
(II)	75–76	90	$C_{22}H_{34}N_2O_2$	—	—	—	—	7.81	8.04
(III)	65–66	95	$C_{16}H_{26}N_2O_2$	69.03	68.83	9.42	9.11	10.07	10.10
(V)	158–160	80	$C_{25}H_{32}N_2O_3$	73.50	73.58	7.90	8.09	—	—
(VIB)	177–178	90	$C_{25}H_{32}N_2O_4$	70.73	70.58	7.60	7.82	6.60	6.54
(VIIA)	188–189	98	$C_{30}H_{34}N_2O_3$	76.56	76.24	7.28	7.15	—	—

tone dissolved or suspended in 300 ml. of dry ether. The excess lithium aluminum hydride was hydrolyzed by the dropwise addition of water. The supernatant ether layer was separated, washed with water and dried over calcium sulfate.

The ether solutions were evaporated to give the crude products. In this way the diamino alcohol (II), recrystallized from methanol and water, was obtained from α,β-dipiperidinobenzylacetone (9). The diamino alcohol (III), which was readily purified by vacuum distillation, was prepared from α,β-bis-[dimethylamino]benzylacetone. The diamino alcohol (IV) was obtained from α,β-di-[*p*-methoxy-N-methylbenzylamino]benzylacetone (10), only as a crude oil which could neither be distilled nor induced to crystallize.

Procedure B. The slightly soluble diamino ketones (0.10 mole) were placed in the cup of a Soxhlet extraction apparatus and refluxed with 500 ml. of dry ether containing 0.10 mole of lithium aluminum hydride until all of the material had dissolved (16 to 30 hours). The products were isolated as in procedure A and purified by recrystallization from aqueous

ethanol. In this way the two racemic mixtures (VIA) and (VIB) were obtained from the high-melting isomer (m.p. 175°) of α,β-dimorpholinobenzylacetophenone (11). The diamino alcohol (V) was prepared from α-morpholino-β-tetrahydroquinolinobenzylacetone (12). The two racemic mixtures (VIIA) and (VIIB) resulted from the reduction of α-morpholino-β-tetrahydroquinolinobenzylacetophenone (13).

Procedure C. A solution of 0.1 mole of the diamino ketone in 500 ml. of dry benzene was mixed slowly with 300 ml. of dry ether containing 0.10 mole of lithium aluminum hydride and the mixture refluxed for five hours. Using this procedure the two racemates (IA) and (IB) were obtained by the reduction of α,β-dimorpholinobenzylacetone (4). The reaction mixture was worked up as decsribed in the above procedures. The racemates were obtained by fractional recrystallization from aqueous ethanol.

Derivatives of the diamino alcohols. The benzoates were prepared by reaction of the diamino alcohols with benzoyl chloride in pyridine solution. The acetates were prepared by reaction with acetic anhydride. Both types of derivatives were recrystallized from aqueous ethanol. See Table II.

1-Phenyl-1,2-dimorpholino-3-chlorobutane. Cooled solutions of 3.35 g. (0.0105 mole) of (IA) in 15 ml. of chloroform and 2.5 g. (0.021 mole) of thionyl chloride in 5 ml. of chlorofrom were mixed and refluxed for 30 minutes. The excess thionyl chloride and chloroform were removed under reduced pressure and the crude product suspended in a mixture of 0.9 gm. of sodium hydroxide, 25 ml. of water, and 150 ml. of ether. The ether layer was separated, washed with water, and dried. Evaporation of the solvent gave a red-colored residue which, after several recrystallizations from benzene and petroleum ether mixtures, gave a colorless product, m.p. 156–157°, wt. 1.10 g. (31% yield).

Anal. Calc'd for $C_{18}H_{27}ClN_2O_2$: C, 63.79; H, 8.03; N, 8.27.

Found: C, 63.89; H, 8.26; N, 8.08.

1-Phenyl-1,2,3-trimorpholinobutane. A 1.88-g. (0.005 mole) sample of the crude dihydrochloride of 1-phenyl-1,2-dimorpholino-3-chlorobutane was mixed with 1.30 g. (0.015 mole) of morpholine in 15 ml. of absolute ethanol. The reaction mixture was warmed for ten minutes on the steam-bath and allowed to stand at room temperature for one day. The solvent was removed under reduced pressure and the residue washed with water. The insoluble portion remaining was recrystallized twice from 95% ethanol to give 1.20 g. (61% yield) of a colorless product, m.p. 178–179°; when mixed with (IA), m.p. 151–160°.

Anal. Calc'd for $C_{22}H_{35}N_3O_3$: N, 10.79. Found: N, 11.08, 10.53.

α,β-Dimorpholinobenzylacetone oxime. A mixture of 9.55 g. (0.03 mole) of α,β-dimorpholinobenzylacetone (4), 4.20 g. (0.06 mole) of hydroxylamine hydrochloride, and 5.95 g. (0.06 mole) of potassium acetate in 100 ml. of 95% ethanol was warmed gently with stirring for 30 minutes and then allowed to stand at room temperature for two days. The precipitated material was removed, washed with water, and dried to give 5.40 g. of a colorless product, m. p. 164–166°. Evaporation of the residual reaction mixture gave 2.50 g. of product, m.p. 161–164°. These two crops were combined and recrystallized from 95% ethanol to give 6.30 g. (63% yield) of colorless crystals, m.p. 167–168°.

Anal. Calc'd for $C_{18}H_{27}N_3O_3$: C, 64.84; H, 8.16; N, 12.61.

Found: C, 65.15; H, 8.42; N, 12.75.

1-Phenyl-1,2-dimorpholino-3-aminobutane. The above oxime was not changed by an attempted catalytic hydrogenation using palladium on charcoal and 50 p.s.i. Only the starting oxime was recovered from an attempted reduction using lithium aluminum hydride according to *Procedure B* as described above.

A 2.20-g. sample of the oxime was dissolved in 50 ml. of boiling absolute ethanol and 2.60 g. of sodium was added slowly to this solution, as small pieces, in 30 minutes. The reaction mixture was cooled to room temperature and 10 ml. of water added to destroy the sodium ethoxide. The solution was made acidic with 6 *N* hydrochloric acid and the solvents removed under a vacuum. The residue was treated with dilute sodium hydroxide. From the oily precipitate was obtained 0.45 g. (21%) of a colorless product, m.p. 139–140°, recrystallized from benzene and petroleum ether mixtures.

Anal. Calc'd for $C_{18}H_{29}N_3O_2$: N, 13.16. Found: N, 12.99.

Benzoylation of this product with benzoyl chloride in benzene solution using ordinary isolation techniques gave a 74% yield of a colorless product, m.p. 179–181°, recrystallized from absolute ethanol and from benzene and petroleum ether mixtures.

Anal. Calc'd for $C_{25}H_{33}N_3O_3$: C, 70.89; H, 7.85; N, 9.92.
Found: C, 71.13; H, 7.55; N, 10.03.

SUMMARY

α,β-Diamino ketones are readily reduced to the corresponding secondary alcohols by lithium aluminum hydride. One of these diamino alcohols was chlorinated to produce an a,β-diamino chloro compound, which was converted to the triamino product by reaction with an amine. A triamino compound was also produced by a sodium-alcohol reduction of an α,β-diamino ketone oxime. The acetyl and benzoyl derivatives of several of these products were prepared.

LINCOLN, NEBRASKA

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RELATIVE EASE OF CYCLIZATION OF 2-, 3-, AND 4-AMINOPYRIDINE DERIVATIVES. SYNTHESIS OF NAPHTHYRIDINES[1]

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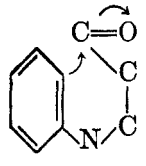
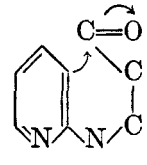
Successful methods for the synthesis of quinolines include the cyclizations of intermediates produced by the reactions of aniline with the ketone group of acetoacetic ester (Conrad-Limpach method), with the ester group of acetoacetic ester (Knorr method), with acetylacetone (Combes method), with ethoxymethylenemalonic ester (EMME method), with glycerine or acrolein (Skraup method), and with benzaldehyde and pyruvic acid (Doebner method). These cyclizations involve carbon-carbon condensations of the ionic type in which a benzene ring serves as the electron-donor and a carbonyl group as the electron-acceptor as indicated in I. By employing 2-, 3-, or 4-aminopyridine instead of aniline, these methods would lead to the formation of naphthyridines. In these cases, a pyridine ring would serve as the electron-donor and the carbonyl group as the electron-acceptor as indicated in II, III, and IV, respectively.



I



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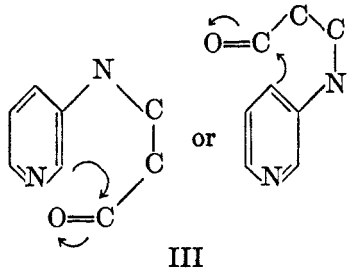
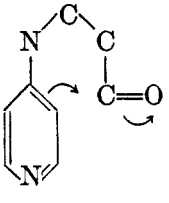


III

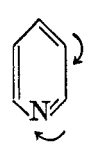


IV

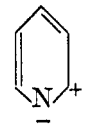
However, these methods have generally not been as successful for the synthesis of naphthyridines as for the synthesis of quinolines. This is not surprising because the pyridine nitrogen tends to withdraw electrons from the remainder of the ring thereby making the pyridine ring a poorer electron-donor in cyclizations II, III, or IV than the benzene ring in I. The pyridine nitrogen tends to withdraw electrons particularly from the 2- and 4-positions as indicated in V; indeed resonance forms such as VI and VII, having positive charges at the 2- and 4-positions,

[1] This work was supported by the Office of Naval Research and by the Duke University Research Council.

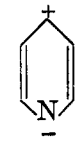
have been considered to make important contributions to the structure of pyridine itself (1).



V

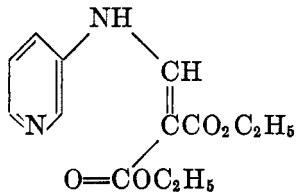


VI

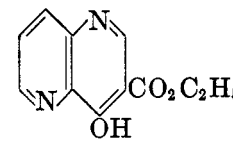


VII

Since 3-aminopyridine derivatives III would have to cyclize at the 2- or 4-position, they might be expected to do so with the greatest difficulty. Actually only one such 3-aminopyridine derivative, that (VIII) obtained with ethoxymethylenemalonic ester, appears to have been cyclized satisfactorily, the 1,5-naphthyridine (IX) being obtained in 70–80% yields (2); even in this case, special conditions (high dilution) were required.

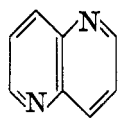


VIII

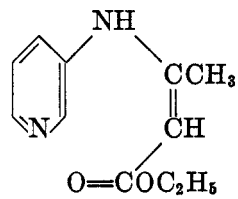


IX

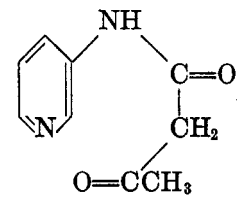
The Skraup reaction with 3-aminopyridine has been reported to form 1,5-naphthyridine (X), but no yield was given (3). We have obtained only a 28% yield of X under the usual Skraup conditions. We have found that, although 3-aminopyridine readily forms the anil or crotonate (XI) and the amide (XII) with acetoacetic ester, these intermediates fail to undergo the Conrad-Limpach and Knorr types of cyclization under the usual conditions.



X



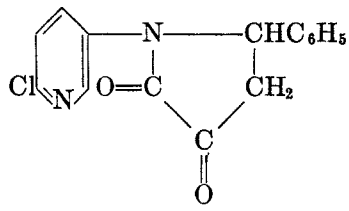
XI



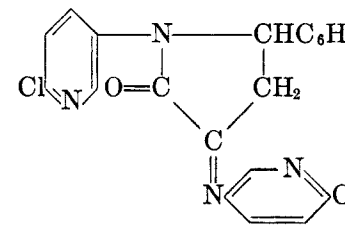
XII

The Combes reaction has been reported to fail with 2,6-dimethyl-3-aminopyridine (4) with which cyclization would have had to occur at the 4-position. Apparently this type of reaction has not been attempted with 3-aminopyridine itself. The Doebner reaction has been reported to fail with 3-aminopyridine and with 6-chloro-3-aminopyridine (5); in the latter case, cyclization occurred out-

side of the pyridine ring to form the pyrrolidine (XIII) which was isolated as its 6-chloro-3-aminopyridine derivative (XIV).



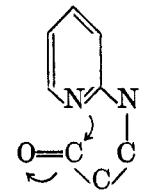
XIII



XIV

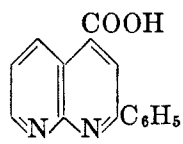
Of course it is possible that some of these cyclizations that fail with 3-aminopyridine might be effected with certain substituted 3-aminopyridines such as 3,5-diaminopyridine in which the 2- and 4-positions would be relatively more reactive.

In contrast to 3-aminopyridine derivatives, 2- and 4-aminopyridine derivatives (II and IV) may cyclize at the least deactivated position, the 3-position, to form 1,8- and 1,6-naphthyridines, respectively. 2-Aminopyridine derivatives may also cyclize at the pyridine nitrogen to form pyrimidines as indicated in XV (6); this course of reaction should be favored by important contributions of resonance structures like VI and VII having negative charges on the pyridine nitrogen.

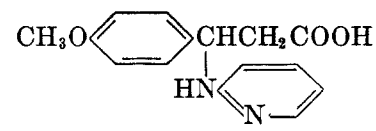


XV

Therefore, it is not surprising that 2- and 4-aminopyridine derivatives generally undergo cyclizations more readily than the corresponding 3-aminopyridine derivatives. 2-Aminopyridine or substituted 2-aminopyridine derivatives usually form pyrimidines under the conditions of the Conrad-Limpach (6), Knorr (7), and EMME (8) methods. 1,8-Naphthyridines appear to be produced only with such substituted 2-aminopyridines as 2,6-diaminopyridine in which the 3-position is activated and the pyridine nitrogen apparently hindered sterically (6, 8). The Doebner reaction with 2-aminopyridine has been reported to form the 1,8-naphthyridine (XVI) (9) but later workers (10, 11) have concluded that the product is not the naphthyridine. Using anisaldehyde in the reaction, Allen and



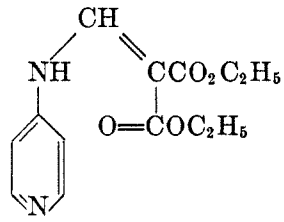
XVI



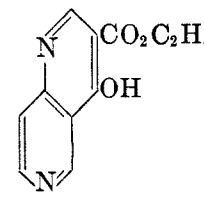
XVII

co-workers (10) obtained compound XVII which is the addition product of 2-aminopyridine and anisalpyruvic acid.

The 4-aminopyridine derivative (XVIII) obtained with ethoxymethylenemalonic ester was found to cyclize to form the 1,6-naphthyridine (XIX) in high yield (82%) under the usual conditions, whereas cyclization of the corresponding 3-aminopyridine derivative has previously been reported to require special conditions (2). Unfortunately we have been unable to prepare the crotonate or amide from 4-aminopyridine and ethyl acetoacetate or the anil from this amine and acetylacetone even though relatively drastic conditions were employed. In this respect, 4-aminopyridine resembles *o*-nitroaniline which has failed to form the crotonate (12) or the amide[2] with acetoacetic ester. These failures appear to be ascribable to the relatively weakly basic nature of the amine. Earlier workers (3) reported that 4-aminopyridine did not undergo the Skraup reaction, and they similarly ascribed this failure to the weakly basic properties of the amine.

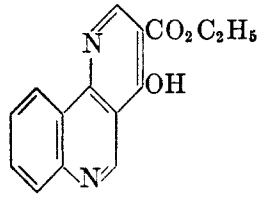


XVIII

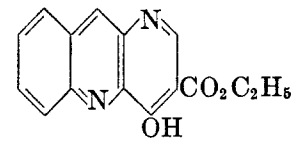


XIX

Although only the intermediate in the EMME method was formed with 4-aminopyridine, intermediates in the EMME, Conrad-Limpach, and Knorr methods were readily produced with 4-aminoquinoline. In agreement with theory, these intermediates cyclized more readily or in better yield than the corresponding intermediates from 3-aminoquinoline. Thus, 4-aminoquinoline and ethoxymethylenemalonic ester formed the 1,6-naphthyridine (XX) in 93% yield whereas 3-aminoquinoline gave the 1,5-naphthyridine (XXI) in only 22% yield. In these cases the intermediate crotonates were not isolated.



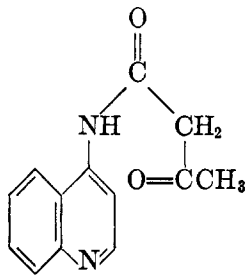
XX



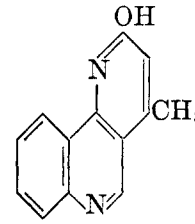
XXI

The amide (XXII) from 4-aminoquinoline and ethyl acetoacetate gave the 1,6-naphthyridine (XXIII) in 58% yield whereas the corresponding amide (XXIV) from 3-aminoquinoline failed to cyclize under similar conditions.

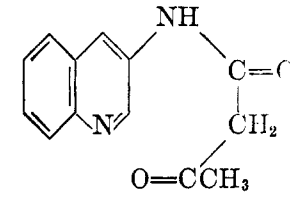
[2] We recovered starting material after refluxing a mixture of *o*-nitroaniline and ethyl acetoacetate for an hour.



XXII

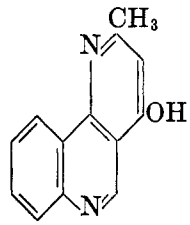


XXIII

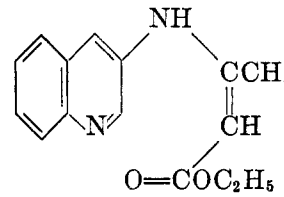


XXIV

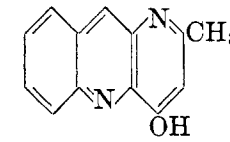
4-Aminoquinoline and ethyl acetoacetate, in the presence of a catalytic amount of acid, reacted at room temperature to form the 1,6-naphthyridine (XXV) whereas 3-aminoquinoline and this β-keto ester yielded only the intermediate crotonate (XXVI) under these conditions, subsequent heating being required to convert the crotonate to the 1,5-naphthyridine (XXVII). The formation of the cyclized product at room temperature is not without precedent; another example is the reaction of 2,6-diaminopyridine with acetoacetic ester to form the corresponding 1,8-naphthyridine (6).



XXV



XXVI



XXVII

EXPERIMENTAL[3]

2-Aminopyridine (m.p. 58–60°) and 3-aminoquinoline (m.p. 92–94°) were Eastman Kodak products.

3-Aminopyridine. This amine was prepared by a modification[4] of the method of Maier-Bode (13). In an iron bomb, having a capacity of one liter, was placed a mixture of 172 g. (1.09 moles) of 3-bromopyridine (b.p. 169–170°),[5] 340 ml. of concentrated ammonium hydroxide (sp. gr. 0.9), and 10 g. of copper sulfate pentahydrate. The bomb was sealed and heated in an oven at 140° for 20 hours. After cooling, the reaction mixture was transferred to a flask, and the bomb washed with hot water. The combined reaction mixture and wash solution was heated on the steam-bath until most of the ammonia had evaporated. The mixture was made strongly alkaline by the slow addition of about 75 g. of solid sodium hydroxide and then saturated with anhydrous potassium carbonate. After filtering, the solid residue was transferred to a beaker and washed with ether. The filtrate was extracted

[3] Boiling points are uncorrected; melting points are corrected. Microanalyses are by Clark Microanalytical Laboratory, Urbana, Illinois.

[4] The procedure described here was developed in this laboratory by Dr. S. T. Amore.

[5] We are indebted to the Dow Chemical Company for a generous supply of this chemical.

with ether until the ether solution was no longer colored. The ether was dried over sodium sulfate, decanted, and concentrated. The residue was distilled *in vacuo*, yielding 24 g. (15%) of recovered 3-bromopyridine, b.p. 60–63° at 15 mm. and 61 g. (60%) of 3-aminopyridine, b.p. 107–109° at 3 mm., m.p. 60–61°.

4-Aminopyridine. This amine was prepared by three methods. In the method of Koenig and Greiner (14), 100 g. (1.76 moles) of pyridine and 300 g. (2.54 moles) of thionyl chloride were reacted to form yellow pyridyl pyridinium dichloride (m.p. 170–173°) in 70% (175 g.) yield. To this dichloride was added 500 ml. of concentrated ammonium hydroxide and the mixture was refluxed for eight hours. After removal of the water, 25 ml. of a concentrated solution of potassium hydroxide was added and the mixture steam-distilled with superheated steam (180°). The distillate was evaporated *in vacuo* and the residue recrystallized from chloroform yielding 4-aminopyridine, m.p. 158–159°. Koenig and Greiner reported a 62% yield from the dichloride, but the best yield obtained by us was 40%. In several runs the yields were much lower.

In the method of Camps (15), 100 g. of 95% γ-picoline (1.02 moles) was oxidized by 170 g. of potassium permanganate in 3 liters of water to isonicotinic acid (m.p. 310°) in 50–58% (65 g.) yield; this acid was esterified to the ethyl ester (b.p. 97° at 9 mm.) in 65–70% (56 g.) yield; this ester was ammoniated to isonicotinamide (m.p. 152–154°) in 98% (44 g.) yield; and finally the amide (21 g., 0.172 mole) was converted to 4-aminopyridine (m.p. 158–159°) by bromine and potassium hydroxide in 1.5 liters of water (Hofmann) in 74% yield. This yield of 4-aminopyridine was obtained only after many ether extractions of the aqueous solution.

In the third method, 96 g. (0.577 mole) of chelidamic acid (m.p. 248° dec.) (16) was decarboxylated to 4-hydroxypyridine (m.p. 149°) (16) in 45% yield and the hydroxy compound (25 g., 0.26 mole) refluxed with 75 ml. of phosphorus oxychloride to form 4-chloropyridine hydrochloride. A mixture of the salt and 125 g. of phenol was heated to 170° and dry ammonia gas passed into the solution for three hours. The cooled mixture was poured into aqueous concentrated sodium hydroxide and the resulting solution thoroughly extracted with ether. The solvent was evaporated and the residue recrystallized from chloroform yielding 7.5 g. (30%) of 4-aminopyridine (m.p. 158–159°).

4-Aminoquinoline. 4-Hydroxyquinoline (m.p. 200°) was prepared in 60% (43 g.) yield from 46.5 g. (0.5 mole) of aniline and 108 g. (0.5 mole) of ethoxymethylenemalonic ester by the method of Price and Roberts (17) for the preparation of 7-chloro-4-hydroxyquinoline. The hydroxy compound was heated for two hours at 110° with 90 ml. of phosphorus oxychloride to give 4-chloroquinoline (m.p. 34–35°) in 86% (41 g.) yield. A mixture of the chloro compound (0.36 mole) and 130 g. (1.38 moles) of phenol was heated to 180° and dry ammonia gas passed in for three hours yielding 25 g. (70%) of the 4-aminoquinoline, m.p. 153–154°; reported m.p. 153–154° (18).

Skraup reaction with 3-aminopyridine. A mixture of 5 g. (0.064 mole) of 3-aminopyridine, 23.6 g. (0.256 mole) of glycerine, 32 g. of concentrated sulfuric acid, and 6 g. of arsenic pentoxide was heated at 170° for six hours. The reaction mixture was poured into 100 ml. of water, excess solid sodium hydroxide added, and the mixture steam-distilled until one liter of distillate was collected. After saturation with solid potassium carbonate, the distillate was extracted with ether. The ethereal solution was dried over Drierite and the solvent removed. The oily residue (3 g.) solidified after standing in the refrigerator overnight. Recrystallization from ligroin (b.p. 90–120°) gave 2.4 g. (28%) of 1,5-naphthyridine (X), m.p. 70–72°; reported m.p. 72–73° (3).

Conrad-Limpach intermediate with 3-aminopyridine. A mixture of 7.1 g. (0.076 mole) of 3-aminopyridine, 9.8 g. (0.076 mole) of ethyl acetoacetate, 10 g. of Drierite, 25 ml. of commercial absolute ethanol, and about four drops of glacial acetic acid were refluxed for twelve hours (see 19). After filtering and removing the ethanol under reduced pressure, the residue was distilled *in vacuo* yielding 9.8 g. (63%) of light yellow *ethyl 2-methyl-2-(3'-aminopyridyl)crotonate* (XI), b.p. 158–160° at 2 mm.

Anal. Calc'd for $C_{11}H_{14}N_2O_2$: N, 13.59. Found: N, 13.43.

Attempts to cyclize the crotonate in refluxing Dowtherm[5] for the usual 15 minutes (19) or for an hour were unsuccessful. After 15 minutes, most of the crotonate was recovered unchanged; after an hour, crotonate and decomposition products were obtained.

Knorr intermediate with 3-aminopyridine. A mixture of 6 g. (0.064 mole) of 3-aminopyridine and 8.7 g. (0.064 mole) of ethyl acetoacetate was refluxed for 20 minutes. On cooling to room temperature, the reaction mixture solidified. The solid was recrystallized from a mixture of benzene and petroleum ether (b.p. 30–60°) yielding 7.5 g. (66%) of the *N-(3-aminopyridyl)acetoacetamide* (XII) melting at 125–129°. After three recrystallizations from the same solvents, white needles, m.p. 137–138° were obtained.

Anal. Calc'd for $C_9H_{10}N_2O_2$: C, 60.66; H, 5.65.
Found: C, 61.07; H, 5.75.

Attempts to cyclize the amide by heating in concentrated sulfuric acid on a steam-bath for one-half hour, essentially according to the usual procedure (19), or for five hours were unsuccessful. Some of the amide was recovered along with 3-aminopyridine which was formed presumably by hydrolysis of the amide.

EMME reaction with 4-aminopyridine. A mixture of 5 g. (0.053 mole) of 4-aminopyridine and 11.5 g. (0.053 mole) of ethoxymethylenemalonic ester was heated in an oil-bath at 110° for one hour and allowed to stand overnight. The solid was recrystallized from ligroin (b.p. 90–120°) yielding 11.5 g. (83%) of *ethyl 1-carbethoxy-2-(4'-aminopyridyl)crotonate* (XVIII) melting at 71–74°. After two more recrystallizations from the same solvent, it had m.p. 74–75°.

Anal. Calc'd for $C_{13}H_{16}N_2O_2$: C, 59.07; H, 6.10; N, 10.60.
Found: C, 59.31; H, 6.26; N, 10.55.

To 25 ml. of refluxing Dowtherm[5] was added 7.5 g. (0.028 mole) of the crotonate and the resulting solution was refluxed for 15 minutes. On cooling, a light tan solid separated. Recrystallization from ethanol gave 5 g. (82%) of the *3-hydroxy-4-carbethoxy-1,6-naphthyridine* (XIX) (m.p. 292–293°).

Anal. Calc'd for $C_{11}H_{10}N_2O_2$: C, 60.54; H, 4.61; N, 12.83.
Found: C, 60.21; H, 4.57; N, 12.92.

Attempts to prepare other intermediates with 4-aminopyridine. This amine (0.043 mole) failed to form the crotonate with ethyl acetoacetate (0.043 mole) on standing in the presence of a catalytic amount of concentrated hydrochloric acid in an evacuated desiccator over sulfuric acid (see 19) for a week or on refluxing in ethanol in the presence of Drierite (19) for 24 hours. Most of the 4-aminopyridine and ethyl acetoacetate were recovered.

4-Aminopyridine (0.053 mole) failed to form the amide with ethyl acetoacetate (0.053 mole) on refluxing the mixture for a few minutes (19) or for three hours. Most of the starting materials were recovered.

4-Aminopyridine (0.043 mole) failed to react with acetylacetone (0.043 mole) on heating the mixture for 24 hours on the steam-bath. Most of the starting materials were recovered.

EMME reaction with 3- and 4-aminoquinoline. A solution of 5 g. (0.035 mole) of 3-aminoquinoline and 7.5 g. (0.035 mole) of ethoxymethylenemalonic ester in 100 ml. of Dowtherm[5] was boiled in an open beaker for 30 minutes. The brown solid which separated on cooling was washed with Skellysolve B. Recrystallization of the solid from a mixture of pyridine and water gave 2 g. (22%) of *3-carbethoxy-4-hydroxy-6,7-benzo-1,5-naphthyridine* (XXI), m.p. 264–265° dec.

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.11; H, 4.50; N, 10.44.
Found: C, 66.91; H, 4.38; N, 10.20.

In a similar manner were reacted 5 g. (0.035 mole) of 4-aminoquinoline and 7.5 g. (0.035 mole) of ethoxymethylenemalonic ester. After washing with Skellysolve, the brown solid was recrystallized from ethanol yielding 7 g. (93%) of *3-carbethoxy-4-hydroxy-7,8-benzo-1,6-naphthyridine* (XX) (m.p. above 300°).

Anal. Calc'd for $C_{15}H_{12}N_2O_3$: C, 67.11; H, 4.50; N, 10.44.
Found: C, 67.25; H, 4.64; N, 10.23.

Conrad-Limpach reaction with 3- and 4-aminoquinoline. A mixture of 5 g. (0.035 mole)

of 3-aminoquinoline, 5.2 g. (0.035 mole) of ethyl acetoacetate, and three drops of concentrated hydrochloric acid was allowed to stand in an evacuated desiccator over sulfuric acid for three days. The oily product solidified on scratching. Recrystallization of the solid from a mixture of benzene and ligroin (b.p. 90–120°) gave 5.2 g. (58%) of *ethyl 2-methyl-2-(3'-aminoquinolyl)crotonate* (XXVI), m.p. 44–45°.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.92. Found: N, 10.73.

Cyclization of 1 g. (0.004 mole) of the crotonate in 25 ml. of refluxing Dowtherm by the usual procedure (19) gave, after washing with Skellysolve B and recrystallization from a mixture of ethanol and water, 0.6 g. (71%) of *2-hydroxy-4-methyl-7,8-benzo-1,5-naphthyridine* (XXVII) (m.p. above 300°).

Anal. Calc'd for $C_{13}H_{10}N_2O$: N, 13.33. Found: N, 12.98.

When a mixture of 5 g. (0.035 mole) of 4-aminoquinoline, 5.2 g. (0.035 mole) of ethyl acetoacetate, and a catalytic amount of hydrochloric acid was reacted in a similar manner there was obtained directly *2-methyl-4-hydroxy-7,8-benzo-1,6-naphthyridine* (XXV) which, after recrystallization from a mixture of benzene and ligroin (b.p. 90–120°), melted at 310°; the yield was 5 g. (70%).

Anal. Calc'd for $C_{12}H_{10}N_2O_2$: N, 13.33. Found: N, 13.20.

Knorr reaction with 3- and 4-aminoquinoline. A mixture of 5 g. (0.035 mole) of 3-aminoquinoline and 5.2 g. (0.035 mole) of ethyl acetoacetate was refluxed for 30 minutes. On cooling, the mixture solidified. Recrystallization of the solid from water yielded 5.95 g. (75%) of *N-(3-quinolyl)acetoacetamide* (XXIV), m.p. 112–113°.

Anal. Calc'd for $C_{13}H_{12}N_2O_2$: C, 68.20; H, 5.31; N, 12.26.
Found: C, 68.39; H, 5.31; N, 12.28.

A solution of the amide (1 g., 0.004 mole) in 5 ml. of concentrated sulfuric acid was heated on the steam-bath for 30 minutes and, after cooling, poured onto ice. Since no solid separated, the solution was neutralized with ammonia and evaporated to dryness. The residue was extracted with hot ethanol. To the ethanolic extract was added an alcoholic solution of picric acid yielding the *picrate* of *3-aminoquinoline* melting at 112–113°, which was identified by mixed melting point. No naphthyridine was obtained.

In a similar manner were reacted 5 g. (0.035 mole) of 4-aminoquinoline and 5.2 g. (0.035 mole) of ethyl acetoacetate. The solid was recrystallized three times from a mixture of benzene and ligroin (b.p. 90–120°) yielding 3.8 g. (50%) of *N-(3-quinolyl)acetoacetamide* (XXIII) melting at 210°. When this amide (1 g., 0.004 mole) was treated with sulfuric acid as described above for the amide from 3-aminoquinoline, there was obtained, after neutralization with ammonia and recrystallization from ethanol and water, 0.47 g. (58%) of *2-hydroxy-4-methyl-7,8-benzo-1,6-naphthyridine* melting above 300°.

Anal. Calc'd for $C_{13}H_{10}N_2O$: N, 13.33. Found: N, 13.53.

SUMMARY

The relative ease of cyclization of corresponding carbonyl derivatives of 2-, 3-, and 4-aminopyridine have been considered.

In general, 2- or 4-aminopyridine intermediates cyclize more readily than the corresponding 3-aminopyridine intermediates; in fact, only one of the latter has been cyclized satisfactorily. Most 2-aminopyridine intermediates cyclize to form pyrimidines. 4-Aminopyridine intermediates cyclize to form 1,6-naphthyridines, but only one such intermediate could be prepared.

Several 4-aminoquinoline intermediates were produced and these were found to cyclize to form 1,6-naphthyridines more readily than the corresponding 3-aminoquinoline intermediates which cyclized to form 1,5-naphthyridines.

Several new naphthyridines were synthesized.

DURHAM, NORTH CAROLINA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF CINCINNATI]

SOME NEW FLUORENE ARSENICALS[1]

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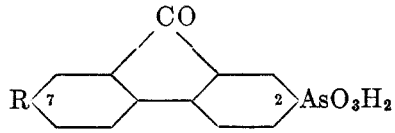
Received June 1, 1950

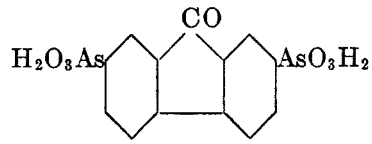
Fluorene arsenicals have been the subject of four papers (1–4). Fluorene, 9-fluorenone, and 9-fluorenol arsenicals have been prepared, all of them derived from fluorene-2-arsonic acid with substituents limited to the 7-position. In several cases, the compounds showed favorable, but not remarkable, pharmacological properties against *Trypanosoma equiperdum*. The more promising of these included 7-acetaminofluorenone-2-arsonic acid, 7-carbamylmethoxyfluorenone-2-arsonic acid, and 7-(carbamylmethylamino)fluorenol-2-arsonic acid. The 2,7-positions, viewed as substituents of the biphenyl system, correspond to the extended *para* (I), a form that would seem to offer the most effective



I

structure type in view of the success of the corresponding benzene analogs.

The new arsenicals prepared by us are all fluorenone derivatives. Some extension of the 2,7-series has been made. Fluorenone-2-arsonic acid was obtained from the corresponding amine by a Scheller reaction involving diazotization in acetone medium followed by decomposition in the presence of arsenic trichloride. This is the first application of the Scheller reaction in this series. Conversion of fluorenone-2-arsonic acid to 7-aminofluorenone-2-arsonic acid was accomplished according to the procedures of Morgan and Stewart (2). The aminoarsonic acid was converted through the diazonium salt to the first of the new arsenicals, fluorenone-2,7-diarsonic acid (II). Reduction of the aminoarsonic acid with hypophosphorous acid, followed by treatment with hydrochloric acid, gave 7,7′-diamino-2,2′-arsenofluorenone dihydrochloride (III).



II

[1] From a thesis submitted to the graduate faculty of the University of Cincinnati in partial fulfilment of the requirements for the Ph.D. degree, June, 1950.

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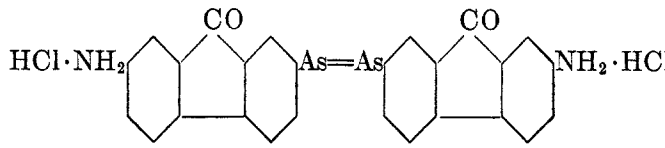
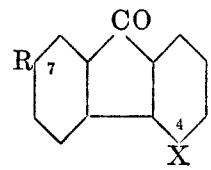


IIII

A new parent arsenical, fluorenone-4-arsonic acid (IV), was obtained by a Scheller reaction on the corresponding amine. From this the water-soluble monosodium salt was prepared. The free acid was then reduced to 4-arsenosofluorenone (V) with sulfur dioxide in hydrochloric acid plus a trace of potassium iodide. Treatment of fluorenone-4-arsonic acid with phosphorus trichloride gave the corresponding fluorenone-4-dichloroarsine (VI). Direct nitration of the arsonic acid (IV) yielded 7-nitrofluorenone-4-arsonic acid (VII). This nitroarsonic acid was reduced with alkaline ferrous hydroxide to the aminoarsonic acid (VIII), and the amine acetylated to give the acetamino derivative (IX). Treatment of the supposed 7-aminofluorenone-4-arsonic acid with chloroacetamide gave 7-(carbamylmethylamino)fluorenone-4-arsonic acid (X). Phosphorus trichloride treatment of 7-nitrofluorenone-4-arsonic acid yielded the corresponding dichloroarsine (XI).

FLUORENONE-4-ARSONIC ACID SERIES



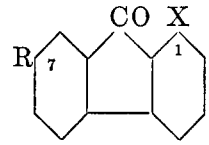
IV.	R = H	X = AsO_3H_2	VIII.	R = NH_2	X = AsO_3H_2
V.	R = H	X = AsO	IX.	R = CH_3CONH	X = AsO_3H_2
VI.	R = H	X = $AsCl_2$	X.	R = $CONH_2 \cdot CH_2NH$	X = AsO_3H_2
VII.	R = NO_2	X = AsO_3H_2	XI.	R = NO_2	X = $AsCl_2$

Proof of structure for 7-nitrofluorenone-4-arsonic acid was accomplished through the known 7-nitro-4-aminofluorenone prepared from fluorenone-4-carboxylic acid using procedures of Moore and Huntress (5). This 7-nitro-4-aminofluorenone was transformed by us into the arsonic acid by a Scheller reaction, and the nitroarsonic acid was then converted, in the usual manner, into the dichloroarsine. This yielded 7-nitrofluorenone-4-dichloroarsine of known constitution, m.p. 231–232°. The supposed 7-nitrofluorenone-4-dichloroarsine, obtained by direct nitration of fluorenone-4-arsonic acid, melted similarly at 231–232°. A mixed melting point showed no depression.

The second new parent arsenical, fluorenone-1-arsonic acid (XII), was prepared from 1-aminofluorenone by a modified Bart reaction using aqueous acetone and alkaline arsenite. A Scheller reaction gave somewhat lower yields. By procedures similar to those employed in the 4-arsonic acid series, the 1-arsonic acid was transformed into 1-arsenosofluorenone (XIII), and fluorenone-1-dichloroarsine (XIV). Direct nitration of XII yielded a mononitroarsonic acid which,

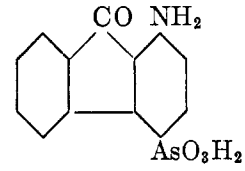
from arguments based on analogy, is very probably 7-nitrofluorenone-1-arsonic acid (XV). Work is in progress along the lines of structure proof and will be reported in a later paper. Reduction of this nitro compound with alkaline ferrous sulfate to 7-aminofluorenone-1-arsonic acid (XVI) was followed by conversion, in the usual way, to 7-acetaminofluorenone-1-arsonic acid (XVII) and 7-(carbamylmethylamino)fluorenone-1-arsonic acid (XVIII). Action of phosphorus trichloride on the nitroarsonic acid XV gave the dichloroarsine (XIX).

FLUORENONE-1-ARSONIC ACID SERIES



XII.	R = H	X = AsO_3H_2	XVI.	R = NH_2	X = AsO_3H_2
XIII.	R = H	X = AsO	XVII.	R = CH_3CONH	X = AsO_3H_2
XIV.	R = H	X = $AsCl_2$	XVIII.	R = $CONH_2 \cdot CH_2NH$	X = AsO_3H_2
XV.	R = NO_2	X = AsO_3H_2	XIX.	R = NO_2	X = $AsCl_2$

Finally, the Bechamp reaction involving direct arsonation with arsenic acid was attempted on 3 amines: 1-aminofluorenone, 2-aminofluorenone, and 4-aminofluorenone. In spite of repeated attempts with a variety of conditions and mole-ratio of reactants, no results were produced with the 2- or 4-amines. It will be noticed that in the case of 2-aminofluorenone, the *para* position is blocked and, at most, very low yields of the 1- or 3-arsonic acid could be expected. In the case of 1-aminofluorenone, however, the *para* position is open for substitution and is also *ortho* to the *ortho-para*-directing phenyl radical. In this case, experiment gave an 11% yield (based on the arsenic acid used) of an aminoarsonic acid which is very probably 1-aminofluorenone-4-arsonic acid (XX).



XX

Structure proof for this compound is in progress. The product gives arsenic contents which are 2–5% too low and is probably contaminated with some arsinic acid (R_2AsO_2H). It will be noted that such a structure would appear to offer much in the way of therapeutic properties, since the similarity to many useful arsenicals is apparent. The possibility that the compound may be 1-aminofluorenone-2-arsonic acid cannot be excluded, however, since direct arsonation of 1-aminonaphthalene gives the 2-arsonic acid (6).

The sodium salts of two of the new arsenicals, fluorenone-1-arsonic acid and fluorenone-4-arsonic acid, have been submitted for screening and the pharmacological values will be reported elsewhere.

Acknowledgement. The helpful suggestions of Dr. E. F. Farnau of the University of Cincinnati, offered during the last stages of this research, are gratefully recognized.

EXPERIMENTAL

Analysis for arsenic. The procedure of Robertson (7) was employed throughout. The method proved reasonably satisfactory in every case.

Melting points. Melting points were obtained with a calibrated thermometer using an aluminum block. Where melting points are not given of the new arsenicals, it may be inferred that such were indefinite or above 300°.

Fluorenone-2-arsonic acid. Ten grams (0.0512 mole) of finely divided 2-aminofluorenone was dissolved in 400 ml. of acetone and 11.5 g. (0.112 mole) of concentrated sulfuric acid was added drop-wise with efficient stirring to precipitate the amine sulfate. The mixture was cooled to 5–10° and diazotized with a solution of 5 g. (0.0725 mole) of sodium nitrite in 15 ml. of water. The mixture was stirred for 30 minutes at a temperature not exceeding 10°, and 20 g. (0.0110 mole) of arsenic trichloride was added all at once. After 30 minutes 1 g. of freshly prepared cuprous bromide was added. After nitrogen evolution ceased (30 minutes) the material was poured, with stirring, into 1500 ml. of water and let stand for 2 hours. The insoluble portion was filtered and extracted with a warm (70–80°) solution of 15 g. of sodium bicarbonate in 800 ml. of water. A second extraction was made and the filtrates were combined and treated with decolorizing carbon. The clear yellow filtrate was acidified with 6 *N* hydrochloric acid until distinctly acid to litmus to give a light yellow precipitate of the arsonic acid. The yield was 6.25 g. (40%).

For analysis, purification was made by solution in sodium bicarbonate at 60–70° and acidification with hydrochloric acid. The well-washed material was dried in an oven at 110–115° for 6 to 7 hours or to constant weight.

Anal. Calc'd for $C_{13}H_9AsO_4$: As, 24.6. Found: As, 24.4.

7-Nitrofluorenone-2-arsonic acid and *7-aminofluorenone-2-arsonic acid.* These compounds were prepared from fluorenone-2-arsonic acid using procedures of Morgan and Stewart (2).

Fluorenone-2,7-diarsonic acid. Ten grams (0.0313 mole) of finely powdered 7-aminofluorenone-2-arsonic acid was dissolved in 100 ml. of water and 5.6 g (0.1 mole) of potassium hydroxide. The solution was cooled to 10° and 2.3 g (0.0334 mole) of sodium nitrite was added and the whole introduced slowly into a mixture of 150 ml. of water and 15 g. (0.146 mole) of concentrated sulfuric acid held at 0°.

An alkaline arsenite solution was prepared from 35 g. (0.626 mole) of potassium hydroxide, 15 g. (0.0760 mole) of arsenious oxide, and 1 g. of copper sulfate in 200 ml. of water. To this, the diazonium solution was added at room temperature in 10-ml. portions with stirring and the mixture was slowly heated on a water-bath to 90° until nitrogen evolution ceased. The filtrate was treated hot with decolorizing carbon, and the resulting clear yellow solution acidified with a slight excess of 6 *N* hydrochloric acid to precipitate the fine yellow-brown diarsonic acid. This was washed well with water and dried to give 9 g. (67%). For purification, the product was dissolved twice in sodium bicarbonate solution with decolorizing treatment in each case and was precipitated with dilute hydrochloric acid. For analysis, a sample of the material was dried in the oven at 110° for 7–8 hours.

Anal. Calc'd for $C_{13}H_{10}As_2O_7$: As, 34.7. Found: As, 34.2.

7,7'-Diamino-2,2'-arsenofluorenone dihydrochloride. A 1-g. portion of finely divided 7-aminofluorenone-2-arsonic acid was suspended in 10 ml. of glacial acetic acid, and 10 ml. of 30% hypophosphorous acid was added. The mixture was stirred in a water bath at 85–90° for 2½ hours. The buff-orange precipitate was transferred quickly to 100 ml. of boiled distilled water. The mixture was made alkaline with 2 *N* potassium hydroxide, the brown free base was filtered and transferred to 100 ml. of 3 *N* hydrochloric acid, and then filtered again as the buff-orange hydrochloride. The product was washed with dilute hydrochloric acid and dried in a vacuum desiccator over sodium hydroxide to give 0.65 g. (68%) of a

light brown material which darkened upon heating for 1 hour at 110°. The compound was analysed as the dihydrochloride.

Anal. Calc'd for $C_{26}H_{18}As_2Cl_2N_2O_2$: As, 24.5. Found: As, 23.7.

Fluorenone-4-arsonic acid. The modified Scheller procedure used by us in the preparation of fluorenone-2-arsonic acid was employed here on 4-aminofluorenone, of m.p. 138–139°; the yield of light yellow arsonic acid was 45%.

Anal. Calc'd for $C_{13}H_9AsO_4$: As, 24.6. Found: As, 24.9.

The monosodium salt was prepared by dissolving the free arsonic acid in a minimum amount of sodium bicarbonate. Dilution with an equal volume of alcohol or acetone resulted, after a time, in the formation of yellow-orange crystals of the salt containing water of hydration. The salt is readily soluble in cold water. After drying at 110° for 5 hours, arsenic analysis indicated the presence of about 2 molecules of water.

4-Arsenosofluorenone. A 1-g. portion of finely divided fluorenone-4-arsonic acid was suspended in 25 ml. of 6 *N* hydrochloric acid, and 0.1 g. of potassium iodide was added. On shaking, a slight iodine color was formed. The suspension was saturated at room temperature with sulfur dioxide, with occasional shaking, heated to boiling, and the solution again saturated with the gas and allowed to stand overnight. The fluffy precipitate of the arsenoso compound was filtered off, washed with dilute ammonia and water, and dried. Yield was practically quantitative (about 1 g.).

Anal. Calc'd for $C_{13}H_7AsO_2$: As, 27.7. Found: As, 27.6.

Fluorenone-4-dichloroarsine. A 1-g. portion (0.00328 mole) of finely divided fluorenone-4-arsonic acid was suspended in 10 ml. of glacial acetic acid and the temperature raised to the boiling point. Heating was interrupted and 1.5 ml. (0.0120 mole) of phosphorus trichloride dissolved in 5 ml. of glacial acetic acid was introduced with swirling. The arsonic acid quickly dissolved to yield a yellow solution. The material was then gently heated to near reflux for 5 minutes and allowed to cool to yield well-formed yellow crystals of the dichloroarsine. Yield 80% (0.85 g.). The melting point after recrystallization from glacial acetic acid was 161–163°.

Anal. Calc'd for $C_{13}H_7AsCl_2O$: As, 21.6. Found: As, 21.5.

7-Nitrofluorenone-4-arsonic acid. A mixture of 32.5 ml. (0.585 mole) of concentrated sulfuric acid and 37.5 ml. (0.880 mole) of fuming nitric acid (d = 1.50) was cooled in an ice-bath and 15 g. (0.0492 mole) of finely divided fluorenone-4-arsonic acid was introduced with stirring. During the addition, the temperature was not permitted to rise above 10°. The mixture was stirred at room temperature for an additional hour and poured into 500 ml. of ice-water. The precipitated yellow product was filtered, washed, and dried. Yield of crude material was 15.5 g. (90%). Purification was readily accomplished by solution in dilute ammonia, followed by charcoal treatment and precipitation with dilute hydrochloric acid. The pure nitroarsonic acid was dried at 110° for 7 hours for analysis.

Anal. Calc'd for $C_{13}H_8AsNO_6$: As, 21.6. Found: As, 21.5.

7-Nitrofluorenone-4-dichloroarsine. A 3-g. portion (0.00865 mole) of finely divided 7-nitrofluorenone-4-arsonic acid was converted to the arsine as previously described. The product weighed 2.70 g. (85% yield). Purification was effected by recrystallization from glacial acetic acid; m. p. 231–232°.

Anal. Calc'd for $C_{13}H_6AsCl_2NO_3$: As, 20.3. Found: As, 20.5.

7-Aminofluorenone-4-arsonic acid. To 200 ml. of water containing 10 ml. of 6 *N* sodium hydroxide was added 16.5 g. (0.0476 mole) of 7-nitrofluorenone-4-arsonic acid and the mixture was stirred and warmed to effect solution. A solution of 100 g. (0.488 mole) of commercial ferrous sulfate (containing about 3 molecules of water of hydration) in 400 ml. of water was made alkaline with 50% sodium hydroxide. To the suspension of ferrous hydroxide was added slowly, with stirring, the solution of the nitroarsonic acid over a period of 30 minutes. The mixture was warmed slowly on the water-bath and maintained at 90° for 1 hour with constant stirring. The material was filtered from the brown-black precipitate of ferric hydroxide and washed with 4 portions of boiling water. The combined deep red filtrates were acidified with 6 *N* hydrochloric acid to the point of precipitation, and precipi-

tation was completed by the addition of a little glacial acetic acid. The precipitated aminoarsonic acid was filtered, washed with water, and dried to give 8.6 g. (56%) of light orange-brown product. For purification, the compound twice was dissolved in hot 3 *N* hydrochloric acid and precipitated by careful neutralization with ammonium hydroxide and acetic acid.

Anal. Calc'd for $C_{13}H_{10}AsNO_4$: As, 23.5. Found: As, 23.2.

7-Acetaminofluorenone-4-arsonic acid. To 8 ml. of acetic anhydride, 1.5 g. of 7-aminofluorenone-4-arsonic acid was added and the mixture was stirred in a water bath at 75–80° for 2 hours. It was poured into ice-water and the bright orange acetyl derivative was filtered and dried; the yield was practically quantitative. The compound is somewhat soluble in hot glacial acetic acid.

Anal. Calc'd for $C_{15}H_{12}AsNO_5$: As, 20.7. Found: As, 20.2.

7-(Carbamylmethylamino)fluorenone-4-arsonic acid. A 2-g. portion (0.00532 mole) of 7-aminofluorenone-4-arsonic acid was mixed with 3.7 ml. of 2 *N* potassium hydroxide solution and 5 ml. of water, then diluted with 15 ml. more of water and treated with 0.1 g. of potassium iodide and 1.5 g. (0.0161 mole) of chloroacetamide. The clear wine-red solution was stirred in a boiling-water bath for 2.5 hours to give a red-purple precipitate of the carbamyl derivative. The insoluble portion was washed with water. The dry yield was 2 g. (85%). The compound may be crystallized from alcohol by the addition of ether. Fine purple crystals result. For analysis, the compound was purified through the ammonium salt and dried at 110°.

Anal. Calc'd for $C_{15}H_{13}AsN_2O_5$: As, 19.8. Found: As, 19.8.

Proof of structure of 7-nitrofluorenone-4-arsonic acid. The known compound, 4-amino-7-nitrofluorenone, was prepared from fluorenone-4-carboxylic acid using the procedures of Moore and Huntress (5). The pure orange-red compound, somewhat soluble in hot alcohol, glacial acetic acid, and acetone melts at 289–290°.

A 4-g. portion (0.0167 mole) of finely divided 4-amino-7-nitrofluorenone was diazotized and treated with arsenic trichloride as previously described. Yield 2.5 g. of product (43%).

The method used previously for the preparation of dichloroarsines was employed on 1.3 g. of the 7-nitrofluorenone-4-arsonic acid of known constitution. Yield was 1.1 g. (80%), which was purified as before by crystallization from glacial acetic acid.

Anal. Calc'd for $C_{13}H_6AsCl_2NO_3$: As, 20.3. Found: As, 20.6.

The purified nitrodichloroarsine melted at 231–232° which corresponded to the nitrodichloroarsine prepared from fluorenone-4-arsonic acid. A mixed melting point of the two gave 231–232°.

Fluorenone-1-arsonic acid. A 15-g. portion (0.0768 mole) of 1-aminofluorenone (m.p. 118–119°) dissolved in 150 ml. of acetone was poured into a mixture of 100 ml. of 12 *N* hydrochloric acid and 400 ml. of water with efficient stirring. The amine was diazotized at 10° with a solution of 7.0 g. (0.096 mole) of sodium nitrite. After 30 minutes, the mixture was added in small portions to a solution of 15 g. (0.0760 mole) of arsenic trioxide, 15 g. of sodium bicarbonate, 50 g. of potassium hydroxide, and 3 g. of copper sulfate dissolved in 600 ml. of water. The addition required 30 minutes and 6 *N* sodium hydroxide was added as necessary to maintain slight alkalinity. The mixture was let stand 3 hours, slowly heated until nitrogen evolution was completed, filtered, and acidified with 6 *N* hydrochloric acid. The pale yellow solid was filtered, washed, and dried to give 10.5 g. (45%) of the arsonic acid. Purification was accomplished through the sodium salt.

Anal. Calc'd for $C_{13}H_9AsO_4$: As, 24.6. Found: As, 24.9.

The monosodium salt was prepared as in the case of fluorenone-4-arsonic acid.

1-Arsenosofluorenone. The procedure used in the preparation of the 4-arsenoso compound was repeated. Yield was 95% of light yellow compound.

Anal. Calc'd for $C_{13}H_7AsO_2$: As, 27.7. Found: As, 27.9.

Fluorenone-1-dichloroarsine. The method of preparation was substantially the same as that used for fluorenone-4-dichloroarsine. The yield of yellow crystalline material was 85%; m.p. 138–140°.

Anal. Calc'd for $C_{13}H_7AsCl_2O$: As, 23.1. Found: As, 23.3.

7-Nitrofluorenone-1-arsonic acid. Direct nitration of fluorenone-1-arsonic acid was effected as in the case of fluorenone-4-arsonic acid. Yield of yellow product was 90%.

Anal. Calc'd for $C_{13}H_8AsNO_6$: As, 21.6. Found: As, 21.1.

7-Nitrofluorenone-1-dichloroarsine. Prepared as in the case of the 4-derivative, the yield of yellow crystals was 80%. The product melted at 215–217°.

Anal. Calc'd for $C_{13}H_6AsCl_2NO_3$: As, 20.3. Found: As, 20.0.

7-Aminofluorenone-1-arsonic acid. 7-nitrofluorenone-1-arsonic acid was reduced to the amine with ferrous hydroxide, using the procedure employed in the 4-arsonic acid series. A light brown compound was obtained in 55% yield.

Anal. Calc'd for $C_{13}H_{10}AsNO_4$: As, 23.5. Found: As, 23.1.

7-Acetaminofluorenone-1-arsonic acid. A 1.2-g. portion of 7-aminofluorenone-1-arsonic acid was treated at near reflux temperature for 2 hours with 10 ml. of acetic anhydride. Yield of the yellow-orange product was 0.6 g. (42%). Since purification through the ammonium or sodium salt seemed attended with hydrolysis, the compound was recrystallized from glacial acetic acid.

Anal. Calc'd for $C_{15}H_{12}AsNO_5$: As, 20.7. Found: As, 20.5.

7-(Carbamylmethylamino)fluorenone-1-arsonic acid. The compound was prepared as in the case of the corresponding 4-arsonic acid derivative. Yield of red-purple compound was 72%. For analysis, purification was effected through the ammonium salt.

Anal. Calc'd for $C_{15}H_{13}AsN_2O_5$: As, 19.8. Found: As, 19.7.

The Bechamp reaction on 1-aminofluorenone. One hundred grams of pure arsenic pentoxide was refluxed with 500 ml. of water for 1 hour. The mixture was cooled and filtered from the small amount of insoluble residue. The clear solution was evaporated with stirring until the concentrated liquor had transformed into a thick paste of crystals. The temperature was kept above 100° but was not permitted to rise above 115°. Upon cooling, the material solidified entirely, and was ground and dried at 110° for 4 hours. It was then quickly transferred to a tightly sealed container.

A 6-g. portion (0.0308 mole) of dry 1-aminofluorenone was placed in a 60-ml. Pyrex test tube and the tube immersed some 1½ inches in an oil-bath. The temperature was elevated to 145° and 3 g. of solid arsenic acid (0.0187 mole, calculated as $H_3AsO_4 \cdot H_2O$) was added over a period of 10 minutes with continual hand stirring. The temperature was then raised to 160–165° and maintained at that level for 2.5 hours. At the end of the first 15–20 minute period, the mixture had thickened considerably and only occasional stirring was then applied. Moisture, collecting on the upper walls of the test tube, was removed by insertion of rolled filter paper from time to time. The material was removed from the oil-bath, cooled, and extracted with four 15-ml. portions of 3 *N* sodium hydroxide. The combined deep yellow filtrates were cooled and acidified with 6 *N* hydrochloric acid until slightly acid. The precipitated orange-yellow aminoarsonic acid (probably 1-aminofluorenone-4-arsonic acid) was filtered off, washed, and dried to give 0.70 g. which corresponded to 11.7% yield based on weight of arsenic acid used. Purification as the sodium or ammonium salt yielded fractions which gave 3–5% low arsenic contents. A better purification was effected by the slow addition, with efficient stirring, of 1 *N* hydrochloric acid to a solution of the sodium salt until about one-third of the material had precipitated. This was then filtered off, and the precipitation was completed by the addition of more hydrochloric acid to the filtrate. The second fraction possesses an arsenic content that comes within 1–2% of the proper value.

SUMMARY

1. Nineteen new fluorenone arsenicals have been described. The chemical structures of fourteen of these have been established. For the remaining five compounds, the probable structures have been indicated.

2. The Scheller reaction has been applied to the preparation of fluorenone-2-

arsonic acid with an improvement in yield. Acetone is recommended as the solvent for Scheller reactions in preference to alcohol or glacial acetic acid.

3. The Bechamp reaction has been applied, for the first time, to the fluorenone amines, resulting, in the case of 1-aminofluorenone, in a new arsenical.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE POLYTECHNIC INSTITUTE OF BROOKLYN]

THE CONDENSATION OF *p*-NITROPHENYLACETIC ACID WITH ACYCLIC ALDEHYDES. I. ACROLEIN

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INTRODUCTION

p-Nitrophenylacetic acid has been condensed with a wide variety of aromatic aldehydes: benzaldehyde (1, 2), *p*-tolylaldehyde (3), *p*-isopropylbenzaldehyde (1), salicylaldehyde (1), *m*-hydroxy- (4) and *p*-hydroxybenzaldehydes (5), *o*-methoxy- (3), *m*-methoxy- (3), and *p*-methoxy-benzaldehydes (1, 5), 2,4-, 3,4-, and 2,5-dimethoxybenzaldehydes (6), *m*-dimethylamino- and *m*-di-*n*-propylamino-benzaldehydes (7), *p*-dimethylaminobenzaldehyde (3), *m*-nitro- (4, 8) and *p*-nitro-benzaldehyde (4, 9, 10), and 1-naphthaldehyde (11). The products of these reactions were α-*p*-nitrophenylcinnamic acids or the corresponding stilbenes resulting from their decarboxylation. One exception is the condensation with salicylaldehyde which leads to 3-(4′-nitrophenyl)coumarin. However, only three non-aromatic aldehydes have been employed: cinnamaldehyde (11), formaldehyde which, in the presence of primary and secondary amines, gives Mannich bases (12), and glyoxal which forms only polymers (13). The present paper is the first to report on the condensation of *p*-nitrophenylacetic acid with acyclic aldehydes.

RESULTS AND DISCUSSION

The condensation of acrolein with *p*-nitrophenylacetic acid was first tried in aqueous solution. An aqueous suspension of the acrolein-potassium bisulfite addition product was refluxed with *p*-nitrophenylacetic acid for two hours. Only *p*-nitrophenylacetic acid was recovered.

Conditions for the Doebner reaction were next tried, but when acrolein and *p*-nitrophenylacetic acid were refluxed in pyridine no acidic product was recovered. *p*-Nitrotoluene was obtained in almost quantitative yield. It was later observed that this decarboxylation of *p*-nitrophenylacetic acid takes place even at steam-bath temperatures. This reaction is to be studied further.

The Kuhn-Winterstein procedure was studied next (14, 15). Acrolein and *p*-nitrophenylacetic acid were heated to reflux in acetic anhydride with litharge as a catalyst. From the resinous-appearing reaction product, about 4–7% of an acidic material was obtained which melted at 170–175°.

Several other metals, in the form of their acetates, were tried in place of lead. These included calcium, cadmium, zinc, and tin. Alumina was also tried in place of litharge. None of the desired product was obtained in any of these experiments; considerable *p*-nitrophenylacetic acid was recovered in all cases. It appears that these metallic acetates are too insoluble in acetic anhydride to achieve much, if any, catalytic effect.

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Sodium acetate, in varying amounts, was also tried as a catalyst under the same conditions. With large amounts of this catalyst, only resinous materials were obtained, while with small amounts, a mixture of resinous material and unreacted *p*-nitrophenylacetic acid resulted.

The next attempted method employed the Oglialoro modification of the Perkin reaction in which the sodium salt of the arylacetic acid, acetic anhydride, and the aldehyde are heated at 180° (16). At this temperature only an ether-insoluble resinous material could be obtained, but when the reaction was carried out at room temperature a 12% yield of the same new acid as obtained previously was recovered. At 35° and 45° the yield was further raised to 21 and 28%, respectively.

The final variation adopted was the application of the Perkin reaction itself; the condensation of *p*-nitrophenylacetic anhydride with acrolein in the presence of anhydrous sodium acetate as the catalyst in a mixture of dioxane and acetic anhydride as the solvent. This procedure gave the same new compound in slightly impure form in 38% yield.

The acid was isolated as a light yellow microcrystalline solid, m.p. 174–176°. Analyses for carbon, hydrogen, and nitrogen were in accord with the values expected for 2-(4′-nitrophenyl)-2,4-pentadienoic acid. It absorbed five moles of hydrogen, indicating the presence of two double bonds and one nitro group. The resulting colorless compound was amphoteric and its analysis for nitrogen corresponded with the expected value for α-(4′-aminophenyl)valeric acid. Both the dienic acid and its reduction product gave the expected neutral equivalents.

The dienic acid did not form an adduct with maleic anhydride, either at room temperature in benzene or in refluxing nitrobenzene. This is taken to confirm the structure, since 1,1-disubstituted butadienes characteristically do not undergo the Diels-Alder reaction. For example, 1,1-dimethyl-1,3-butadiene gives no adduct, but polymerizes when heated with maleic anhydride (17).

The above series of reactions, combined with the analytical work, indicated that the new product is the expected 2-(4′-nitrophenyl)-2,4-pentadienoic acid.

An attempt to decarboxylate 2-(4′-nitrophenyl)-2,4-pentadienoic acid in quinoline at 180–200° using Adkins-Connor catalyst (15, 18) gave a neutral red residue which could not be induced to crystallize.

EXPERIMENTAL

All temperatures are uncorrected.

Starting materials. *p*-Nitrophenylacetic acid was prepared from benzyl chloride in the following series of reactions (19, 20):

$$C_6H_5CH_2Cl \rightarrow C_6H_5CH_2CN \rightarrow p\text{-}NO_2C_6H_4CH_2CN \rightarrow p\text{-}NO_2C_6H_4CH_2CO_2H$$

The *p*-nitrobenzyl cyanide and the *p*-nitrophenylacetic acid were crystallized several times to remove all traces of the *ortho*-acid. The final product had m.p. 152–153°.

Acrolein was a commercial product furnished by the Shell Chemical Corporation. It contained 0.01 per cent of hydroquinone and was used as such without further purification.

Aqueous procedure. Acrolein (2 ml., 0.03 mole) was added dropwise with shaking and cooling to a suspension of 3.54 g. (0.016 mole) of potassium metabisulfite in 10 ml. of water.

To this was added 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid. The mixture was refluxed for two hours, cooled, made alkaline with dilute sodium hydroxide, filtered, and acidified with dilute hydrochloric acid. After crystallizing the solid (2.3 g.) from water, a mixture melting point (m.m.p.) with *p*-nitrophenylacetic acid gave no depression.

Doebner procedure. A mixture of 2 ml. (0.03 mole) of acrolein, 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid, and 10 ml. of pyridine was heated for one hour on the steam-bath and then refluxed for an additional hour. The reaction mixture was poured into 100 ml. of water containing 10 ml. of concentrated hydrochloric acid, cooled, and extracted with 100 ml. of ether. The ether solution was washed successively with dilute hydrochloric acid, twice with dilute sodium hydroxide solution, twice with water, dried over calcium chloride, and evaporated. A red oil remained with solidified on cooling and weighed 2.06 g. Recrystallization from dilute ethanol gave m.p. 52–53° (m.m.p. with authentic *p*-nitrotoluene, 53–54°).

Kuhn-Winterstein procedure. A mixture of 2.71 g. (0.015 mole) of *p*-nitrophenylacetic acid, 1.11 g. (5 mmole) of litharge, and 20 ml. of acetic anhydride was refluxed under a stillhead equipped with a condensate take-off. Ten milliliters of condensate were collected to remove acetic acid presumably formed during conversion of the *p*-nitrophenylacetic acid to its anhydride. After cooling to room temperature, which precipitated most of the lead salt, 1.0 ml. (0.015 mole) of acrolein was added. The flask was loosely stoppered and heated on the steam-bath for four hours. Water (25 ml.) was added and heating continued for a short time to hydrolyze the anhydride.

After cooling, ether (50 ml.) was added followed by 1:1 hydrochloric acid (15 ml.) to precipitate the lead, and the ether and water layers were decanted into a separatory-funnel. The residue in the flask was washed with 50 ml. of ether and the washings added to the separatory-funnel. The ether layer was washed twice with water to remove acetic acid and then extracted with 10% sodium carbonate solution. Acidification of the extract gave a yellow solid (1.83 g.). Four crystallizations from dilute alcohol gave 0.22 g. (1.0 mmole; 7%) of a light yellow product, m.p. 172–174° (dec.).

Oglialoro procedure. p-Nitrophenylacetic acid (10.8 g., 0.06 mole) was dissolved in a solution of 3.18 g. (0.03 mole) of anhydrous sodium carbonate in 50 ml. of water. The water was distilled and the residual salt partially dried by the addition of three 50-ml. portions of absolute alcohol, which were removed by distillation at atmospheric pressure and then at reduced pressure. Acrolein (4 ml., 0.06 mole) and acetic anhydride (10 ml.) were added and the flask was stoppered and shaken. Heat was evolved and the temperature rose to 35°, which was maintained for three hours by external warming, with occasional shaking. Most of the salt dissolved after one hour and then the mixture became a semi-solid, yellow mass.

A mixture of hydrochloric acid (10 ml.) and water (50 ml.) was added and the solution heated on the water-bath for one hour. The reaction mixture was cooled, taken up in 150 ml. of ether, washed twice with water, and extracted with three portions (100 ml. total) of 10% sodium carbonate solution. Acidification gave 7.1 g. of crude acid, m.p. 135–155° (dec.). After washing with hot water the residue weighed 4.7 g. and melted at 158–164° (dec.). Crystallization from petroleum ether (b.p. 125–135°) gave 2.75 g. of light yellow needles, m.p. 168–172°. Recrystallization raised the melting point to 172–174°.

The extracted ether solution was evaporated leaving 3.0 g. of a neutral red oil which solidified on cooling. Crystallization from dilute alcohol and petroleum ether gave a light yellow product, m.p. 64–65°. This compound proved to be *ethyl p-nitrophenylacetate* [reported m.p. 62.8–63.3° (21), 65–66° (22), 65–67° (23), 65.5–66° (24)]. A mixed melting point with ethyl *p*-nitrophenylacetate prepared from the acid according to Maxwell (24) showed no depression.

Anal. of compound m.p. 64–65°. Calc'd for $C_{18}H_{11}NO_4$: C, 57.41; H, 5.31; N, 6.69; Mol. wt., 209. Found: C, 57.12; H, 4.95; N, 6.69; Mol. wt. (cryoscopic, benzene), 196, 203.

The adjusted yield of recrystallized acid, m.p. 168–176°, was thus 28% based on *p*-nitrophenylacetic acid.

Perkin procedure. A number of experiments were performed to determine optimum con-

ditions for the synthesis of *p*-nitrophenylacetic anhydride [previously prepared by refluxing a suspension of sodium *p*-nitrophenylacetate with *p*-nitrophenylacetyl chloride in benzene (25)].

p-Nitrophenylacetic acid (100 g., 0.55 mole) and 400 ml. of acetic anhydride (b.p. 138–139.5°) were heated to reflux (this took 10 minutes) and maintained at reflux for 20 minutes. The acetic acid and excess anhydride were distilled at reduced pressure until the residue solidified. Crystallization from chlorobenzene followed by washing with petroleum ether and drying gave 71.5 g. (0.21 mole; 77%) of a pale yellow solid, m.p. 148–149° [reported m.p. 153° (25)].

One gram of the anhydride refluxed with 10 ml. of aniline for one hour gave 0.55 g. (74%) of yellow anilide, m.p. 209–212°. Crystallization from ethyl acetate—isopropanol (1:3) raised the melting point to 211–212° [reported 198° (26), 211.7–213.2° (21)].

Acrolein (1 ml., 0.015 mole) was added to a mixture of *p*-nitrophenylacetic anhydride (2.4 g., 0.007 mole), 1.23 g. (0.015 mole) of anhydrous sodium acetate, 8 ml. of dioxane, and 5 ml. of acetic anhydride. The anhydride dissolved slowly with a slight evolution of heat. After heating the mixture at 55° for 16 hours, the product was isolated as in other experiments and crystallized from dilute alcohol to give 1.17 g. (38%) of a crude acid, m.p. 165–175° (dec.).

Characterization of the product. After recrystallization from petroleum ether (b.p. 125–135°), the acid melted 172–174° (dec.). It was unsaturated towards bromine in carbon tetrachloride and potassium permanganate in acetone.

Anal. Calc'd for $C_{11}H_9NO_4$: C, 60.27; H, 4.14; N, 6.39; Neut. equiv., 219.
Found: C, 60.45, 59.77; H, 4.26, 4.58; N, 6.36, 6.21; Neut. equiv., 221.

The acid (6.3 g., 0.029 mole) was hydrogenated at 731 mm. in acetic acid solution over a 5% palladium-on-charcoal catalyst. It absorbed 96.5% of the calculated volume of hydrogen (assuming saturation of two double bonds and reduction of the nitro-group to an amino group). The filtered solution was poured into 300 ml. of ice-water, taken up in ether, filtered, and then extracted with dilute hydrochloric acid. Upon neutralizing the solution to *p*H 5 (optimum) 1.20 g. of a colorless compound separated, which after two crystallizations from dilute ethanol had m.p. 137–138°. Concentration and extraction of the mother liquors gave an additional 1.23 g. (total yield 2.43 g., 44%).

Anal. Calc'd for $C_{11}H_{15}NO_2$: N, 7.25; Neutral equivalent, 193.
Found: N, 7.26, 7.22; Neutral equivalent, 195.

Extraction of the ether solution with dilute sodium hydroxide gave, after neutralization, 0.1 g. of an acid, m.p. 170–171°. This proved to be the acetyl derivative as verified by acetylating 0.46 g. (2.4 mmole) of α-(*p*-aminophenyl)valeric acid in 5 ml. of acetic anhydride followed by dilution with water, concentration at reduced pressure, and recrystallization twice from ethanol, m.p. 172–173°, showing no depression in a mixed melting point with the previous product.

Anal. of compound m.p. 172–173°. Calc'd for $C_{13}H_{17}NO_3$: N, 5.95; Neut. equiv., 235.
Found: N, 5.94, 5.93; Neut. equiv., 238.

The acid (11 g., 0.05 mole) in acetic acid (100 ml.) was treated portionwise with bromine (8 g., 0.05 mole) in 40 ml. of acetic acid. The color was discharged rapidly until near the end of the addition. The solution was diluted with 75 ml. of water, allowed to stand in an ice-chest for 24 hours, filtered, and the solid crystallized six times from 50–55% ethanol to give 1.52 g. of dibromide, m.p. 162–162.5°. The filtrate gave an additional 2.20 g., m.p. 159–161°.

Anal. Calc'd for $C_{11}H_9Br_2NO_4$: N, 3.70; Neutral equivalent, 379.
Found: N, 3.72; Neutral equivalent, 390, 389.

When 0.55 g. (2.5 mmole) of the acid was treated with 0.8 g. (5 mmole) of bromine, the color was not discharged on heating for one-half hour at 70°. The same product was isolated.

Attempted decarboxylation. Ten grams of 2-(4′-nitrophenyl)-2,4-pentadienoic acid and 1 g. of Adkins-Connor catalyst were heated to 180–200° in 50 ml. of quinoline with mechanical stirring for 15 minutes. Evolution of carbon dioxide began at 180° and ended after 12 min-

utes. The reaction mass was diluted with ether, filtered (most of the material was insoluble in ether), washed with dilute sodium hydroxide, water, and then evaporated to dryness. Neither the ether-insoluble material nor the ether-soluble material could be induced to crystallize. The alkaline extracts were acidified, but no acid precipitated.

SUMMARY

A number of procedures were investigated for effecting the condensation of acrolein with *p*-nitrophenylacetic acid. The best yield (38%) of 2-(4′-nitrophenyl) -2,4-pentadienoic acid was obtained by a low-temperature modification of the Perkin reaction. Several derivatives of this acid were prepared.

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[CONTRIBUTION FROM THE EASTERN REGIONAL RESEARCH LABORATORY][1]

MIXED ESTERS OF LACTIC AND CARBONIC ACIDS. *n*-ALKYL CARBONATES OF VARIOUS LACTATES[2]

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Previous papers (1–3) have described five homologous series of carbonates of *n*-alkyl lactates, in addition to several miscellaneous esters. Three additional homologous series—the *n*-alkyl carbonates of tetrahydrofurfuryl lactate, 2-butoxyethyl lactate and 2-(2-butoxyethoxy)ethyl lactate—are described in this paper. Data on the use of most of these esters as plasticizers have been presented (4), but will be published elsewhere.

The esters, shown in Table I, were made by treating the lactate with an alkyl chloroformate in the presence of pyridine (1). As in the previous studies, boiling points, refractive indices, densities, and viscosities of the products were determined (Table I), and these physical properties were correlated with the number of carbon atoms in the members of each homologous series.

Boiling points and vapor pressures. Figures 1–3 show the boiling points of the esters as a function of the pressure. As in the previous papers, the temperature scale of Figures 1–3 are laid off as linear functions of $1/(t + 193)$, where t is the temperature in °C.

For each series, straight lines were obtained by plotting the logarithm of the vapor pressure at any fixed temperature *versus* the number of carbon atoms (x) in the compounds. These lines, equations for which are shown in Table II, had a common point of intersection for each family as follows: tetrahydrofurfuryl series, $\log P = 5.8$, $x = -14$; butoxyethyl series, $\log P = 5.3$, $x = -9.3$, and butoxyethoxyethyl series, $\log P = 9.0$, $x = -32$. Also, the slope (a) of these lines for each series was found to be a linear function of the absolute temperature: for the tetrahydrofurfuryl series, $a = 0.156 - 152/T$; for the butoxyethyl series, $a = 0.275 - 165/T$; and for the butoxyethoxyethyl series, $a = 0.027 - 92.8/T$ By use of these equations for the slope, and the common points of intersection given above, equations similar to those in Table II may be calculated for the vapor pressures of the members of either of the three series of esters at any temperature.

At any fixed pressure, the squares of the boiling points (°K) varied linearly with the number of carbon atoms in the esters of each series. Coefficients for the equations for these lines are shown in Table III. For each series, the lines defined by the equations of Table III had a common point of intersection having the following coordinates: For the tetrahydrofurfuryl esters: $10^{-4}T^2 = -1.8$,

[1] One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture.

[2] Many of the compounds reported in this paper have been tested to determine their utility as plasticizers, and the results were included in a paper presented before the Division of Paint, Varnish and Plastics Chemistry at the Washington Meeting of the American Chemical Society, August-September, 1948.

TABLE I

ALKYL CARBONATES OF LACTIC ESTERS

REACTANTS		YIELD, %	n_D^{20}	n_D^{40}	d_4^{20}	d_4^{40}	MOL. REFRACTION		VISCOSITY, CPS.		C		H	
Chloroformate	Lactate						Calc'd	Found, 20°	At 20°	At 40°	Calc'd.	Found	Calcd.	Found
Ethyl	Tetrahydrofurfuryl	73	1.4430	1.4358	1.1384	1.1195	57.39	57.36	22.86	10.37	53.6	53.2	7.4	7.3
n-Butyl	Tetrahydrofurfuryl	59	1.4451	1.4381	1.0958	1.0785	66.63	66.64	28.41	12.23	56.9	56.6	8.1	8.1
n-Hexyl	Tetrahydrofurfuryl	50	1.4470	1.4400	1.0632	1.0479	75.86	76.00	30.98	13.81	59.6	59.4	8.7	8.7
n-Octyl	Tetrahydrofurfuryl	43	1.4486	1.4416	1.0370	1.0221	85.10	85.39	34.98	14.40	61.8	61.8	9.1	8.9
n-Decyl	Tetrahydrofurfuryl	66	1.4500	1.4430	1.0166	1.0020	94.34	94.75	39.99	16.13	63.7	63.7	9.6	9.7
n-Dodecyl	Tetrahydrofurfuryl	57	1.4510	1.4438	0.9990	0.9861	103.57	104.17	45.63	18.52	65.3	65.8	9.9	10.2
Ethyl	2-(2-Butoxyethoxy)ethyl	—	1.4330	1.4252	1.0507	1.0322	75.09	75.78	14.44	6.95	54.9	55.3	8.6	8.6
n-Amyl	2-(2-Butoxyethoxy)ethyl	74	1.4366	1.4296	1.0247	1.0070	88.94	89.02	18.69	8.70	58.6	58.6	9.3	9.3
n-Octyl	2-(2-Butoxyethoxy)ethyl	56	1.4402	1.4330	0.9984	0.9823	102.80	103.14	22.39	10.22	61.5	61.4	9.8	9.8
n-Decyl	2-(2-Butoxyethoxy)ethyl	31	1.4422	1.4350	.9864	.9698	112.04	112.32	26.51	11.86	63.1	63.2	10.1	10.1
n-Dodecyl	2-(2-Butoxyethoxy)ethyl	52	1.4444	1.4372	.9734	.9571	121.27	121.95	32.64	14.44	64.6	65.0	10.4	10.7
Ethyl	2-Butoxyethyl	69	1.4268	1.4195	1.0481	1.0292	64.21	64.24	9.70		54.6	54.9	8.5	8.5
n-Amyl	2-Butoxyethyl	54	1.4314	1.4242	1.0112	0.9930	78.06	78.07	12.98	6.33	59.2	59.3	9.3	9.4
n-Decyl	2-Butoxyethyl	62	1.4392	1.4320	0.9640	.9479	101.15	101.21	19.30	9.14	64.1	64.6	10.2	10.5
n-Hexyl	2-Phenoxyethyl	69	1.4812	1.4740	1.0861	1.0685	88.31	88.70	84.68	25.13	63.9	63.7	7.7	7.6
n-Hexyl	2-*n*-Hexyloxyethyl	78	1.4367	1.4286	0.9841	0.9670	91.92	92.17	17.05	8.02	62.4	62.4	9.9	9.8
n-Hexyl	Diethylene glycol	61	1.4454	1.4380	1.0847	1.0678	124.58	124.41	150.9	44.47	56.9	56.6	8.4	8.4
Ethyl	Diethylene glycol	70	1.4396	1.4324	1.1844	1.1654	87.63	87.67	321.0	60.25	48.7	48.4	6.7	6.8
Methyl	*n*-Decyl	59	1.4330	1.4258	0.9793	0.9622	76.42	76.53	12.71	6.16	62.5	62.5	9.8	9.7

$x = -14.5$; for the butoxyethyl esters: $10^{-4}T^2 = -2.0$, $x = -9.0$; for the butoxyethoxyethyl esters: $10^{-4}T^2 = 3.5$, $x = -5.0$. Also, the slopes (a) of these lines varied linearly with the logarithm of the pressure: for tetrahydrofurfuryl esters: $\log P = 5.75 - 3.91/a$; for butoxyethyl esters: $\log P = 5.34 - 4.35/a$; for butoxyethoxyethyl esters: $\log P = 4.00 - 2.80/a$. By use of these slopes and

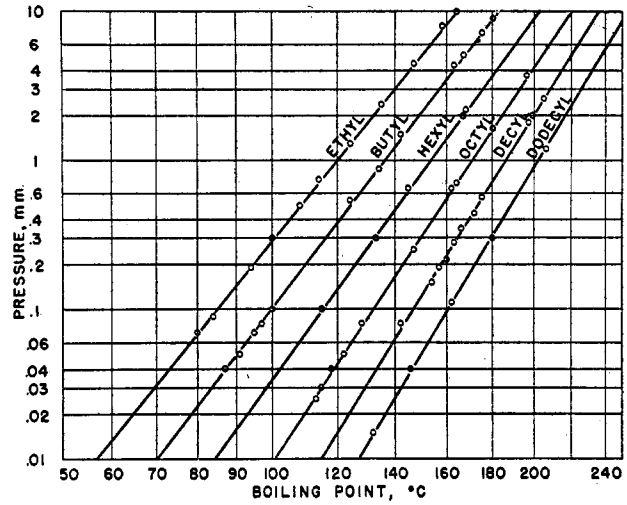

FIG. 1. BOILING POINTS OF n-ALKYL CARBONATES OF TETRAHYDROFURFURYL LACTATE

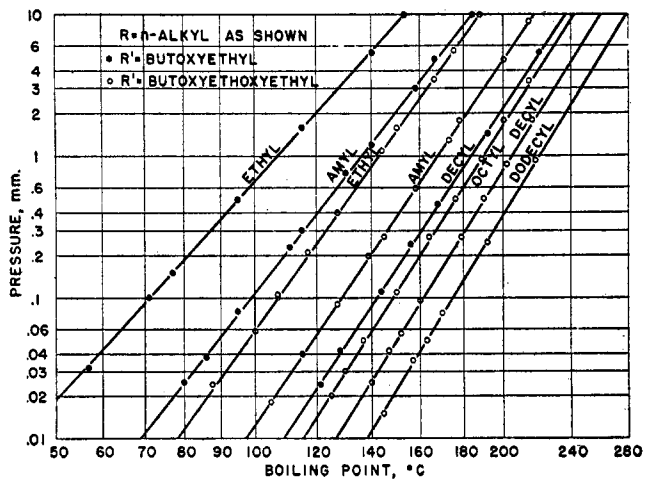

FIG. 2. BOILING POINTS OF CARBONATES, ROOCOCH(CH_3)COOR′

the common points given above, equations similar to those in Table III may be calculated for any pressure.

A more general, but less accurate, equation for the boiling points of carbonates of lactates ROCOOCH(CH_3)COOR′ is

$$A = 0.49\ (B + C) - 14$$

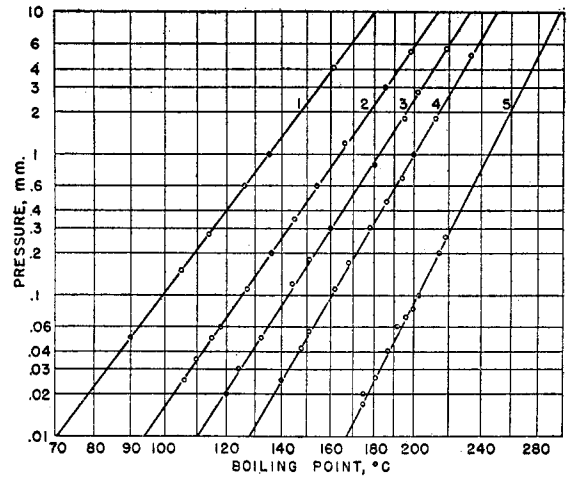

FIG. 3. BOILING POINTS OF MISCELLANEOUS CARBONATES: 1. Methyl carbonate of decyl lactate. 2. *n*-Hexyl carbonate of 2-*n*-hexyloxyethyl lactate. 3. *n*-Hexyl carbonate of 2-phenoxyethyl lactate. 4. Ethyl carbonate of diethylene glycol dilactate. 5. *n*-Hexyl carbonate of diethylene glycol dilactate.

TABLE II

EQUATIONS RELATING VAPOR PRESSURE (P) AT VARIOUS TEMPERATURES TO THE NUMBER OF CARBON ATOMS (*x*) IN *n*-ALKYL CARBONATES OF LACTATES

$\log P = ax + b$

TEMP., °C.	*a*	*b*	DEVIATIONS[a], %	
			Max.	Av.
Carbonates of Tetrahydrofurfuryl Lactate				
100	−0.252	2.28	6	4
150	−.203	2.96	5	3
200	−.166	3.47	5	3
Carbonates of Butoxyethoxyethyl Lactate				
100	−.222	1.865	1	1
150	−.191	2.87	10	6
200	−.168	3.59	10	6
250	−.151	4.18	1	0.4
Carbonates of Butoxyethyl Lactate				
110	−.256	2.90	4	3
135	−.229	3.16	5	4
160	−.206	3.44	16	14

[a] Deviations from the pressures read from Figures 1 and 2. A deviation of 5% corresponds to a difference in boiling point of about 1°.

where A = boiling point of the ester at 1-mm. pressure, and B and C are the normal boiling points of the alcohols ROH and R′OH. This equation shows a

maximum deviation of 13° and an average deviation of 2.9° from the observed boiling points of 55 esters reported in this paper and the preceding papers of this series.

Densities and refractive indices. These physical properties were measured at 20 and 40° (Table I). As in the previous papers, linear relationships were found between certain functions of these physical constants and the number of carbon atoms in the esters in each series. These equations are shown in Table IV. Such equations are useful, not only for calculating the properties of homologs not

TABLE III

EQUATIONS RELATING BOILING POINTS (°K) AT VARIOUS PRESSURES TO THE NUMBER OF CARBON ATOMS (x) IN n-ALKYL CARBONATES OF LACTATES

$10^{-4}T^2 = ax + b$

PRESSURE, MM.	a	b	DEVIATIONS, °K.	
			Max.	Av.
Carbonates of Tetrahydrofurfuryl Lactate				
0.01	0.502	5.36	2	1.2
.10	.580	6.50	2	1.2
1.00	.686	8.00	2	1.0
10.0	.826	10.17	2	1.0
Carbonates of Butoxyethyl Lactate				
0.01	0.593	3.33	0	0
.10	.687	4.17	2	0.5
1.00	.816	5.34	2	.7
10.0	.996	7.00	3	1.0
Carbonates of Butoxyethoxyethyl Lactate				
0.01	0.462	5.81	1	0.3
.10	.572	6.35	1	.8
1.00	.714	7.15	2	.9
10.0	.923	8.12	3	1.5

prepared but for checking the purity of those studied and the accuracy of the physical measurements made on them.

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EXPERIMENTAL

Lactates. The preparation of tetrahydrofurfuryl, 2-butoxyethyl, 2-(2-butoxyethoxy)-ethyl, and n-decyl lactates has been described (5–7).

2-Hexyloxyethyl and 2-phenoxyethyl lactates were prepared from methyl lactate by the alcoholysis procedure (7).

In attempts to prepare diethylene glycol dilactate by the reaction of equivalent amounts of diethylene glycol and methyl lactate, 30 to 40% yields of lactide were obtained. An equal

amount of monolactate was produced, but the yield of dilactate was much lower. A small fraction, thought to be a trilactate, was obtained (Table V). Despite many experiments, no satisfactory procedure was found for the preparation of a glycol dilactate.

The lactates not previously reported in the literature are shown in Table V.

TABLE IV

EQUATIONS FOR THE DENSITY AND REFRACTIVE INDEX OF CARBONATES OF LACTATES

EQUATION	DEVIATIONS	
	Max.	Av.
Carbonates of Tetrahydrofurfuryl Lactate		
$1/(x + 10) = -1.857\ n_D^{20} + 2.7272$	0.0002	0.0001
$1/(x + 10) = -1.700\ n_D^{40} + 2.4876$	.0005	.0002
$1/(x + 2) = 0.240\ d_4^{20} - .1963$	.0004	.0002
$1/(x + 2) = .251\ d_4^{40} - .2040$	.0008	.0003
Carbonates of Butoxyethyl Lactate		
$1/(x + 25) = -0.3889\ n_D^{20} + 0.5818$	.0003	.0003
$1/(x + 25) = -.3887\ n_D^{40} + .5787$	.0004	.0003
$1/(x + 12) = .1242\ d_4^{20} - .0885$	.0004	.0002
$1/(x + 12) = .1282\ d_4^{40} - .09027$	.0001	.0000
Carbonates of Butoxyethoxyethyl Lactate		
$1/(x + 25) = -0.458\ n_D^{20} + 0.6819$	.0003	.0002
$1/(x + 25) = -.440\ n_D^{40} + .6527$	.0003	.0001
$1/(x + 10) = .156\ d_4^{20} - .1225$	.0023	.0009
$1/(x + 10) = .162\ d_4^{40} - .1258$	.0021	.0010

TABLE V

PREPARATION OF LACTATES

LACTATE	YIELD, %	B.P., °C.	PRESS., MM.	n_D^{20}	d_4^{20}	MOL. REFRACT.		SAPON. EQUIV.		C		H	
						Calc.	Found	Calc.	Found	Calc.	Found	Calc.	Found
2-Hexyloxyethyl	83	86	1	1.4362	0.9829	57.82	58.09	218.3	223.3	60.5	60.9	10.2	10.5
2-Phenoxyethyl	30	102	0.2	1.5102	1.1613	54.22	54.16	210.2	199	62.8	62.4	6.7	6.9
Diethylene glycol monolactate	39	96	.1	1.4560	1.1819	40.87	40.98	178.2	177.6	47.2	47.5	7.9	8.0
dilactate	14	120	.1	1.4582	1.2088	56.38	56.52	125.1	121.7	48.0	48.0	7.2	7.2
trilactate	3	145	.1	1.4588	1.2160	71.89	72.44	107.4	110.8	48.4	49.0	6.9	7.1

Preparation of carbonates and determination of physical constants. The lactates were treated with the alkyl chloroformates (used as received) in the presence of equivalent amounts of pyridine, as described in the earlier papers of this series. Similarly, the previously described procedures were used for the determination and correlation of physical constants.

SUMMARY

Nineteen alkyl carbonates of lactic esters, comprising three homologous series, were prepared. In each series, the vapor pressures, boiling points, refractive indices, densities and viscosities were correlated with the number of carbon atoms in the compounds.

PHILADELPHIA 18, PA.

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[CONTRIBUTION FROM THE INSTITUTO DE QUÍMICA, UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

N-BROMOMETHYLPHTHALIMIDE AS A REAGENT FOR THE CHARACTERIZATION OF ALCOHOLS AND PHENOLS

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Although there is available already a great variety of reagents for the formation of derivatives of compounds containing hydroxyl groups, we have investigated the use of N-bromomethylphthalimide (I) for the identification of alcohols and phenols because it offers the following advantages over known reagents:

a. N-bromomethylphthalimide is easily prepared starting from phthalimide.

b. It can be stored for prolonged periods of time without taking special precautions.

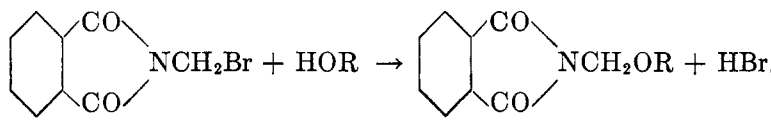
c. It forms solid derivatives even with alcohols of low molecular weight.

d. The formation of derivatives is rapid and the products are easily isolated.

e. The reaction does not require the anhydrous conditions which are necessary with many other reagents.

f. Usually there is no formation of undesirable side products during the reaction.

The bromine atom of N-bromomethylphthalimide has considerable activity, and reacts easily with substances containing hydroxyl groups to form phthalimidomethylene ethers of formula II



I II

In Table I we have summarized the results obtained in the preparation of the phthalimidomethylene ethers of a series of alcohols and phenols.

From the preparation of the derivatives mentioned in Table I we have inferred some general rules which may serve as a guide for the preparation of other similar compounds:

a. The reaction must proceed in acid medium, and it is convenient to use the crude N-bromomethylphthalimide, which always contains traces of hydrogen bromide.

b. The presence of a small amount of powdered potassium iodide seems to favor the reaction rate, probably due to the *in situ* formation of the corresponding iodo derivative.

c. The time required for the reaction depends on the nature of the alcohol. Phenols and alcohols of low molecular weight react more readily than long chain

[1] From a thesis submitted by Olga Lemberger to the Escuela de Ciencias Químicas de la Universidad Nacional Autónoma de México, in partial fulfillment of the requirements of the degree of Químico.

alcohols: for instance, ethanol reacts completely in one hour while octadecanol requires eight hours. Secondary alcohols require longer time than primary alcohols.

d. It was not possible to obtain derivatives of tertiary alcohols where a possibility of dehydration existed. On the other hand, triphenyl carbinol reacted normally in four hours. In the case of benzopinacol, with two tertiary hydroxyl groups, only one of them reacted with bromomethylphthalimide.

e. Judging from the behavior of propylene glycol, it is reasonable to assume that both hydroxyl groups will react in other glycols.

TABLE I

PHTHALIMIDOMETHYLENE ETHERS

ALCOHOL	FORMULA OF DERIVATIVE	YIELD %	M.P., °C. (UNCORR.)	N		CRYST. FROM
				Calc'd	Found[b]	
Methanol[a]	$C_{10}H_9NO_3$	—	120–121	7.3	—	Ethanol
Ethanol[a]	$C_{11}H_{11}NO_3$	92	81–83	6.8	6.8	Hexane
1-Butanol	$C_{13}H_{15}NO_3$	78	46–47	6.0	5.8	Hexane
Isobutanol	$C_{13}H_{15}NO_3$	48	58–59	6.0	5.9	Acetic acid-water
1-Tetradecanol	$C_{23}H_{35}NO_3$	83	65–66	3.7	3.3	Hexane
1-Hexadecanol	$C_{25}H_{39}NO_3$	66	70–71	3.5	3.4	Methanol
1-Octadecanol	$C_{27}H_{43}NO_3$	97	80–81	3.2	3.0	Hexane
Cyclohexanol	$C_{15}H_{17}NO_3$	94	81–83	5.4	5.5	Hexane
Phenethyl	$C_{17}H_{15}NO_3$	86	72–74	5.0	5.0	Hexane
2,2-Diphenylethanol	$C_{23}H_{19}NO_3$	65	111–112	3.9	3.8	Benzene-hexane
Thymol	$C_{19}H_{19}NO_3$	69	142–143	4.1	4.1	Benzene-hexane
Triphenyl carbinol	$C_{28}H_{21}NO_3$	50	124–125	3.3	3.1	Benzene-hexane
Benzopinacol	$C_{35}H_{27}NO_4$	95	136–138	2.7	2.4	Benzene-hexane
Propylene glycol	$C_{21}H_{18}N_2O_6$	50	136–146	7.1	7.1	Acetic acid-water
Phenol	$C_{15}H_{11}NO_3$	62	204–205	5.5	5.4	Benzene
β-Naphthol	$C_{19}H_{13}NO_3$	63	196–198	4.6	4.6	Acetic acid

[a] Previously reported by Sachs, *Ber.*, **31**, 1229 (1898).

[b] All nitrogen determinations by the macro Kjeldahl method.

f. Benzene is the most advantageous solvent for the reaction and it can be used without previous drying. When the alcohol and bromomethylphthalimide form a homogeneous mixture, the reaction can be carried out in the absence of a solvent. In one case it was necessary to use dioxane because the alcohol (propylene glycol) was insoluble in benzene and it did not dissolve the reagent.

g. The use of ethanol is not recommended for the crystallization of the derivatives due to possible transetherification. This phenomenon was observed in the case of the derivative of isobutanol, which yielded ethoxymethylenephthalimide after treatment with hot ethanol. Two other derivatives (from β-naphthol and phenethyl alcohol) could not be induced to suffer this change, even after long treatment with ethanol in alkaline or acid solution.

EXPERIMENTAL

N-bromomethylphthalimide. Phosphorus tribromide (30.6 g.) was added in small portions to a stirred suspension of 50 g. of N-hydroxymethylphthalimide (1) in 150 cc. of anhydrous benzene, and the mixture was refluxed for two hours. The clear solution was decanted while hot from the phosphorous acid which remained at the bottom of the flask, and the residue was washed with 50 cc. of hot benzene. On cooling the combined benzene solution, the bromo compound (54.1 g.) separated in crystalline form. A further amount was obtained by concentration of the mother liquor to 50 cc. and cooling. The total yield was 65.6 g. (96.5%), m.p. 149–150°.

Alternative methods for the preparation of this compound are described by Sachs (2) and Gabriel (3).

Derivatives. Two examples will suffice to illustrate the methods of preparation of the derivatives listed in Table I.

N-(β-phenylethoxymethyl)phthalimide. A mixture of 1.5 g. of bromomethylphthalimide and 1 g. of phenethyl alcohol was heated on the steam-bath for 1.5 hours. On cooling the mixture, a solid mass formed which was extracted several times with boiling hexane. The product (1.5 g., 86%) separated from the concentrated solution in the form of rosettes of colorless needles m.p. 70–72°. Recrystallization from benzene-hexane gave the pure ether, m.p. 72–74°.

N-(1-octadecyloxymethyl)phthalimide. A solution of 1 g. of bromomethylphthalimide and 1 g. of 1-octadecanol in 10 cc. of benzene containing 0.1 g. of powdered potassium iodide was refluxed for six hours. The benzene was removed and the residue was crystallized from hexane after filtering the potassium iodide. The yield of the derivative was 1.74 g. (97%), m.p. 76–78°. After three recrystallizations from benzene-hexane the pure product was obtained in the form of fine needles, m.p. 80–81°.

SUMMARY

The use of N-bromomethylphthalimide as a reagent for the characterization of alcohols and phenols has been suggested and its use exemplified by the preparation of a number of derivatives.

MEXICO, D. F., MEXICO

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[CONTRIBUTION FROM THE SCHOOL OF CHEMISTRY OF THE UNIVERSITY OF MINNESOTA]

MECHANISM OF THE PYROLYSIS OF ESTERS[1]

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Although there has been considerable interest in the thermal decomposition of esters as a means of preparing olefins since Krafft (1) in 1883 explored this reaction, only a limited amount of work has been directed toward the mechanism of this high temperature decomposition.[3]

Pure *cis*- and pure *trans*-2-methylcyclohexyl acetates have now been pyrolyzed at 495° in a stainless steel tube in an atmosphere of nitrogen. The olefinic products from each pyrolysis were isolated in 75% yield and qualitatively and quantitatively analyzed from infrared absorption data. 1-Methyl- and 3-methyl-cyclohexenes were the only olefinic products found in the hydrocarbon fraction. The olefinic mixture resulting from the *trans*-ester consisted of 55% 1-methylcyclohexene and 45% 3-methylcyclohexene. From the *cis*-ester the mixture contained only 25% 1-methylcyclohexene and 75% 3-methylcyclohexene. There was no 4-methylcyclohexene found in either product.

DISCUSSION

Esters that undergo pyrolysis may be divided into two classes; first, esters with β-hydrogen atoms on the alkyl portion of the molecule and, second, esters without β-hydrogen atoms. Although a few workers (2) believe that all esters decompose thermally by the same mechanism, others (3) believe that the mechanism is not the same in the two cases. They base their belief on the contrasting conditions of pyrolysis and the products resulting. Pyrolysis of esters without β-hydrogens in the alkyl portion requires higher temperatures and the products are suggestive of a free radical type mechanism (3). However, if β-hydrogen atoms are available and the temperature of pyrolysis is optimum, only the expected olefins and acids result. Only esters belonging to the latter class were studied in this investigation.

Inasmuch as the reaction is stereospecific as shown by the difference in the ratio of the two olefinic products resulting from the pyrolysis of the isomeric esters, it was concluded that it is quite unlikely that the mechanism by which this pyrolysis proceeds is either an ionic mechanism as illustrated in "A" or a free radical mechanism as illustrated in "B". If the pyrolysis proceeded by either

[1] Abstracted from a thesis presented to the Graduate Faculty of the University of Minnesota by G. G. Smith in partial fulfilment of the requirements for the degree of Doctor of Philosophy, July 1949. Presented at the Pacific Northwest Regional Meeting of the American Chemical Society in Richland, Washington, June 9, 1950.

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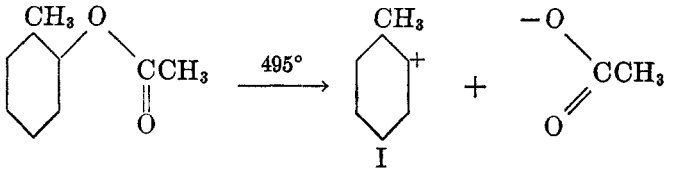
[3] Since this work was completed a paper on the same subject using different examples from ours but reaching the same conclusions was published by Alexander and Mudrak, *J. Am. Chem. Soc.*, **72**, 1810 (1950).

of these mechanisms the two expected olefins would have been formed in the same ratio from either isomeric ester.

A.



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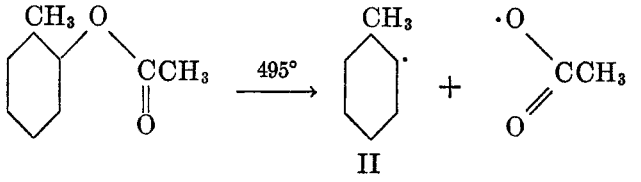
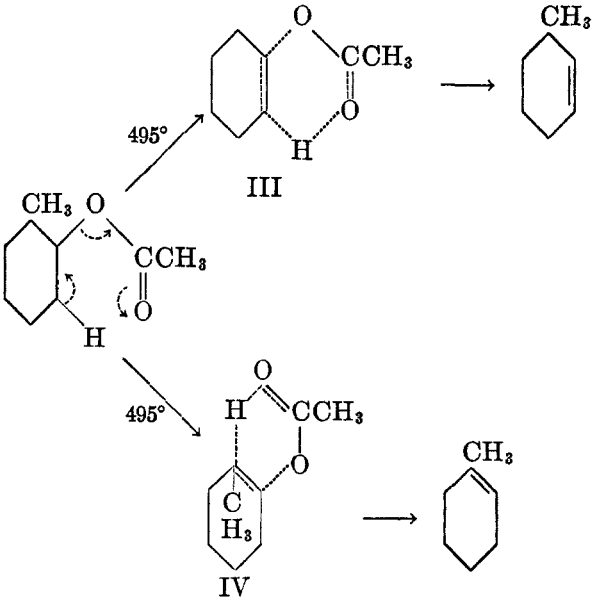


If a carbonium ion such as indicated in I were formed during the pyrolysis it is likely that rearrangement would result from pyrolysis of esters of neopentyl type alcohols. Cramer and Mulligan (4) pyrolyzed the acetate of 3,3-dimethylbutanol-2 and noted no rearrangement products, the sole olefinic product being 3,3-dimethylbutene-1. Wibaut and Smittenberg (5) have reported the lack of isomerication in the pyrolysis of the acetate of 2,2-dimethyl-3-pentanol to 2,2-dimethylpentene-3.

A third possible mechanism (C) by which these esters may thermally decompose involves a transient cyclic intermediate (III, IV) similar to the one proposed by Hurd and Blunck (3). Here a hydrogen bridge would link the β-hydrogen of the alkyl group and the oxygen of the acetyl, and of course would be of importance only in the transition state.

C.



It appears credible from the information now available that the β-hydrogen is expelled simultaneously with the acetoxy group.

From this work on the pyrolysis of acetates of the isomeric 2-methylcyclohexanols it is apparent that a *cis*-elimination of the β-hydrogen and the acetoxy group is preferred over a *trans*-elimination. *cis*-2-Methylcyclohexyl acetate gave largely 3-methylcyclohexene while *trans*-2-methylcyclohexyl acetate gave approximately equal amounts of both isomers. The slightly larger quantity of 1-methylcyclohexene obtained from the *trans*-acetate would be expected from the stabilization resulting from hyperconjugation of the methyl group in the transition state.

EXPERIMENTAL

trans-2-Methylcyclohexyl 3,5-dinitrobenzoate (6, 7) was prepared from 2-methylcyclohexanol (Eastman Kodak, containing approximately 74% *trans*) with 3,5-dinitrobenzoyl chloride and pyridine. The *trans*-3,5-dinitrobenzoate was separated from the *cis*-isomer by carefully dissolving the more soluble *cis*-ester from the less soluble *trans*-ester with methanol and crystallizing each fraction from this solvent. From 122 g. (1.06 moles) of 2-methylcyclohexanol, 131 g. (40.5%) of pure *trans*-ester, m.p. 113.5–115° was obtained. Several other fractions, m.p. 70–94°, were collected whose melting points could not be changed by repeated crystallization.

trans-2-Methylcyclohexanol (7, 8, 9). A mixture of 123.5 g. (0.4 mole) of pure *trans*-2-methylcyclohexyl 3,5-dinitrobenzoate, 127 g. (2.27 moles) of potassium hydroxide, 1400 cc. of methyl alcohol, and 750 cc. of water was heated under reflux for two hours. The reaction mixture was concentrated by distillation and the product isolated by ether extraction. Vacuum-distillation through six inches of glass helices yielded 35 g. (85%) of pure *trans*-2-methylcyclohexanol, b.p. 60.7–61° (10.5 mm.), n_D^{20} 1.4611, n_D^{25} 1.4596, η^{25} 0.335 poise, d^{25} 0.9229.

cis-2-Methylcyclohexyl 3,5-dinitrobenzoate (6, 7) was prepared from 2-methylcyclohexanol obtained by the reduction of 2-methylcyclohexanone with Adams platinum oxide catalyst in acid medium. After two crystallizations from ethyl alcohol, a 57% yield of ester, m.p. 97–98°, was obtained.

cis-2-Methylcyclohexanol (7, 9) was obtained in 77% yield by the hydrolysis of the 3,5-dinitrobenzoate; b.p. 161.4°, n_D^{20} 1.4641, n_D^{25} 1.4620, η^{25} 0.170 poise, d^{25} 0.9307. Most of the *cis*-2-methylcyclohexanol used in this study was prepared by the catalytic reduction of 2-methylcyclohexanone with brown platinum oxide and hydrogen in glacial acetic acid containing approximately 5% concentrated hydrochloric acid. Since some of the 2-methylcyclohexanol so formed was esterified under the conditions of the reduction, it was necessary to hydrolyze the organic material before isolation of the *cis*-2-methylcyclohexanol. Distillation of the hydrolysate yielded 70% of *cis*-2-methylcyclohexanol, b.p. 43–45° 1–2 mm.), n_D^{25} 1.4620, η^{25} 0.171 poise, d^{25} 0.9310. From viscosity data this material was estimated to be at least 96% *cis*.

trans-2-Methylcyclohexyl acetate (8). A solution of 18 g. (0.23 mole) of acetyl chloride in 22 cc. of anhydrous chloroform was slowly added (two hours) to a well-stirred mixture of 25 g. (0.22 mole) of pure *trans*-2-methylcyclohexanol, 18 g. (0.23 mole) of anhydrous pyridine, and 79 cc. of anhydrous chloroform. The reaction was cooled with an ice-bath during the addition, then allowed to stand at room temperature for several hours. The chloroform solution was filtered to remove pyridine hydrochloride, washed once with water, twice with 5% sodium carbonate, dried over magnesium sulfate, and distilled. Distillation of the residue yielded 29 g. (84.6%), of pure *trans*-2-methylcyclohexyl acetate, b.p. 63–64° (11.5 mm.), n_D^{25} 1.4353.

cis-2-Methylcyclohexyl acetate (8). *cis*-2-Methylcyclohexyl acetate was prepared in the

same manner as the *trans*-acetate. Distillation of the crude product produced 28.4 g. (83.3%), b.p. 68.5–69.5° (16 mm.), n_D^{25} 1.4376, of pure *cis*-2-methylcyclohexyl acetate.

Pyrolysis of trans-2-methylcyclohexyl acetate. Over a period of two hours 28.1 g. (0.18 mole) of pure *trans*-2-methylcyclohexyl acetate was dropped through a clean hot tube swept with a stream of nitrogen. The contact time in the tube was one to two minutes. The temperature of the tube was maintained between 490–500°. Any material not condensed with water condensers was caught in a Dry Ice trap. Following the addition of the ester the tube was swept with nitrogen for 10 minutes. The amber-colored olefin and acetic acid mixture, which was in two phases, was washed twice with small quantities of water, once with 5% sodium carbonate, and dried over potassium carbonate. Distillation produced 13 g. of clear liquid, b.p. 103–110°, n_D^{20} 1.4477, and 0.5 g. of high-boiling residue. The yield was 76.5% on the basis of pyrolyzed acetate. Very little carbon was found inside the tube.

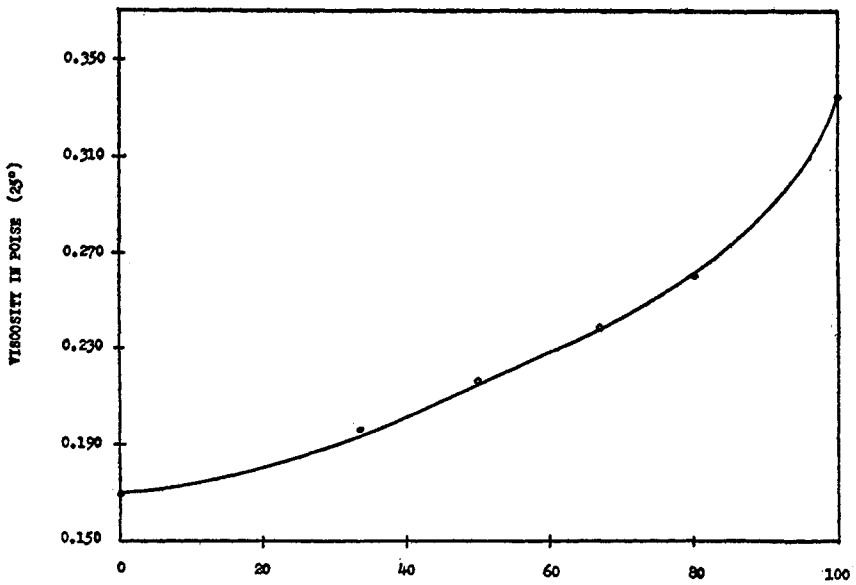


FIG. 1 *trans*-2-METHYLCYCLOHEXANOL, %

Pyrolysis of cis-2-methylcyclohexyl acetate. Pure *cis*-2-methylcyclohexyl acetate, 28 g. (0.18 mole), was pyrolyzed using the same procedure described above. Distillation of the olefinic product produced 12.2 g. of clear liquid, b.p. 100–105°, n_D^{20} 1.4458, and 1.5 g. of high-boiling residue. The yield was 75% on the basis of pyrolysed acetate.

Viscosity measurements. Viscosities were measured using 5 cc. of the sample in an Ostwald type viscosimeter Number 200. This model has a large capillary, and the time of flow for the compounds analyzed was between 167 and 330 seconds at 25°. The constant for the viscosimeter was determined using a 60% sucrose solution which has a viscosity of 0.439 poise at 25° (10). All substances were freshly distilled before measurements were taken. The viscosities agree well with those previously reported (8, 9). A plot of the per cent composition *versus* viscosity is given in Figure 1. The 2-methylcyclohexanol obtained from Eastman Kodak had a viscosity of 0.250 poise at 25°; this should contain approximately 74% *trans*-2-methylcyclohexanol.

Isomeric methylcyclohexenes. 1-Methylcyclohexene, b.p. 109–109.5°, n_D^{20} 1.4503, was prepared by distilling from iodine the tertiary alcohol, which resulted from the addition of methylmagnesium iodide to cyclohexanone (11, 12). 3-Methylcyclohexene, b.p. 100–100.8°, n_D^{20} 1.4442, was obtained through a series of reactions beginning with the bromination of

cyclohexene using N-bromosuccinimide (13) and subsequent conversion of the allyl bromide to the cyclic olefin with methylmagnesium iodide (14). The third isomer, 4-methylcyclohexene (15), b.p. 102–103°, n_D^{20} 1.4418, was prepared by pyrolysis of the acetate of 4-methylcyclohexanol.

Analysis of the olefinic mixture from pyrolysis. Infrared absorption curves were taken of pure samples of the three isomeric methylcyclohexenes[4] (1-methyl-, 3-methyl-, and 4-methyl-cyclohexene) and of six mixtures of the 1-methyl and 3-methyl isomers on a Perkin-Elmer infrared spectrophotometer, model 12C, with a rock salt prism. By plotting the optical density at several of the peaks against concentration, curves were obtained which were used for the analysis of the pyrolysis products. The average of analyses from five absorption bands gave 75 ± 5% 3-methylcyclohexene and 25 ± 5% 1-methylcyclohexene from the pyrolysis of *cis*-2-methylcyclohexyl acetate and 45 ± 5% 3-methylcyclohexene and 55 ± 5% 1-methylcyclohexene from the *trans*-isomer. No 4-methylcyclohexene was found in either pyrolysis product.

SUMMARY

The acetates of *cis*- and *trans*-2-methylcyclohexanol have been pyrolyzed at 495°. A qualitative and quantitative analysis was made of the pyrolysis products. The reaction has proved to be stereospecific. A mechanism involving a quasi six-membered ring as the transition state is proposed for the thermal decomposition of esters containing β-hydrogens in the alkyl portion of the molecule.

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[4] The infrared absorption curves for these isomeric olefins have been published as 897, 898, and 899 in the Catalog of Infrared Spectrograms of the American Petroleum Institute, Research Project 44 at the National Bureau of Standards. We are indebted to Dr. Bryce Crawford and Mr. John Lancaster for the infrared analyses.

[CONTRIBUTION FROM THE DIVISION OF BIOCHEMISTRY, SCHOOL OF MEDICINE, UNIVERSITY OF CALIFORNIA]

THE SYNTHESIS OF SARCOSINE AND BETAINE WITH C^{14} IN THE METHYL GROUP[1]

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In synthesizing C^{14}-labeled sarcosine and betaine for use in metabolic studies it was necessary to devise special methods with particular attention being paid to the problem of recovery of the radioactive by-products. The preparation of methylamine hydrochloride was based on the procedure of Naegeli, Grüntuch, and Lendorff (1). The C^{14}-labeled methylamine was reacted with bromomalonic acid as described by Knoop and Oesterlin (2). Since a great excess of methylamine had to be employed in this reaction efficient recovery of the unreacted methylamine was worked out. We have been successful in changing the above methods so that they give a more satisfactory yield of products than the other methods given in the literature.

The following scheme of synthesis was adopted:

$$C^{14}H_3C^{14}OONa \longrightarrow C^{14}H_3C^{14}OCl \xrightarrow{NaN_3} C^{14}H_3NC^{14}O \xrightarrow[-C^{14}O_2]{HCl} C^{14}H_3NH_2 \cdot HCl \quad (a)$$

$$C^{14}H_3NH_2 + BrCH(COOH)_2 \rightarrow C^{14}H_3NHCH(COOH)_2 \xrightarrow[-CO_2]{} C^{14}H_3NHCH_2COOH \quad (b)$$

Step (a) led to a 72–76% yield based on the acetyl chloride used, whereas, step (b) gave 65–68% of sarcosine as calculated from the bromomalonic acid employed. Direct methylation of sarcosine with methyl sulfate led to betaine chloride in 80% yield. This method was a change from the procedure of Novak (3) inasmuch as we used sarcosine as the starting material. On the basis of the activities found, it was safe to assume that the exchange between the labeled methyl group of the sarcosine and the methyl group of the methyl sulphate may have amounted to 18%.

EXPERIMENTAL

Preparation of $C^{14}H_3NH_2 \cdot HCl$. To 3.5 ml. (3.87 g., 49.3 mM) of acetyl chloride, prepared from doubly labeled sodium acetate,[3] kept cold in a Dry Ice ethyl-alcohol bath was added 12 ml. of anhydrous benzene. After 3.85 g. of sodium azide (59.2 mM) was added, the flask was fitted with a double reflux condenser (the lower half cooled with running water and the upper half with Dry Ice and alcohol) and allowed to come to room temperature overnight with the upper condenser in operation and the system closed. The apparatus was equipped with a carbon dioxide trap containing 400 ml. of a solution of 16 g. of barium hydroxide (octahydrate) and protected from carbon dioxide. With the reaction flask in an ice-bath, 12 ml. of concentrated hydrochloric acid was added quickly from the dropping-funnel to the benzene solution by applying a very slight vacuum to the soda-lime as the

[1] This work was supported by a grant from the National Cancer Institute, U. S. Public Health Service.

[2] U. S. Public Health Service Special Fellow.

[3] The authors are indebted to Dr. H. A. Barker, Division of Plant Nutrition, University of California, for his help in the bacteriological work in the preparation of doubly labeled acetic acid. This acid was used because it was easily prepared biologically.

stopcock was opened, and then the stopcock was immediately closed. The flask was slowly brought to 75°, kept at this temperature for 6 hours, and left to stand overnight at room temperature with the trap closed off. The recovered $C^{14}O_2$ yielded 6.63 g. (33.7mM) of barium carbonate with an activity of 450 μc/g.

The reaction products were transferred with water to a 250-ml. round-bottom flask and evaporated to dryness under a vacuum on a steam-bath. The residue was extracted three times with 25-ml. portions of ethyl alcohol and the alcohol was removed under a vacuum on a water-bath leaving the dry salt residue behind. This residue was extracted four times with 50-ml. portions of isopropyl alcohol. The extracts were pooled and concentrated to a small volume under a vacuum on a water-bath. Then 250 ml. of anhydrous ethyl ether was added and the precipitate was collected by centrifuging and placed in a desiccator. Yield of $C^{14}H_3NH_2 \cdot HCl$, 2.58 g. (76%) (38.2 mM); m.p. 226–227°.

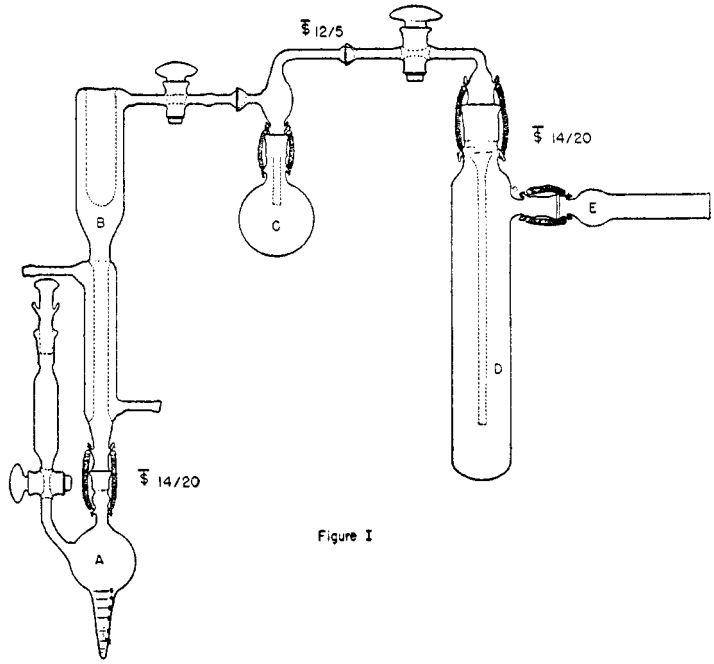

Figure I

FIGURE 1. A, 50 ml. reaction vessel; B, double cold-finger condenser; C, 100 ml. trap; D, 500 ml. carbon dioxide trap; E, absorption tube filled with Drierite.

Preparation of $C^{14}H_3NHCH_2COOH$. The methylamine hydrochloride was combined with 5.62 g. of sodium methylate ($NaOCH_3 \cdot 2CH_3OH$) (47.6mM) in a 50-ml. round-bottom flask equipped with a dropping-funnel. Meanwhile 1.3 g. of bromomalonic acid (7.1 mM) were dissolved in 5 ml. of methyl alcohol in a 60-ml. glass bomb equipped with a pressure stopcock. The flask and bomb were connected to the high vacuum isotope line and frozen with liquid nitrogen and then evacuated. Next 10 ml. of methyl alcohol was added to the flask from the dropping-funnel while the flask was cold from the liquid nitrogen. (The connection between the funnel and the flask must not be so cold as to freeze the alcohol). The C^{14}-methylamine and methyl alcohol were distilled into the bomb still immersed in liquid nitrogen. The flask was warmed to room temperature so that there was no excessive bumping and the last traces of C^{14}-methylamine and methyl alcohol were driven off by warming the flask on a water-bath to about 35°. At the conclusion of the distillation the bomb was closed off and allowed to stand in an ice-box.

After three days, crystallization of the N-methylaminomalonic acid on the walls of the bomb was complete. The excess C^{14}-methylamine and methyl alcohol was distilled on the high vacuum line into a flask containing an excess of frozen 1 *N* hydrochloric acid. Since

the methyl alcohol had a tendency to bump, a Kjeldahl trap was used to connect the bomb to the vacuum line. After thawing the distillate, it was evaporated to dryness on a steam-bath, yielding 1.10 g. of $C^{14}H_3NH_2 \cdot HCl$ with an activity of 1.0 μc./mg.

The residue in the bomb and the trap was washed twice with 5-ml. portions of methyl alcohol. The crystals in the bomb were then dissolved in water and the solution washed from the bomb and trap into a centrifuge tube, using about 20 ml. of water in all. Lead acetate (trihydrate) (2.68 g.) was dissolved in 5 ml. of water and added to the above solution and the centrifuge tube was placed in the ice-box. After two-days standing and occasional scratching the walls of the tube were coated with crystals of the lead salt of N-methylaminomalonic acid. These were centrifuged down and the supernatant liquid was returned to the ice-box to allow further crystallization. The crystals were suspended in 20 ml. of water, saturated with hydrogen sulfide to remove lead, and the residue was centrifuged and washed; the supernatant liquid and wash waters were pooled and removed under a vacuum at 35–40°. The white solid remaining, which was N-methylaminomalonic acid, was slowly heated in an oil-bath to 160° in order to complete the decarboxylation. The flask was then protected from moisture and was left to cool. The resultant white powder was pure sarcosine. The yield was 350.6 mg. (3.93 mM) with an activity of 0.78 μc/mg. (69.4 μc/mM). A second crop was recovered from the mother liquor increasing the total yield to 430.6 mg. (76%).

Preparation of $[(C^{14}H_3)_3N^+CH_2COOH] \cdot Cl^-$. Methyl-labeled sarcosine (270 mg.) prepared by the method described above was dissolved in a minimum of water and neutralized with potassium hydroxide solution. Then 560 mg. of potassium hydroxide in 5 ml. of water and 1.0 ml. of methyl sulfate were added alternately in small portions (with due caution to keep the solution alkaline throughout the methylation). The solution was boiled 15 minutes, cooled, carefully neutralized with about 2.2 ml. of 5% sulfuric acid, concentrated to a syrup under a vacuum at 60°, and extracted three times with 15-ml. portions of 95% ethyl alcohol. At this point 45 ml. of water was added and the mixture, as above, was again concentrated under a vacuum to a light-yellow colored syrup which was then dissolved in a minimum of hot water. A small portion of 1 *N* hydrochloric acid was added and the solution was boiled for half an hour. A 20% solution of barium chloride was then added until no more precipitate formed. The mixture was centrifuged and, after the supernatant clear solution was filtered off, the sediment was washed with distilled water and centrifuged again. The supernatant solutions were pooled and concentrated by heating on a steam-bath for three hours with the addition of water from time to time to keep the solution from going to dryness. The concentrate was tested for sulfate with a drop of barium chloride solution. It was evaporated to dryness under a vacuum and extracted twice with 95% ethyl alcohol. The alcohol was removed under a vacuum and the residue recrystallized from hot absolute alcohol. On cooling, white crystals of betaine hydrochloride separated. A second crop was obtained by precipitating betaine hydrochloride with absolute ethyl ether from its alcoholic mother liquor. Total yield, 375 mg. (80% based on the sarcosine used). Activity, 0.37 μc/mg. (56.8 μc/mM).

Anal. Calc'd for $C_5H_{12}ClNO_2$: N, 9.12; Cl, 23.13.
Found: N, 9.03; Cl, 22.92.

SUMMARY

The synthesis of C^{14}-methyl-labeled sarcosine and betaine hydrochloride is described. The methods employed, adapted to radioactive work, led to more satisfactory yields than other methods given in the literature.

BERKELEY, CALIFORNIA

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY

THE ALKALINE OXIDATION OF CELLULOSE. I. MECHANISM OF THE DEGRADATIVE OXIDATION OF CELLULOSE BY HYDROGEN PEROXIDE IN PRESENCE OF ALKALI

J. F. HASKINS AND M. J. HOGSED[1]

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The alkaline oxidation of cellulose is a process of considerable economic importance. Most of the literature of oxidized cellulose, loosely termed oxycellulose, is of an empirical nature not subject to accurate chemical interpretation. The purpose of this investigation was to throw some light on the mechanism of the oxidation by an examination of the fragments obtained by hydrolysis of a partially oxidized cellulose. The oxidizing agent used was hydrogen peroxide. The oxidation was carried out at room temperature and in the presence of 3.4 *N* sodium hydroxide, thus approximating the conditions of the process of "aging" of alkali cellulose as in the manufacture of viscose.

INTRODUCTION

The action of oxidizing agents on cellulose results in products whose physical and chemical nature depend on the oxidizing agent used and, especially, on the acidity or alkalinity of the medium in which the oxidation is carried out. In particular it may be pointed out that in the presence of sodium hydroxide of 12% or higher concentration, cellulose undergoes a change recognized by an alteration of the x-ray diagram and by a pronounced change in physical properties (mercerization). It would not be unexpected, then, to find a difference in the mechanism of oxidation under these conditions.

Acidic oxidizing agents produce oxycelluloses which generally have marked reducing power. These oxycelluloses may have a degree of polymerization, when measured by viscosity of nitrated oxycellulose, not greatly different from that of the starting material. Most of them, however, are very sensitive to the action of alkalies, and are extensively degraded as the result of such action. Oxycelluloses prepared under alkaline conditions are usually nonreducing, and are resistant to the further action of alkali. Their degree of polymerization is generally considerably less than that of the starting material.

Davidson (1) has suggested that the oxidation of cellulose does not in general lead directly to rupture of the chain molecules but renders the linkages near the points of attack very susceptible to alkaline cleavage. This is the basic concept in later work on oxycellulose.

INFLUENCE OF THE NATURE OF THE OXIDIZING AGENT

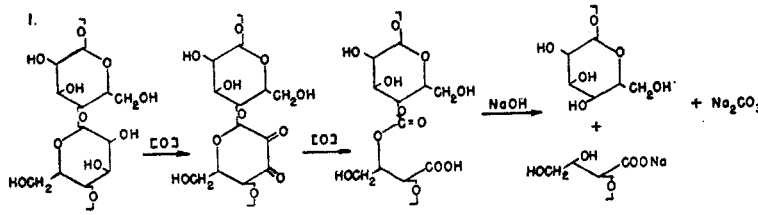
There is considerable evidence that different oxidizing agents act in different ways on the cellulose. Thus, the action of potassium permanganate on a solution of cellulose in cuprammonium hydroxide leads to the formation of glucuronic

[1] Allied Chemical and Dye Corp. Fellow 1947–1948.

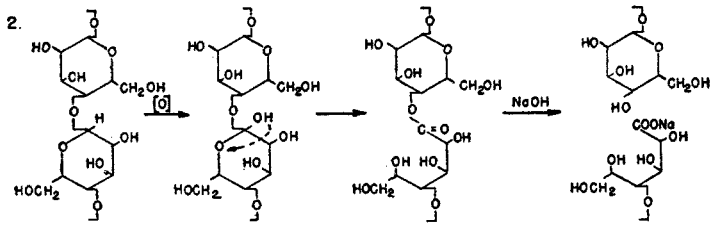
acid units, which appear to remain linked together (2). Glucuronic acid was obtained from the hydrolysate of cellulose so oxidized. The action of nitrogen dioxide on dry cellulose converts the primary alcohol groups to carboxyl groups without degradation (3), while periodic acid is said to oxidize only the secondary alcohol groups of carbon atoms 2 and 3 (4). Complete hydrolysis of the cellulose so oxidized yielded glyoxal and D-erythrose in about 20% of the theoretical yield.

With the exception of the cuprammonium hydroxide solution, the above oxidations were carried out in neutral or acid media and there is little or no direct evidence as to the course of oxidation in strongly alkaline solutions. It may be assumed either that a preliminary oxidation takes place, much as it does in acid media, this being followed by the action of alkali on the weak spot so formed, or that the alkali alters the structure of the cellulose in such a way as to create positions in the chain which are particularly sensitive to oxidation.

Several mechanisms have been proposed, but with little experimental evidence. Thus, Staudinger and Sohn (5) suggest that the two secondary alcohol groups are oxidized. The resulting carbonic ester linkage would be easily saponified by alkali, thus accounting for the rupture of the chain. If this is the mechanism, the hydrolytic products should contain erythronic or tartaric acid (see scheme 1).



Heuser and Haskins (6) postulate a primary oxidation on the number 1 carbon atom with direct formation of a saponifiable ester linkage (scheme 2).

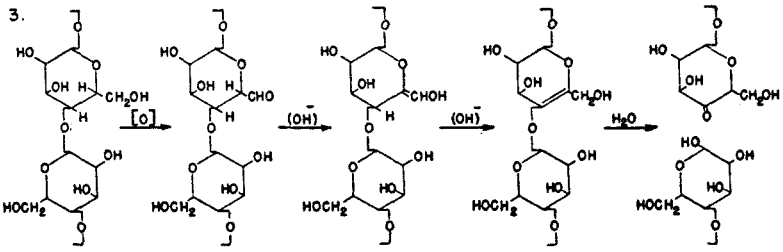


If this were the mechanism it should be possible to isolate gluconic acid or a compound derived from it from the products of hydrolysis of the oxycellulose.

Ivanov and Kaversneva (7) explain the sensitivity of reducing oxycelluloses, in terms of the work of Gehrman, Kreider, and Evans (8), as resulting from an original oxidation of the primary hydroxyl group to an aldehyde group, followed by enolization and migration of the double bond in the presence of an alkali (8). The result would be a double bond between the 4 and 5 carbon atoms. This

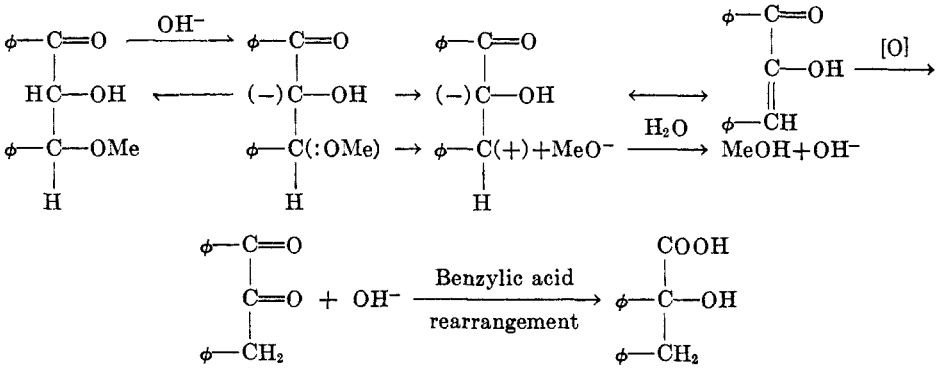
according to Gehrman, Kreider, and Evans causes the glycosidic linkage to be easily saponified (scheme 3).

3.



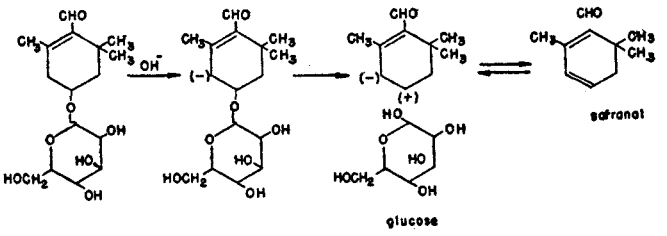
Another alternative explanation of the alkali sensitivity of reducing oxycellulose is that of an aldol dehydration.

Nicolet (9) found that α-hydroxy-β-methoxy-β-phenyl propiophenone rearranged in the presence of alkali to yield α,β-diphenyl lactic acid and proposed an aldol dehydration mechanism for this transformation. In terms of the mechanism proposed by Hauser and Breslow (10) for aldol dehydration, this rearrangment may be formulated as in 3a.



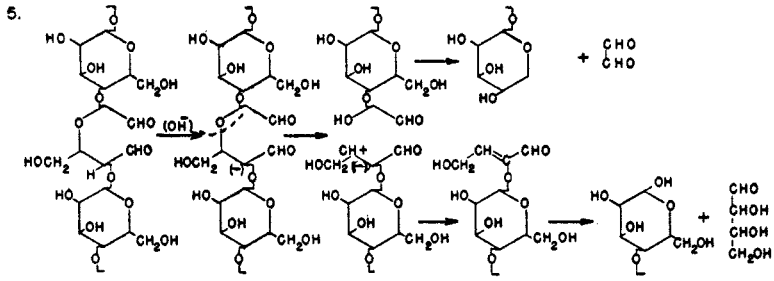
Helferich (11) has studied the behavior of various glycosides in alkali and found that, when the glycosidic group is on a carbon atom *beta* to a strong electron attracting group, the glycosidic linkage is cleaved by alkali. Thus glycosides of the type Gl-O-$CH_2(CH_2)_n$-CH_2NO_2 will reduce Fehling's solution only when n = 0. Similarly, picrocrocin yields safranal (12) on treatment with alkali, the *alpha,beta*-double bond making the *gamma* hydrogen atoms acidic Isbell (13) has interpreted the cleavage in the manner of scheme 4.

4.



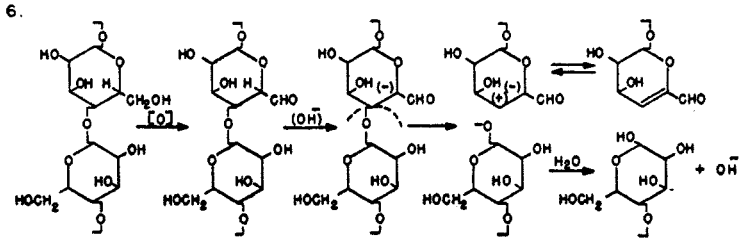
In a similar way the alkali sensitivity of periodate oxycellulose may be rather simply interpreted in terms of aldol dehydration.[2]

5.



The formation of glucuronic acid (2, 14) by air oxidation of cellulose in cuprammonium solution is indicative of the existence, at some time, of the uronaldehyde, and the degradation may be interpreted as in 6.

6.



In support of this mechanism Ivanov (15) has reported monotrityl cellulose to be stable towards atmospheric oxygen when air is passed through a suspension of monotrityl cellulose in cuprammonium hydroxide. On the basis of this evidence he concludes that oxidation of cellulose, at least by oxygen, must proceed by reaction with the primary hydroxyl. This is, however, a questionable conclusion since trityl cellulose is insoluble in cuprammonium hydroxide, is very difficult to wet, and is not, therefore, likely to react. Moreover, the assumption that the trityl group is always on the primary hydroxyl might be disputed.

DISCUSSION OF THE PROBLEM

The oxidation of cellulose in the presence of alkali is the process used industrially to lower the viscosity of solutions of cellulose derivatives. The primary interest in this study is, therefore, in the mechanism by which the cellulose chain is broken during such oxidation, rather than in the products formed by more extensive oxidation of the fragments. The plan, then, was to carry out a partial oxidation such, for example, as might be expected to lower the average degree of polymerization from 750 to about 50. It was planned to follow this oxidative degradation by hydrolysis of the oxidized cellulose, and to attempt to

[2] The writers are indebted to Professors M. S. Newman and M. L. Wolfrom for suggesting the applicability of the aldol dehydration mechanism to the case of periodate oxycellulose.

find the fragments which represent the end groups. It should be clear that the amount of such end groups would not be very large as compared to the size of the original sample.

The cellulose used in this work was a bleached cotton linters whose intrinsic viscosity is 3.06, corresponding to a degree of polymerization of about 750. The oxidation was carried out by the action of hydrogen peroxide on cellulose steeped in 3.4 *N* sodium hydroxide solution. The insoluble portion of the oxycellulose so obtained was acetolyzed with acetic anhydride and sulfuric acid. The acetolysis product was then further degraded using hydrogen chloride in methanol. The hydrolysis was completed by the action of dilute hydrochloric acid. After removal of the hydrochloric acid, the acidic fraction was isolated using Amberlite ion exchange resins, since it was not generally possible to isolate so small a quantity as the barium salt by precipitation with alcohol. The acids so obtained were converted into the cadmium salts, and the latter were acetylated by the action of acetic acid saturated with hydrogen chloride (16). The acetylated acids were then chromatographed on silicic acid using a 5% solution of acetic acid in benzene as the developer. Crystalline D-arabonic acid tetraacetate was obtained. The water-soluble oxycellulose was hydrolyzed separately and D-arabonic acid was isolated as the acetate. The total quantity of D-arabonic acid obtained was equivalent to 172.5 mg. per hundred grams of cellulose oxidized.

Large amounts of carbon dioxide and formic acid, some oxalic acid and a small amount of lactic acid were found among the water-soluble oxidation products. These, however, are of no help in the understanding of the course of the reaction since they could be formed from highly degraded products.

In order to check the efficiency of the isolation procedure which was used, a recovery check was run on a solution containing 200 mg. of potassium D-arabonate and 10 g. of dextrose. Only 24% of the arabonic acid was isolated by use of the ion exchange resins. It is obvious, therefore, that the 172.5 mg. of arabonic acid actually isolated per 100 g. of cellulose oxidized was only a small fraction of the total arabonic acid produced by the oxidation.

Since glycosido-glucoses are known to be oxidized by alkaline hydrogen peroxide to give moderate yields of glycosido-arabonic acids, the quantity of D-arabonic acid obtained may be assumed to be an indication of the amount of reducing end groups in cellulosic material, though it is in no sense even an approximately quantitative relationship.

DISCUSSION OF THE RESULTS

It is known from the work of Spoehr (17), Glattfeld (18), Glattfeld and Hanke (19), and Isbell (20), that moderate yields of glycosido-arabonic acids are obtained by oxidation of glycosido-glucoses with hydrogen peroxide in presence of alkali. It may then be assumed that the arabonic acid found among the products of hydrolysis of oxycellulose formed by the action of hydrogen peroxide in presence of alkali is a measure of the number of reducing end groups formed by the oxidative splitting of the cellulose chains, although it is in no sense a quantitative measure. From the intrinsic viscosity of cellulose in cuprammonium

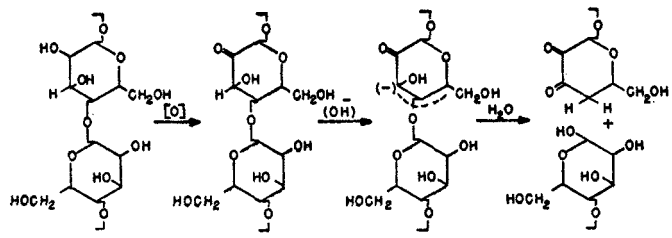
hydroxide, the degree of polymerization may be calculated. If the cellulose sample is fairly homogenous as to molecular weight distribution, the degree of polymerization represents, for our purposes, an acceptable estimate of the number of reducing end groups. Chemical cotton linters having a degree of polymerization of 750 would produce a theoretical yield of 135 mg. of arabonic acid per 100 g. of cellulose oxidized by alkaline hydrogen peroxide, if no splitting occurred. Since the method actually used in this investigation is capable of isolating at most a fourth of the arabonic acid produced by oxidation, and since the yield of glycosido-arabonic acids by oxidation of glycosido-glucoses is only moderate, the 174 mg. of arabonic acid isolated per 100 g. cellulose oxidized, is very suggestive of a mode of alkaline cleavage of the initial oxidation product such as to increase the number of free reducing glucose end groups. Thus mechanisms of alkaline oxidative degradation which require an increase in the number of reducing end groups are to be preferred to those which could not explain an increase.

The mechanism offered by Ivanov and the aldol dehydration scheme derived from the work of Helferich, Isbell and others both require an increase in the number of reducing end groups.

The alternative interpretations given below to explain the formation of new reducing end groups are consistent with the experimental results of this investigation.

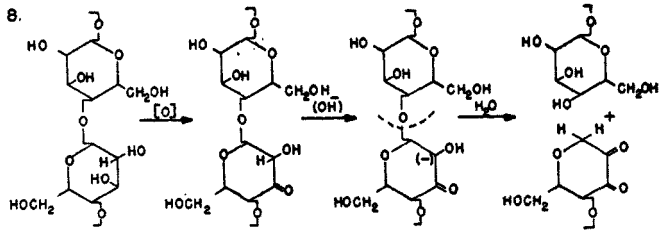
(a) Oxidation of the 2-secondary alcohol group (scheme 7).

7.



(b) Oxidation of the 3-secondary alcohol group (scheme 8).

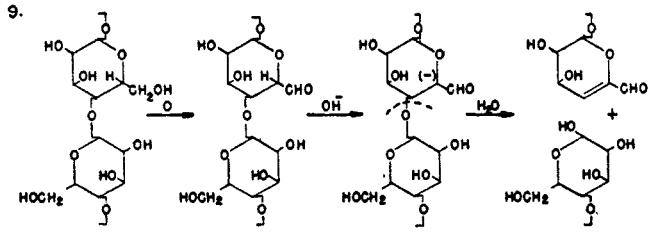
8.



The 3-keto derivative might also undergo rearrangement to the 2-keto form which may be cleaved as shown above.

(c) Oxidation of the primary alcohol group (scheme 9).

9.



In short, oxidation of any of the hydroxyl groups will produce a product which can readily undergo aldol dehydration.

EFFECT OF HYDROLYTIC AGENTS

In the course of this work several methods of hydrolysis of the oxycellulose were tried. The usual method, in which cellulose is treated with 72% sulfuric acid and the hydrolysis completed, after dilution, by warming, proved to be unsatisfactory because the sulfuric acid itself acts as an oxidizing agent.

EXPERIMENTAL

1. *Oxidation of cellulose with alkaline hydrogen peroxide.* Chemical grade cotton linter[8] (150 g., 5.8% moisture, intrinsic viscosity 3.06) was added to an oxidation mixture of 1500 ml. of carbonate-free 3.4 *N* sodium hydroxide and 150 ml. of 29.2% hydrogen peroxide, with protection from carbon dioxide. The flask was placed in a 20° constant temperature room. After eight days an additional 150 ml.-portion of 29.2% hydrogen peroxide was added. After a total time of oxidation of 31 days the reaction mixture was made slightly acidic with dilute sulfuric acid, and the oxycellulose was filtered and washed with distilled water until the filtrate was free of sulfate ions. After extracting most of the water with acetone there was obtained upon drying 119 g. of oxycellulose. Ash content was 0.13%.

2. *Examination of the water-soluble oxidation products.* Prior to acidification of the reaction mixture from the oxidation, the carbonate content was determined by acidifying a measured quantity of the solution and absorbing the carbon dioxide evolved in a standard Ascarite bulb absorption train. Based on the dry weight of the cellulose the carbon dioxide formed amounted to 0.0294 g. per gram of cellulose oxidized.

The filtrate and wash water fron the filtration of the oxycellulose, following acidification were concentrated under a vacuum to remove volatile acids. Distilled water was added to the residue and the vacuum distillation was repeated until the distillate was no longer acidic. After neutralization of the distillate with barium hydroxide, filtration, concentration, acidification, and redistillation, the formic acid content was determined, separately, by alkaline permanganate and by reduction of mercuric chloride (21). The two methods checked within less than one per cent. The amount of formic acid found was 7.6 g., or 0.054 g. per gram of cellulose oxidized.

The residue from the distillation of the volatile acids was freed of most of the sodium sulfate by addition of ethanol. Following removal of the ethanol, the nonvolatile, water-soluble products were extracted with ether in a continuous extractor. The ether-extractible acids were converted into zinc salts, and after much difficulty, 0.115 g. of a crystalline zinc salt was obtained which had approximately the composition of zinc lactate trihydrate:

Loss in weight on drying	19.3%
Calculated for zinc lactate trihydrate	18.4%
Zinc oxide, found	26.11%
Zinc oxide, calculated	27.35%

The material remaining after the ether extraction was treated with an excess of barium hydroxide and filtered. The precipitate so obtained was acidified with excess hydrochloric acid and filtered to separate the acids soluble in hydrochloric acid. This filtrate was again neutralized with barium hydroxide. The salt so obtained had a reducing value 96% of that calculated for barium oxalate. The acid regenerated from the barium salt gave a phenylhydrazine salt characteristic of oxalic acid.

The ether-insoluble, barium hydroxide-soluble material was acidified with dilute sulfuric acid and hydrolyzed at 80° for two days. After treatment with excess barium carbonate, filtration and concentration, the barium salts (2 g.) were precipitated by ethanol. One-fourth of these salts (0.50 g.) was converted to the free acids. The solution was passed through a 2.5 x 50 cm. column of analytical grade Amberlite IR-100 cation-exchanger to remove the barium, and the resin column was washed with distilled water until the filtrate was neutral. The barium-free solution was then passed slowly through the 2.5 x 50 cm. anion-exchanger of analytical grade Amberlite IR-4 to remove the acidic material from the neutral fraction. After washing the anion-exchanger with about 500 ml. of water, the acidic material was flushed from the column with 80 ml. of 5% ammonium hydroxide. The exchanger was then washed with distilled water, 500 ml., until the filtrate was no longer basic. The ammoniacal filtrate was then put through the regenerated cation-exchanger to remove the ammonia. Distilled water was run through the anion-exchanger until the filtrate was neutral. The glucose-free solution containing the acidic material was concentrated under vacuum to about 100 ml. and heated with excess cadmium carbonate at 50° for one day. After filtering and concentrating the solution, the cadmium salts were precipitated with ethanol and ether. The salts were then dried and acetylated with 5 ml. of acetic anhydride saturated with hydrogen chloride (21). After stirring the mixture for one hour at 0°, the acetylation was completed by heating at 50° for one hour. Excess acetic anhydride was removed under a vacuum and a few grams of ice was added. The acetylated products were isolated by extraction with chloroform, and dried with sodium sulfate. Chromatography of the acetylated material on a 70-cm. column of 3 silicic acid/1 Celite, using 250 ml. of 20 benzene/1 acetic acid developer, gave a column which was quite complex. Upon streaking with alkaline permanganate, there were three zones in the middle of the column, two faint and one sharp. There was, in addition, a zone at the very top and one near the bottom of the column. From the sharp middle zone there was obtained 66 mg. of crystalline material having the melting point 132–135°, and giving an undepressed melting point when mixed with a known sample of D-arabonic acid tetraacetate; literature (22) melting point, 135–136°. The rotation, $[\alpha]_D^{26}$ +31.1° (2.1% in chloroform), is in agreement with the literature value (21), $[\alpha]_D$ +32.5°, for D-arabonic acid tetraacetate. From the water-soluble fraction the amount of arabonic acid tetraacetate isolated amounts to 264 mg./141.3 g. cellulose oxidized or 93 mg. of arabonic acid/100 g. cellulose oxidized.

As will be shown later, sulfuric acid is capable of oxidizing as well as hydrolyzing cellulose. To show that the dilute sulfuric acid used in the hydrolysis did not produce the arabonic acid isolated, twenty grams of C.P. dextrose was dissolved in two liters of 1.5 *N* sulfuric acid and the solution was heated in an 80° oven for two days. After neutralizing with barium carbonate, the acidic material was isolated as described above. The amorphous cadmium salts were acetylated with acetic anhydride and hydrogen chloride (16). Chromatography of small quantity (108 mg.) of acetylated products so obtained on 3 silica/1 Celite, using 5% acetic acid in benzene as the developer, gave several zones. That no arabonic acid pentaacetate was present, was shown by running a comparative chromatogram of the same solution to which a small quantity of D-arabonic acid pentaacetate had been added. This gave rise to a new, well-defined zone in a predictable region of the chromatogram.

3. *Examination of the water-insoluble oxidation products. Isolation of* D-*arabonic acid following hydrolysis.* (a) *Hydrolysis by sulfuric acid.* On the basis of the work of Godman, Haworth, and Peat (23) it was thought that hydrolysis of the oxycellulose could be most conveniently effected by use of 72% sulfuric acid. With this method, however, the quantity

of barium salts obtained was much greater than seemed probable. In order to check the effect of 72% sulfuric acid on cellulose, the hydrolysis and isolation of the acids was repeated using chemical cotton linters. Eighteen grams of cotton linters was dissolved in 90 ml. of 72% sulfuric acid and allowed to stand at room temperature for six days. After dilution to two liters, the solution was placed in an oven at 80° for 36 hours. The resulting solution was stirred vigorously and carefully neutralized with two-thirds of the calculated quantity of barium hydroxide solution in such a manner as to avoid any local alkalinity. The remainder of the acid was neutralized with excess barium carbonate. After filtration, concentrating to 100 ml. and decolorizing, the barium salts were precipitated by pouring the solution into 500 ml. of boiling ethanol. After standing overnight in an ice-box the solution was decanted from the amorphous precipitate, which weighed 2.36 g., $[\alpha]_D^{26}$ +42.3° (H_2O, *c*, 5.6%). The salts were dissolved in a minimum quantity of water and reprecipitated with boiling methanol. After two additional reprecipitations to assure complete removal of glucose, the barium salts were dried. The rotation, $[\alpha]_D^{26}$ +45° (*c*, 4.6%), was measured in water. This material gave a slight test with Fehling's solution and a positive uronic acid test with naphthoresorcinol. A test for sulfur was negative. Analytical results indicate nothing more than that the material is probably a mixture of barium salts of aldonic and aldobionic acids.

Anal. Found: C, 30.1, 29.84; H, 4.76, 4.95; Ba, 21.95, 21.71.

No further attempt to identify these acids was made. The amount formed is surprising, and such as to show that 72% sulfuric acid oxidizes the cellulose. This fact throws strong doubt on the validity of any conclusions which might be made as a result of hydrolyzing oxycelluloses with 72% sulfuric acid. This method of hydrolysis was, therefore, abandoned.

(b) *Acetolysis as a means of degradation.* It is well known that cellulose can be degraded to cellobiose octaacetate by the combined action of acetic anhydride and sulfuric acid. It was thought that this method would be suitable for the preliminary degradation of oxycellulose.

An acetolysis mixture commonly used for the preparation of cellobiose octaacetate was used for the acetolysis of oxycellulose. Acetic anhydride, 100 ml., was cooled to 0° and 14 ml. of concentrated sulfuric acid was added slowly with stirring. Twenty grams of oxycellulose was broken into a coarse powder, and 92 ml. of the acetolysis mixture, cooled to 0° was added slowly. The cooled mixture was well mixed with a glass rod to prevent the formation of local warm spots, which cause extensive degradation, as shown by the development of a very dark brown color. After the oxycellulose was acetylated and a doughy mass formed, it was removed from the ice-bath and the reaction allowed to proceed with frequent stirring. The reaction was forced by placing the flask in a water-bath at 85° for half an hour. The thin, light brown solution resulting was poured on cracked ice. After an hour the water was saturated with salt to prevent emulsion formation and extracted four times with chloroform. After removal of the chloroform by evaporation the solids were dried in a vacuum desiccator.

The dried acetolysis product was dissolved in 500 ml. of 6% hydrogen chloride in absolute methanol. The methanolysis was carried out by refluxing the solution for one day. Concentration of the solution under a vacuum gave a sludge which was dissolved in sufficient water to give 500 ml. of a solution still containing considerable hydrochloric acid. After hydrolysis at 80° for two days, 30 g. of basic lead carbonate was added. The following day the lead chloride was removed and the solution saturated with hydrogen sulfide to remove the lead. After filtering, 20 g. of freshly precipitated silver carbonate was added and the chloride-free solution was filtered and saturated with hydrogen sulfide. After filtration, decolorization and aeration, the solution was treated with excess barium carbonate for one day at 50°, and filtered. Vacuum concentration of the filtrate gave a syrup, to which was added five volumes of absolute ethanol. So small an amount of insoluble material was deposited that this method of isolating the acidic fraction did not appear promising. The alcohol was removed under a vacuum and the syrup was diluted with distilled water. The acidic material was isolated by use of ion-exchange columns in a manner

similar to that described above. The glucose-free solution of the acidic material was converted to the cadmium salts (0.146 g.). A 92% yield of crystalline glucose isolated from the neutral fraction indicates the completeness of the hydrolysis.

The cadmium salts of the acidic fraction of the oxycellulose hydrolysis were acetylated with 5 ml. of acetic anhydride saturated with hydrogen chloride as previously described. The acetylated acids (110 mg.) were separated by chromatography. The entire sample dissolved in chloroform was put on a 70-g. column of 3 silicic acid/1 Celite, using 400 ml. of 20 benzene/1 acetic acid as the developer. Three zones were found on streaking the column with alkaline permanganate. After removal of the stripe, the column was sectioned and the sections eluted with acetone and the material isolated by evaporation. The acetylated substances which had become fixed at the top of the column weighed 20 mg. and gave a positive uronic acid test with naphthoresorcinol. No crystalline products were isolated from this zone. This material could have been an aldobiuronic acid, since these acids are difficult to hydrolyze. The zone near the bottom of the column yielded 36 mg. of material which was not crystallized. This fraction gave a faint uronic acid test and is believed to be acetylated lactones.

The middle zone gave 52 mg. of amorphous material which was crystallized from hot toluene and petroleum ether solution to yield 38 mg. of crystalline material. The rotation of this material was measured in chloroform. $[\alpha]_D^{27}$ +33.4°, (*c*, 1.49%). On recovery of the material and recrystallization, a product was obtained which had m.p. 134–135°, mixed m.p., with an authentic sample of D-arabonic acid tetraacetate, 134–135°. Analysis gave C, 46.73; H, 5.68. Calc'd: C, 46.71; H, 5.43. Literature constants for D-arabonic tetraacetate, m.p. 135–136°, $[\alpha]_D$ +32.5°, $CHCl_3$. This amounts to 81 mg. arabonic acid/100 g. cellulose oxidized.

(c) *Check on oxidizing power of sulfuric acid in acetolysis.* Since it had been shown that sulfuric acid has an oxidizing effect on cellulose, the possible oxidizing action of the sulfuric acid in acetolysis was investigated by carrying out an acetolysis of cotton linters by the process described above.

Chromatography of the acetylated acidic material gave three zones. The very weak middle zone, however, was closer to the top than would be expected for D-arabonic acid tetraacetate. A portion of the acetylated products was mixed with a small amount of D-arabonic acid tetraacetate and the mixture chromatographed on a small silicic acid column, using 5% acetic acid in benzene as the developer. In addition to the three zones mentioned there was an additional strong zone in the position expected for the arabonic acid tetraacetate as determined by a blank run with arabonic acid tetraacetate only. This indicates the absence of D-arabonic acid tetraacetate in the acetylated acidic products from the cotton linter.

SUMMARY

1. D-Arabonic acid has been identified, in the form of the tetraacetate, as one of the products of the oxidation of cellulose by hydrogen peroxide in presence of strong alkali.

2. Several proposed mechanisms for the oxidation of cellulose have been discussed.

3. A mechanism has been proposed which is consistent with the behavior of β-alkoxycarbonyl compounds in alkali.

COLUMBUS 10, OHIO

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE OHIO STATE UNIVERSITY]

THE ALKALINE OXIDATION OF CELLULOSE. II CHROMATOGRAPHY OF ACETYLATED CARBOHYDRATE ACIDS

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In the course of an investigation of the composition of oxycellulose prepared by peroxide in presence of alkali (1) it was necessary to develop a chromatographic method for separating acetylated carbohydrate acids. The method developed is described in this paper.

The experimental technique commonly referred to as chromatographic analysis has been extensively investigated as to its applications to carbohydrates, by Wolfrom and his coworkers. McNeeley, Binckley, and Wolfrom (2) were able to achieve separation of sugar acetates on Magnesol using aqueous alkaline permanganate as the brush reagent. Georges, Bower, and Wolfrom (3) applied the brush technique to the chromatography of sugars on Silene as the adsorbent. Bower and Wolfrom (4) have separated sugar acids, as the acetylated amides, on Silene EF, a hydrated sodium aluminum silicate. Hoffman and Wolfrom (5) used acid washed Silene EF for chromatography of the unacetylated sugar acids. An excellent review of the literature and of practical laboratory procedures has been written by Binckley and Wolfrom (6).

After investigating several adsorbents it was found that Mallinckrodt silicic acid, Analytical Reagent Grade, effected separation of several different types of acetylated carbohydrate derivatives when benzene solutions of either acetic acid or acetone were used as developers. An undesirable feature of silicic acid noted is that the adsorbent has poor filtration properties, but this may be corrected by mixing in Celite, an inactive diatomaceous earth.

The quantitative work on chromatographic analysis carried out in this investigation is summarized in table I. All runs were made on 70 g. columns of 3 silicic acid/1 Celite. The loading ordinarily used was much below capacity. Based on run E, 10 mg. of material per gram of adsorbent is quite practical even for two compounds which are relatively difficult to separate. The strength and amount of developer used depends not only on the nature of the compounds being chromatographed, but also on the amount of moisture in the silicic acid. The silicic acid-Celite adsorbent was made up by mixing the undried silicic acid with the Celite.

EXPERIMENTAL

Standard chromatographic procedure. A fairly typical separation is described below.

A typical chromatographic tube, 35 mm. diameter, was fitted to a one-liter suction flask, connected to a water aspirator pump. Seventy grams of a mixture of three parts Mallinckrodt A.R. silicic acid to one part Celite was poured into the tube with the ap-

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paratus under a slight vacuum. Under full vacuum the sides of the tube were tapped with a cork ring until all of the adsorbent was settled. After breaking the vacuum slowly, a wad of cotton was placed on the top of the column to prevent turbulence from disturbing

TABLE I

CHROMATOGRAPHIC SEPARATIONS

COMPOUND	WEIGHT IN MG.	DEVELOPER	POSITION	% RECOVERY	M. P., °C	
					Found	Lit.
A. Gluconic acid pentaacetate	127	500 ml. 15/1 benzene-acetic acid	Upper	87	110–111.5	110–111 (7)
and						
Arabonic acid tetraacetate	120		Lower	91	135–135.5	135–136 (8)
B. Gluconic acid pentaacetate	127	300 ml. 30/1 benzene-acetic acid	Upper	81	111–111.5	110–111 (9)
and						
D-α-Glucoheptonolactone pentaacetate	163		Lower	83	130–131	128 (9)
C. Galactonamide pentaacetate	135	600 ml. 20/1 benzene-acetic acid	Upper	82	164–164.5	165–166 (10)
and						
Galactonic acid pentaacetate	142		Lower	83	131–131.5	131–132 (7)
D. Pentaacetylgluconic phenylhydrazide	129	600 ml. 20/1 benzene-acetic acid	Upper	81	153–153.5	152–154 (11)
and						
Gluconic acid pentaacetate	134		Lower	84	111–111.5	110–111 (7)
E. Gluconamide pentaacetate	388	700 ml. 20/1 benzene-acetic acid	Upper	87	183–184	184–185 (10)
and						
Pentaacetylgluconic phenylhydrazide	402		Lower	82	152–153	152–154 (11)
F. D-α-Glucoheptonolactone pentaacetate	123	300 ml. 50/1 benzene-acetic acid	Upper	88	130–131	128 (9)
and						
Glucononitrile pentaacetate	134		Lower	82	82- 83	84 (12)

the adsorbent. Gluconic acid pentaacetate, 127 mg., and D-α-glucoheptonolactone tetraacetate, 163 mg., were dissolved in 20 ml. of U.S.P. chloroform. After pre-wetting the adsorbent column with 50 ml. of benzene, the chloroform solution was added, and the column was developed with 300 ml. of a developer made up of thirty parts of benzene to one part acetic acid. Following the development of the column, full vacuum was applied,

and the chromatogram was dried for a few minutes and extruded with the aid of a wooden dowel.

A stripe of alkaline permanganate (1% potassium permanganate, 20% sodium hydroxide) was painted the length of the column using a glass wool brush. As soon as the two well-defined zones were located, the column was sectioned with a spatula, discarding the non-reducing zones. After removal of the indicator stripe, the two reducing zones were eluted with 200 ml. of acetone each, allowed to stand for about an hour, filtered on a sintered glass funnel, and the adsorbent was washed with two 500-ml. portions of acetone.

The acetone was removed from each eluate by evaporation in stream of air. After drying completely, each flask was washed with chloroform. The chloroform was filtered to remove silica, which is difficult to remove entirely from the acetone solution. After evaporation of the chloroform and drying the residues in a vacuum desiccator, the solid material in each flask was recrystallized from a hot mixture of toluene and petroleum ether.

The material isolated from the top zone of the column melted at 111–111.5°, and therefore was gluconic acid pentaacetate; recovery: 81%, literature m.p. (8) 110–111°.

The crystalline material from the lower zone melted at 130–131°. Upson and Bartz (10) have reported the melting point of D-α-glucoheptonolacton tetraacetate as 128°; recovery: 83%.

Experience with tetraacetyl gluconic acid indicated that if there were a free hydroxyl in the acetylated lactone as reported (10), the hydroxylactone acetate would have been much more strongly adsorbed, and therefore, more slowly developed than was observed. Analytical data indicate that the lactone is the pentaacetate. Found, C: 49.15, 48.80; H: 5.17, 5.23; mol. wt. 422, 398. Theory for D-α-glucoheptonolactone pentaacetate requires C: 48.80, H: 5.30, and mol. wt. 418. Theory for the tetraacetate requires C: 47.87, H: 5.36, and mol. wt. 376.

Results obtained in separating several mixtures of several derivatives of sugar acids are shown in table I.

SUMMARY

1. A chromatographic method for the separation of acetylated carbohydrate acids and derivatives has been developed.

2. The order of adsorption, on silicic acid, of various acetylated carbohydrate derivatives has been determined to be amides > phenyl hydrazides > acids > lactones > nitriles.

COLUMBUS 10, OHIO

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[CONTRIBUTION FROM THE PURDUE RESEARCH FOUNDATION AND THE DEPARTMENT OF CHEMISTRY, PURDUE UNIVERSITY]

SYNTHESIS OF SUBSTITUTED QUINOLYLAMINES. DERIVATIVES OF 4-AMINO-7-CHLOROQUINOLINE

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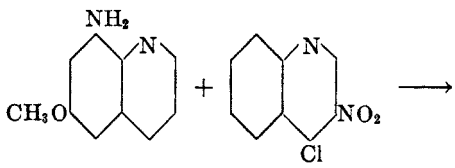
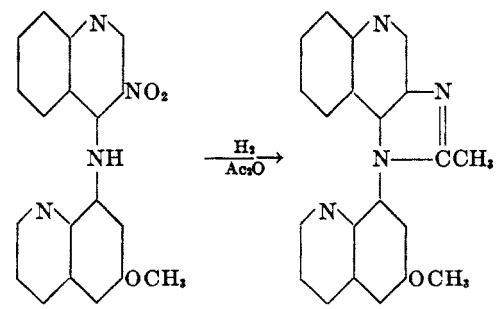
The high antimalarial activity of 4-(5′-diethylamino-2′-pentylamino)-7-chloroquinoline (SN 7618, chloroquine) has suggested the use of 4,7-dichloroquinoline in the synthesis of other antimalarials. It was the purpose of this investigation to prepare derivatives of 4-amino-7-chloroquinoline containing other side-chains, particularly side-chains of the type previously found active on the 4-amino-6-methoxyquinoline nucleus and reported from these laboratories (1). These side-chains were formed from 1,3-bis(dialkylamino)-2-propylamines obtained by reduction of the Mannich condensation products from nitromethane, formaldehyde, and secondary amines. The new compounds prepared are shown in Table I. The side-chain for compound 5 was one of a series of complex amines recently described by one of us (2). Compound 6 was prepared from an amine whose preparation from nitromethane, formaldehyde, and isopropylamine was recently described by Senkus (3).

Certain new derivatives of 8-amino-6-methoxyquinoline (I) have also been obtained and submitted for testing as antimalarials. The first of these (III) resulted from the condensation of I with 4-chloro-3-nitroquinoline (II). It gave an imidazole (IV) upon reduction in the presence of acetic anhydride.



I II



III IV

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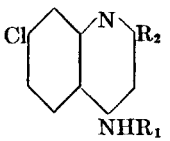
TABLE I

N-SUBSTITUTED 4-AMINO-7-CHLOROQUINOLINES

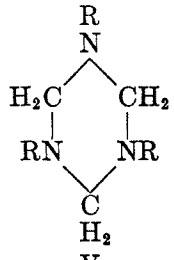


SUBSTITUENTS		YIELD, %	Q.E.[a]	M.P., °C.	FORMULA	ANALYSES	
R_1	R_2					Calc'd	Found
1. 1,3-Bis(dimethylamino)-2-propyl-	H	58		126	$C_{16}H_{23}ClN_3$	C, 62.61	62.50, 62.53
trihydrochloride			4.0	263–264		H, 7.56	7.52, 7.64
2. 1,3-Bis(dipropylamino)-2-propyl-	H	45		150			
triphosphate			0.8		$C_{24}H_{48}ClN_4O_{12}P_3$	N, 7.86	7.62, 7.79
3. 1,3-Bis(dibutylamino)-2-propyl-	H	40					
triphosphate			i	161	$C_{28}H_{56}ClN_4O_{12}P_3$	N, 7.28	7.29, 7.47
4. 1,3-Bis(diisobutylamino)-2-propyl-	H						
trihydrochloride		31.7	i	158–160	$C_{28}H_{50}Cl_4N_4$	N, 9.58	9.83, 9.88
5. 4-Aza-5,5-dimethyl-6-hydroxyhexyl-	H	42.9		149	$C_{16}H_{22}Cl_3N_3O$	C, 62.40	62.29, 62.42
dihydrochloride			0.64	258–259		H, 7.21	7.15, 7.19
6. 1,3-Diisopropyl-5-hexahydropyrimidyl-	H						
trihydrochloride dihydrate		63.4	1.2	245–250[b]	$C_{19}H_{34}Cl_4N_4O_2$	N, 11.38	11.37, 11.51
7. 1,3-Bis(methylisobutylamino)-2-propyl-	H	61	1.6	86–88[c]			
trihydrochloride				205	$C_{22}H_{35}N_4Cl \cdot 3HCl$	N, 11.19	11.05
8. 1,3-Bis(dimethylamino)-2-propyl-	CH_3	52		108–110	$C_{17}H_{25}ClN_4 \cdot H_2O$	N, 16.55	16.80
trihydrochloride methylate			i	253–255	$C_{17}H_{25}ClN_4 \cdot 3HCl \cdot CH_3OH$	N, 12.15	12.41
9. 1,3-Bis(dimethylamino)-2-propyl	*p*-ClC_6H_4	63		156–157	$C_{22}H_{26}Cl_2N_4$	N, 13.42	13.28
trihydrochloride isopropylate			i	250–252	$C_{22}H_{26}Cl_2N_4 \cdot 3HCl \cdot C_3H_7OH$	N, 9.56	9.53

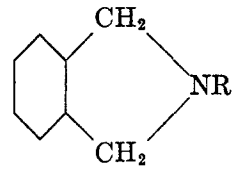
[a] The letters Q.E. are an abbreviation for quinine equivalent. [b] Sinters at 178–180°. [c] B.p. 185–188° at 0.5–1 mm.

Unsuccessful attempts were made to prepare diquinolylamines by condensations of I or its *p*-toluenesulfonate (sodium salt) with 2- or 8-chloro-5-nitroquinoline. Only tars or no reactions were obtained. On the other hand, I gave the expected 6-methoxy-8-(7′-chloro-4′-quinolyl)aminoquinoline with 4,7-dichloroquinoline.

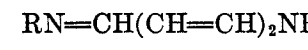
With formaldehyde I gives mainly polymer, but a small amount of a pyridine-soluble compound analyzing correctly for V was also obtained. With formaldehyde and hydrogen sulfide a non-crystalline yellow powder was obtained. *o*-Xylylene chloride and I give the isoindoline (VI).



V



VI



VII

R = 6-methoxy-8-quinolyl-

Buu-Hoï (4) has described the preparation of colored compounds from the reaction of sulfanilamides with pyridine and cyanogen bromide. Although no yields, physical constants, or analyses were reported, structures were proposed, and the products were found to be effective against bacteria. With pyridine and cyanogen bromide I gave a purple crystalline solid which could not be recrystallized because of its insolubility in most solvents and its instability in acids. If its structure is analogous to those proposed by Buu-Hoï it may be represented by VII.

Pharmacological testing. None of the compounds showed antimalarial activity except those listed in Table I. It is interesting to note the activity of those compounds containing side chains derived from ditertiary monoprimary amines and the dependence of this activity on the presence of at least one methyl or methylene group attached to each tertiary nitrogen atom (*cf.* compounds 1, 6, and 7). This activity is largely lost if other alkyl groups replace the methyl or methylene groups (compounds 2, 3, and 4) or if a substituent is introduced at the 2-position on the quinoline nucleus (compounds 8 and 9). Efforts are now being made to prepare more active related antimalarials in which the tertiary nitrogens are separated from the primary nitrogens of the side chain amines by more than 3 carbon atoms.

Acknowledgment. We wish to express our gratitude to Eli Lilly and Company of Indianapolis and to the Purdue Research Foundation for financial support and to the former for pharmacological testing.

EXPERIMENTAL

All melting points and boiling points are corrected and all analyses were carried out by the Huffman Microanalytical Laboratories, Denver, Colorado unless otherwise indicated.

4-[1′,3′-Bis(dimethylamino)-2′-propylamino]-7-chloroquinoline. Twenty grams (0.085 mole) of 4,7-dichloroquinoline hydrochloride, 12.3 g. (0.085 mole) of 1,3-bis(dimethylamino)-2-propylamine, and 100.0 ml. of *n*-amyl alcohol were heated at reflux temperature for 24 hours. The solution was saturated with anhydrous hydrogen chloride, filtered, and the yellow precipitate dissolved in dilute hydrochloric acid. On addition of 10% sodium hydroxide a gray precipitate formed. Recrystallization from hexane gave 15.3 g. (58%) of white needles, m.p. 126°.

Anal. Calc'd for $C_{16}H_{23}ClN_3$: C, 62.61; H, 7.56.
Found: C, 62.50, 62.63; H, 7.52, 7.64.

The *trihydrochloride* was best obtained from the free base in ethanol with anhydrous hydrogen chloride. It recrystallized from ethanol and was a white solid, m.p. 263–264°.

4-(4′-Aza-5′,5′-dimethyl-6′-hydroxyhexylamino)-7-chloroquinoline. A mixture of 27.2 hexg. (0.14 mole) of 4,7-dichloroquinoline and 20.0 g. (0.14 mole) of 6-amino-3-aza-2,2-dimethylanol was heated, with stirring, at 145–150° for a period of 24 hours. The temperature tended to rise above this point due to heat evolution; therefore, the flask was cooled periodically. At room temperature the contents of the flask became solid. The product was pulverized, dissolved in hot 5% acetic acid, and made alkaline with 4 *N* potassium hydroxide. The free base was recrystallized from isopropyl ether to give 18.0 g. (42.9%) of white product, m.p. 149°.

Anal. Calc'd for $C_{16}H_{22}ClN_3O$: C, 62.40; H, 7.21.
Found: C, 62.29, 62.42; H, 7.15, 7.19.

The *dihydrochloride* was obtained by saturating an ethanolic solution of the free base with anhydrous hydrogen chloride and diluting with isopropyl ether. Recrystallization from ethanol-isopropyl ether gave a crystalline dihydrochloride, m.p. 258–259°.

The 4-[1′,3′-bis(dipropylamino)-, (dibutylamino)-, and (diisobutylamino)-2′-propylamino][3] (3), and 4-(1′,3′-diisopropyl-5′-hexahydropyrimidyl)- derivatives of 7-chloroquinoline were prepared by procedures similar to those above, but the first two were characterized as the triphosphates, which were recrystallized from methanol-water-isopropanol.

6-Methoxy-8-(7′-chloro-4′-quinolyl)aminoquinoline dihydrochloride hydrate. Thirteen grams (0.055 mole) of 4,7-dichloroquinoline hydrochloride and 9.65 g. (0.055 mole) of 8-amino-6-methoxyquinoline in 40 ml. of *n*-butanol were heated at reflux temperature for 48 hours. On cooling, a dark yellow solid formed, which turned orange upon contact with air. It was dissolved in hot pyridine and diluted with water. The yellow crystalline product, after recrystallization from ethanol, weighed 10.0 g. (53.8%); m.p. 203–205°. Anhydrous hydrogen chloride was added to a chloroform solution of the free base and after removal of the chloroform the residue was recrystallized from moist methanol-isopropyl ether. The *dihydrochloride* obtained showed a transition point at 150° and melted at 276°. A sample dried at 100° over phosphorus pentoxide showed no change before melting at 276°. This indicated that the original product was a hydrate.

Anal. Calc'd for $C_{19}H_{16}Cl_3N_3O$: N, 10.28. Found: N, 10.20, 10.15.

6-Methoxy-8-(3′-nitro-4′-quinolyl)aminoquinoline (III). A mixture of 4.2 g. (0.024 mole) of 8-amino-6-methoxyquinoline and 5.0 g. (0.024 mole) of 4-chloro-3-nitroquinoline (5) in 40 ml. of ethanol was stirred at room temperature for five hours. The orange solid was filtered, dissolved in hot pyridine, and diluted with water. Orange needles formed upon cooling. Recrystallization from ethanol gave 7.25 g. (87.5%) of the diquinolylamine, m.p. 230–232°.

Anal. Calc'd for $C_{19}H_{14}N_4O_3$: C, 65.88; H, 4.08; N, 16.18.
Found: C, 65.88, 65.75; H, 4.03, 4.10; N, 16.21, 16.32.

1-(6′-Methoxy-8′-quinolyl)-2-methylquinolino-[3,4-d]imidazole (IV). A mixture of 14.0 g. (0.04 mole) of the above diquinolylamine, 70.0 ml. of glacial acetic acid, 80.0 ml. of acetic

[3] The intermediate 1,3-bis(diisobutylamino)-2-nitropropane from which this amine was prepared was previously reported as a yellow oil (1). We found it to be a yellow solid, m.p 86.0–87.5°.

anhydride, and 100 mg. of platinum oxide catalyst was reduced under 60 pounds hydrogen pressure. During reduction the orange solid dissolved. After hydrogen uptake had ceased the mixture was filtered, and the filtrate was evaporated to dryness. The residue was dissolved in hydrochloric acid, decolorized, and made alkaline with ammonia. The precipitate was recrystallized from ethanol to give 7.0 g. (51.2%) of white crystalline product, m.p. 253–254°.

Anal. Calc'd for $C_{21}H_{16}N_4O$: C, 74.1; H, 4.74; N, 16.40.
Found: C, 73.73, 73.79; H, 4.80, 4.84; N, 16.05, 16.10.

6-Methoxy-8-(p-toluenesulfonyl)aminoquinoline. Eleven grams (0.058 mole) of *p*-toluenesulfonyl chloride was added in portions to 10.0 g. (0.057 mole) of 8-amino-6-methoxyquinoline in 50 ml. of pryidine. After the initial reaction had subsided the mixture was allowed to stand for two hours at room temperature and then for ten minutes over a steam-cone. Pouring into water gave a gray precipitate. Recrystallization from ethanol gave 11.6 g. (61.5%) of a white crystalline product, m.p. 133–134°.

Anal.[a]: Calc'd for $C_{17}H_{16}N_2O_3S$: C, 62.18; H, 4.91.
Found: C, 61.90, 62.05; H, 5.09, 5.21.

1,3,5-Tris(6'-methoxy-8'-quinolyl)hexahydro-sym-triazine (V). A mixture of 17.4 g. (0.1 mole) of 8-amino-6-methoxyquinoline, 4.05 g. (0.05 mole) of 37% formalin solution, and 40.0 ml. of acetone was refluxed for six hours, then cooled. The acetone was removed under reduced pressure and the resinous product was heated with pyridine. Only a small amount of the product was soluble, the remainder being polymer. Three recrystallizations from pyridine gave 1.0 g. (5%) of a yellow product, m.p. 203–205°.

Anal. Calc'd for $C_{33}H_{30}N_6O_3$: C, 70.95; H, 5.41.
Found: C, 71.32, 71.23; H, 5.79, 5.80.

Condensation of 8-amino-6-methoxyquinoline, formaldehyde, and hydrogen sulfide. A 20% aqueous-ethanolic formaldehyde solution (0.086 mole) saturated with hydrogen sulfide was added to an ethanolic solution of 10.0 g. (0.058 mole) of 8-amino-6-methoxyquinoline and the mixture was refluxed for 30 minutes. A yellow oil formed which solidified on cooling. The solvent was removed and the product was purified by repeated reprecipitation from a pyridine-water mixture. The yield of the yellow solid, m.p. 185-190° (with decomposition), was 7.0 g. (61.9%).

Anal. Calc'd for $C_{33}H_{30}N_6O_3 \cdot H_2S$: C, 66.86; H, 5.44; N, 14.19; S, 5.41.
Found: C, 66.88, 66.99; H, 5.27, 5.39; N, 14.01, 14.07; S, 5.33, 5.43.

2-(6'-Methoxy-8'-quinolyl)isoindoline (VI). A mixture of 5.0 g. (0.024 mole) of *o*-xylylene chloride, 8.25 g. (0.047 mole) of 8-amino-6:methoxyquinoline, 4.1 g. (0.05 mole) of anhydrous sodium acetate, and 15 ml. of 95% ethanol was stirred at room temperature for four days and then refluxed for 1½ hours. After cooling, the inorganic salt was filtered and the dark filtrate was evaporated to dryness. Decolorization with Norit and recrystallization from ethanol-water gave 1.0 g. (12.65%) of a white crystalline product, for m.p. 141–142°.

Anal.[a]: Calc'd for $C_{18}H_{16}N_2O$: C, 78.2; H, 5.8; N, 10.1.
Found: C, 78.6, 78.7; H, 5.7, 5.8; N, 10.1, 10.2.

Condensation of 8-amino-6-methoxyquinoline with cyanogen bromide and pyridine (VII). A solution of 3.25 g. (0.05 mole) of potassium cyanide and 2.60 ml. of bromine in 80.0 ml. of water was added to a warm (60°) mixture of 17.4 g. (0.10 mole) of 8-amino-6-methoxyquinoline, 3.95 g. (0.05 mole) of pyridine, 660.0 ml. of water, and 40.0 ml. of ethanol. On standing a purple crystalline solid formed which could not be recrystallized because of its insolubility. It was purified by washing with water, ethanol, and ether respectively, and finally by continuous extraction with benzene. The purple residue, 8.0 g. (39%), decomposed at 134–135°.

Anal. Calc'd for $C_{25}H_{22}N_4O_2$: N, 13.65. Found: N, 16.68, 16.80.

4,7-Dichloroquinaldine. 4-Hydroxy-7-chloroquinaldine (6), 50 g., was refluxed with phosphorus oxychloride, 150 ml., for two hours. The cooled mixture was poured on ice, neutra-

[a] Analyses by Dr. H. Galbraith, Purdue University.

lized with a saturated potassium carbonate solution, and the solid precipitate extracted with chloroform. The chloroform was dried and the product crystallized by evaporation of the solvent. This procedure removed a major portion of the contaminating red color that seemed to go along with the desired product. The pink crystals were recrystallized from methanol (Norit) to yield long white needles, m.p. 101–102°.

Anal. Calc'd for $C_{10}H_7Cl_2N$: N, 6.62. Found: N, 6.66.

4-[1',3'-Bis(dimethylamino)-2'-propylamino]-7-chloroquinaldine. 4,7-Dichloroquinaldine, 25.5 g., 1,3-bis(dimethylamino)-2-propylamine, 28 g., potassium iodide, 0.2 g., and hydrogen chloride, 3.8 g., were held at 165° for eight hours. The mixture was cooled and shaken with a mixture of 75 ml. of ether and 200 ml. of 2 *N* hydrochloric acid until solution had been effected. The aqueous phase was separated, neutralized with dilute sodium hydroxide, and the solid precipitate, 18.2 g. (52%) taken up in methanol (Norit) and the methanol concentrated to about 50 ml. Crystallization of the free base monohydrate, m.p. 108–110°, was effected by the addition of hot water to incipient precipitation and then allowing to stand. The free base was taken up in methanol and added to a saturated ethanol-hydrogen chloride solution. The resultant hydrochloride had m.p. 253–255° (from ethanol-methanol).

7-Chloro-4-hydroxy-2-p-chlorophenylquinoline. Distilled *m*-chloroaniline, 12.7 g., ethyl *p*-chlorobenzoylacetate, 21.4 g., glacial acetic acid, 6.0 ml., and one drop of concentrated hydrochloric acid were refluxed at 55–65° in the presence of petroleum ether, 130 ml., and the water formed was removed by azeotropic distillation. After 24 hours, the solvent was removed under a vacuum and the residue added to 2 l. of Finol stirred at 250–255°. The addition was effected over a period of 20 minutes, distilling out the water as rapidly as formed. It was noted that a period of heating longer than 30 minutes resulted in a darker product. The Finol mixture was cooled and about 200 ml. of petroleum ether was added. The mixture was filtered and the residue was removed and washed several times with hot isopropanol, which resulted in a product essentially pure for the chlorination step; yield, 17 g. (58%).

4,7-Dichloro-2-p-chlorophenylquinoline. 7-Chloro-4-hydroxy-2-*p*-chlorophenylquinoline, 50 g., was refluxed with phosphorus oxychloride, 150 ml., for two hours. The black solution was cooled, poured on ice, neutralized with potassium carbonate, and the solid precipitate removed and washed with a small amount of hot methanol to remove a blue color. If the washing was omitted the product became darker blue when exposed to the air. The blue impurity, when crystallized by concentration of the methanol washings had m.p. 119–120°. It was not identified. The remaining undissolved 4,7-dichloro compound had m.p. 158–159° which was raised to 162–163° by recrystallization from chloroform. The yield was 48 g.

Anal. Calc'd for $C_{15}H_8Cl_3N$: N, 22.04. Found: N, 22.01.

4-[1',3'-Bis(dimethylamino)-2'-propylamino]-7-chloro-2-p-chlorophenylquinoline. Thirty grams of the 4-chloro compound was added to 100 ml. of hexanol containing 25 g. of 1,3-bis(dimethylamino)-2-propylamine and the mixture refluxed for 44 hours. The hexanol was removed under a vacuum and the residue shaken with a mixture of water and ether. The solid at the interface of the two liquids (32 g.) was separated by filtration, air-dried, and crystallized from benzene, m.p. 156–157°. A mixed melting point with the starting material was 135°. From isopropanol the *trihydrochloride* had m.p. 250–252°. It was found to contain one mole-equivalent of isopropanol. Ethanol was also found to be a satisfactory solvent for recrystallization.

1,3-Bis(methylisobutylamino)-2-propylamine. Fresh aqueous formaldehyde, 79.5 g., was slowly added to methylisobutylamine, 78 g., at 0° (stirring). After 10 minutes, distilled nitromethane, 28.7 g., was slowly added to the cold solution at 0°. The solution was stirred for ten hours at ice temperature, allowed to warm to room temperature, stirred for two hours, and the organic layer taken up in ether. The ether layer was washed thoroughly with 20% potassium hydroxide and water, the ether removed under a vacuum, and the product held under a high vacuum at room temperature for five hours. The oil, 110 g., (71%) was hydrogenated batchwise, at 60 pounds pressure, using freshly prepared Raney nickel and two volumes of ethanol as solvent. Cooling was effected with a jacketed condenser through which air could be blown. Absorption was controlled at the rate of one pound of hydrogen

per minute. The alcoholic solution, after filtration, was dried and the desired amine was obtained by distillation; yield 63 g., (63.3%), b.p. 85–88° (1 mm.), n_D^{25} 1.4422.

Anal. Calc'd for $C_{13}H_{31}N_3$: N, 18.32. Found: N, 18.45, 18.56.

4-[1',3'-Bis(methylisobutylamino)-2'-propylamino]-7-chloroquinoline. 4,7-Dichloroquinoline, 20 g., 1,3-bis(methylisobutylamino)-2-propylamine, 25 g., hexanol, 50 ml., hydrogen chloride, 4 g., and potassium iodide, 0.5 g., were held at reflux for 24 hours. The mixture was cooled, shaken with 250 ml. of ether, and extracted with dilute hydrochloric acid. The acidic solution was made basic with sodium hydroxide and extracted with ether. The ether solution, after drying, was distilled, yielding 24 g. (61%) of product, b.p. 175–195° (0.5–1 mm.). A yellow oil was obtained on redistillation, b.p. 185–188° (0.5–1 mm.) which solidified on cooling to a solid, m.p. 86–88°. An attempt was made to crystallize the phosphate (obtained by precipitation of the free base) from propanol with 85% phosphoric acid, but only an oil was obtained. The phosphate oil was reconverted to the free base and taken up in methanol containing slightly more than three equivalents of hydrogen chloride and the methanol removed under vacuum. A faintly-yellowish crystalline residue was obtained, m.p. 205° (45 seconds).

SUMMARY

1. A number of N-substituted 4-amino-7-chloroquinolines have been prepared and submitted for testing as antimalarials.

2. Some miscellaneous derivatives of 8-amino-6-methoxyquinoline have also been synthesized and characterized.

3. Active antimalarials have been found in the series of 4-alkylamino-7-chloroquinolines in which the alkyl group contains the skeletal structure $-C[CN(CH_3)R]_2$ where R is methyl or larger.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE RICE INSTITUTE]

FORMALDEHYDE CONDENSATION IN THE PYRAZOLE SERIES

ISAAC DVORETZKY AND GEORGE HOLMES RICHTER

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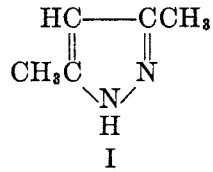
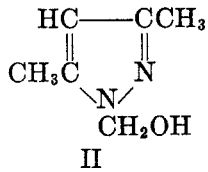
A study of the reaction of several representative pyrazoles with formaldehyde has shown that those compounds in which the 1-position of the heterocyclic ring is unsubstituted react in both neutral and acidic media to give the corresponding 1-carbinols. Furthermore, the same nuclei react with formaldehyde in acid medium to form alcohols resulting from condensation in the 4-position. Pyrazoles containing a substituent in the 1-position undergo no reaction in neutral solution, but condense with the aldehyde in the presence of acid to yield the 4-carbinols. No product of the condensation of formaldehyde with a side-chain methyl group could be obtained, even in basic solution.

The investigation described here had its origin in the work of Landua (1) on the chloromethylation of 3,5-dimethylpyrazole (I). Landua studied the reaction

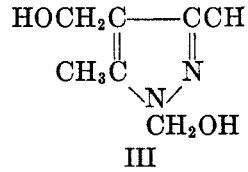


I

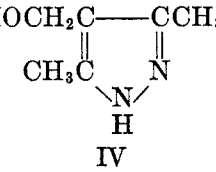
of this compound with paraformaldehyde and hydrochloric acid in the absence of a catalyst under a variety of conditions. By successive extraction of the basic reaction mixtures with ether and alcohol he obtained three products, which have subsequently been shown to be 3,5-dimethylpyrazole-1-carbinol (II), 3,5-dimethylpyrazole-1,4-dicarbinol (III), and 3,5-dimethylpyrazole-4-carbinol (IV). These results of the attempted chloromethylation of I suggested a systematic study of the reaction of the pyrazole nucleus with formaldehyde.



II



III



IV

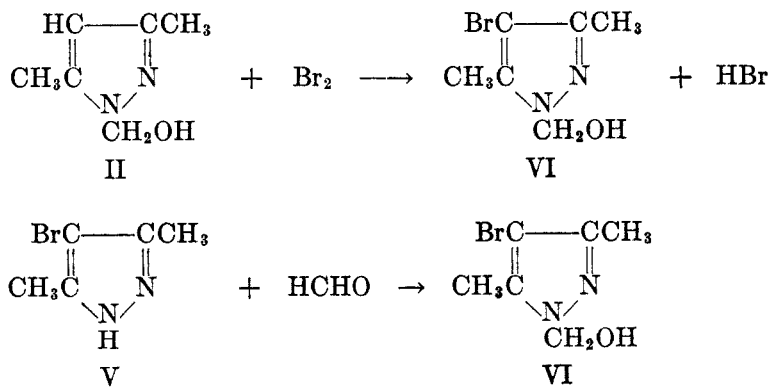
The reaction between equimolar proportions of I and formalin at room temperature was found to result in a 71% yield of II. Higher condensation products could not be obtained by the use of an excess of formalin. The effect of a higher temperature on the reaction was studied by allowing a molten mixture of equivalent amounts of I and paraformaldehyde to react at 110–120°. The 1-carbinol was again obtained, this time in a yield of 90%. An excess of paraformaldehyde gave identical results.

Since no product other than II could be obtained from I and formaldehyde alone, the effect of acid on the reaction was determined. Inasmuch as II is formed

both in the presence and in the absence of hydrochloric acid, a reaction was carried out between the 1-carbinol, paraformaldehyde, and hydrochloric acid. From these reactants there was obtained III in a yield of 24%.

Several experiments in which I was allowed to react with paraformaldehyde and hydrochloric acid at room temperature were carried out. The mixture of products consisted predominantly of II; smaller amounts of III were formed, and only traces of IV could be isolated. At higher temperatures, the reaction yielded polymeric substances from which no definite compounds could be isolated. The introduction of acid catalysts, such as zinc and stannic chlorides, produced a similar effect.

The presence of the alcoholic groups in the above compounds was verified by combustion analysis, but the determination of their positions required further study. Direct bromination of II yielded a new compound (VI). It was found also that 4-bromo-3,5-dimethylpyrazole (V) reacts with formalin to give the same product (VI). Combustion analysis of the common product indicated that it is a bromodimethylpyrazolecarbinol. The carbinol group is excluded from the 4-position because of the presence of the bromine atom; it is therefore located either in the 1-position or on the side chain. The distinction between the latter two possibilities was based upon a characteristic property of pyrazoles which contain an unsubstituted imino hydrogen atom—the formation of a nitric acid-soluble precipitate with silver nitrate solution. It was found that I and V react with alcoholic silver nitrate immediately, while II and VI give a precipitate only on standing. The slow formation of the precipitates by the two carbinols suggests that the alcoholic group is located in the 1-position and not on the side chain, and that the precipitates resulted from displacement of formaldehyde by silver ion. This explanation is supported by the fact that II on treatment with ammoniacal silver nitrate slowly formed both a precipitate and a silver mirror. Posner (2) has observed that 3,5-dimethylpyrazole-1-carbonamide also gives a precipitate with silver nitrate. It follows, therefore, that VI is 4-bromo-3,5-dimethylpyrazole-1-carbinol, and that it was formed according to the equations



The 4-carbinol (IV) was prepared independently of formaldehyde condensation by reduction of 4-carbethoxy-3,5-dimethylpyrazole with lithium aluminum

hydride. The product thus obtained was shown by a mixed-melting point test to be identical with the compound which resulted from formaldehyde condensation.

Since the dicarbinol (III) was produced by reaction of the 1-carbinol with formaldehyde, one of its two carbinol groups is located in the 1-position. Furthermore, III was found to lose formaldehyde when heated, the residue being IV. It follows that the second alcoholic group is in the 4-position.

EXPERIMENTAL PART

Reaction of 3,5-dimethylpyrazole with formalin. To a solution of 3.27 g. (0.034 mole) of 3,5-dimethylpyrazole, prepared according to the procedure of Knorr and Rosengarten (3), in 58 ml. of water and 5 ml. of ethanol, 3.00 ml. (0.037 mole) of 35% formalin was added. After standing at 30° for 42 hours, the mixture was extracted with three 25-ml. portions of chloroform, and the solvent from the combined extracts evaporated. Recrystallization of the residue from benzene yielded 3.03 g. (71%) of 3,5-dimethylpyrazole-1-carbinol in the form of colorless prisms, m.p. 108–109°.

Anal. Calc'd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99.

Found: C, 57.18; H, 7.76.

Reaction of 3,5-dimethylpyrazole with paraformaldehyde. A mixture of 0.96 g. (0.01 mole) of 3,5-dimethylpyrazole and 0.30 g. (0.01 mole) of paraformaldehyde (Eastman trioxymethylene) was immersed for 20 minutes in an oil-bath maintained at 110–120°. Recrystallization of the solidified melt from benzene yielded 1.13 g. (90%) of 3,5-dimethylpyrazole-1-carbinol.

Reaction between 3,5-dimethylpyrazole-1-carbinol, paraformaldehyde, and hydrochloric acid. A mixture of 1.2 g. (0.01 mole) of 3,5-dimethylpyrazole-1-carbinol and 0.40 g. (0.013 mole) of paraformaldehyde was dissolved in 8.5 ml. (0.10 mole) of conc'd hydrochloric acid. After standing at 30° for one week, the mixture was subjected to distillation at the water-pump until 4 ml. of distillate had been collected. The residue was then carefully neutralized with potassium carbonate, and the potassium chloride removed by filtration. After addition of 15 ml. of ethanol to the filtrate, the solution was saturated with potassium carbonate, and the alcoholic layer separated. Evaporation of the alcohol at room temperature left a solid residue contaminated with inorganic material. The organic product was most readily purified by recrystallization from *n*-propyl alcohol. The yield of white, granular 3,5-dimethylpyrazole-1,4-dicarbinol, m.p. 138–140°, was 0.35 g. (24%).

Anal. Calc'd for $C_7H_{12}N_2O_2$: C, 53.82; H, 7.74.

Found: C, 52.49; H, 7.30.

When heated above its melting point, the dicarbinol evolved formaldehyde and yielded a residue of 3,5-dimethylpyrazole-4-carbinol, m.p. 174–176°.

Anal. Calc'd for $C_6H_{10}N_2O$: C, 57.12; H, 7.99.

Found: C, 57.40; H, 7.79.

Preparation of 4-bromo-3,5-dimethylpyrazole-1-carbinol. (*a*). A solution of 1.16 g. (0.0066 mole) of 4-bromo-3,5-dimethylpyrazole, prepared from 3,5-dimethylpyrazole and N-bromosuccinimide by the method of Ziegler (4), and 5.7 ml. (0.066 mole) of 35% formalin in 5 ml. of water and 3 ml. of ethanol was allowed to stand at 30° for four weeks. The mixture was extracted with three 3-ml. portions of chloroform, and the solvent from the combined extracts evaporated. After two recrystallizations from water the yellow residue furnished 0.88 g. (65%) of 4-bromo-3,5-dimethylpyrazole-1-carbinol in the form of white needles, m.p. 133–134°.

(*b*). A mixture of 0.50 g. (0.004 mole) of 3,5-dimethylpyrazole-1-carbinol and 1.00 g. (0.008 mole) of sodium acetate was dissolved in 10 ml. of water. Dropwise addition of 0.5 ml. (0.009 mole) of bromine to the well-stirred solution resulted in precipitation of a pale-yellow solid. After the excess bromine had been removed by heating on the steam-bath, the white suspension was filtered, and the precipitate recrystallized from water. The weight of the product, m.p. 133–134°, was 0.70 g. (85%).

Anal. Calc'd for $C_6H_7BrN_2O$: C, 35.14; H, 4.42.
Found: C, 34.94; H, 4.38.

Reduction of 4-carbethoxy-3,5-dimethylpyrazole. A solution of 0.98 g. (0.0058 mole) of 4-carbethoxy-3,5-dimethylpyrazole, prepared according to the procedure of Knorr and Rosengarten (3), in 40 ml. of anhydrous ether was placed in a three-necked flask fitted with a dropping-funnel, reflux condenser, and mercury-sealed stirrer. To the stirred solution of the ester, 40 ml. of an ether solution of 0.32 g. (0.0084 mole) of lithium aluminum hydride was added over a period of ½ hour. After decomposition of the excess hydride with 3 ml. of water, the ether was removed by distillation and the residue extracted with 30 ml. of warm ethanol. Evaporation of the solvent from the extract left a crystalline residue, recrystallization of which from ethanol yielded 0.47 g. (64%) of white prisms of 3,5-dimethylpyrazole-4-carbinol, m.p. 179–180°.

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[JOINT CONTRIBUTION FROM THE RESEARCH LABORATORIES OF SYNTEX, S. A., AND THE INSTITUTO DE QUÍMICA DE LA UNIVERSIDAD NACIONAL AUTÓNOMA DE MÉXICO]

STEROIDS. X.[1] AROMATIZATION EXPERIMENTS IN THE CHOLESTEROL SERIES

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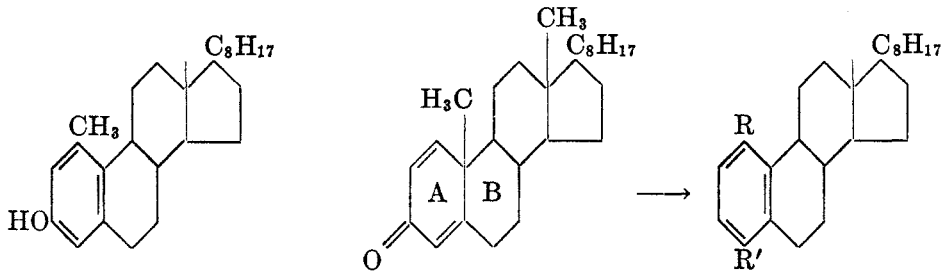
The preparation of sterols in which the hydroaromatic ring A with the angular methyl group at C-10 is replaced by a phenolic ring has been attempted several times. In 1936, Marker and co-workers (1) reported in a preliminary communication that dehydroneoergosterol afforded the phenol tetrahydrodehydroneoergosterol on reduction with sodium in amyl alcohol. The experimental details have never been reported and the claim could not be substantiated by other workers (2). In 1941, Inhoffen and Zühlsdorff (3) applied the acid-catalyzed dienone-phenol rearrangement to 1,4-cholestadien-3-one (I) and ascribed structure II to the resulting product. This would constitute the partial synthesis of an aromatic cholesterol analog with a methyl group in position 1, but the recent synthesis of 1-methyl-3-hydroxy-19-nor-1,3,5-cholestatriene (II) in this laboratory (4) clearly demonstrated that Inhoffen's product (3) belongs to the "x-methylheterophenol" series and most likely possesses structure III or IV (5). Earlier attempts to prepare the aromatic cholesterol analog (VII) *lacking* the methyl group at C-1 by thermal treatment of 1,4-cholestadien-3-one (I) failed (3, 6).

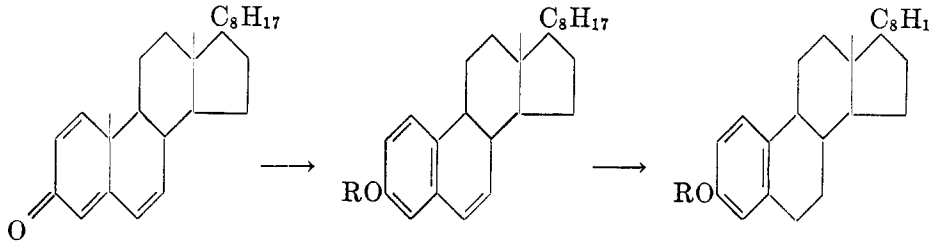


II I III R = CH_3; R′ = OH
IV R = OH; R′ = CH_3

It has recently been reported (7, 8) that vapor phase aromatization of 1,4,6-trien-3-ones of the androstane series leads to 6-dehydrophenols of the estrogen series, which can be hydrogenated to the natural estrogens in high yield. The present report deals with the application of this method to the first successful synthesis of a cholesterol derivative possessing an aromatic ring A and no methyl group at C-1.

Initial attempts to aromatize 1,4,6-cholestatrien-3-one (V) in mineral oil solution (7, 8, 9) failed because the resulting product was too soluble to crystallize from that medium. Substitution of tetralin (10) for mineral oil and a temperature of 670–700° proved to be satisfactory, since evaporation of the solvent left an

[1] For paper IX of this series, see Romo, Djerassi and Rosenkranz (4).



V

VIa R = H
b R = *p*-$NO_2C_6H_4CO$
c R = C_6H_5CO
d R = CH_3CO

VIIa R = H
b R = *p*-$NO_2C_6H_4CO$
c R = C_6H_5CO
d R = CH_3CO

oil, which readily yielded a crystalline *p*-nitrobenzoate (VIb). Saponification afforded the free phenol, 3-hydroxy-19-nor-1,3,5,6-cholestatetraene (VIa), and on esterification the benzoate (VIc) and acetate (VId). The negative rotation and ultraviolet absorption spectrum (main maximum at 266 mμ) are fully consistent with that formulation (4, 8). The phenol VIa smoothly absorbed one mole of hydrogen in the presence of 5% palladium-on-charcoal catalyst and led to the desired aromatic cholesterol analog, 3-hydroxy-19-nor-1,3,5-cholestatriene (VIIa), which was further characterized by three derivatives (VIIb, c, d). It is noteworthy that the corresponding derivatives in the tetraene (VI) and triene (VII) series possess nearly identical melting points but as observed already in the estrogen series (8), hydrogenation of the 6,7-double bond resulted in a large dextrorotatory shift of the specific rotation, and the ultraviolet absorption spectrum (maximum at 284 mμ and minimum at 250 mμ) was typical of that of a simple phenol. Just like the corresponding derivatives bearing a 1-methyl group (4), the presently described phenols (VIa and VIIa) were only very slightly soluble in 5% aqueous alkali and gave no color with alcoholic ferric chloride solution. Both phenols were rather sensitive to atmospheric oxidation.

EXPERIMENTAL[2]

3-Hydroxy-19-nor-1,3,5,6-cholestatetraene (VI). A solution of 40 g. of 1,4,6-cholestatrien-3-one (V) (4, 7, 8) in 3 l. of freshly distilled tetralin was dropped through a vertical glass tube (32 × 3.0 cm.) filled with Pyrex helices and heated to 670–700° over a period of 100 minutes. The condensate was concentrated to a small volume *in vacuo* and the remainder of the tetralin was removed by steam-distillation. Extraction of the residue with ether, drying, and evaporation left 34 g. of a brown oil, which was dissolved in 200 cc. of pyridine. After addition of 34 g. of *p*-nitrobenzoyl chloride, the mixture was briefly warmed on the steam-bath and then left at room temperature overnight. The *p*-nitrobenzoate (VIb) was isolated by dilution with water, extraction with chloroform, thorough washing with dilute hydrochloric acid and sodium carbonate solution, drying, concentration, and addition of methanol. The dark brown precipitate (25 g.) was dissolved in a mixture of 300 cc. of benzene and 100 cc. of hexane and filtered through a column of 300 g. of alumina. Evaporation

[2] All melting points are corrected and were determined on the Kofler block. Unless indicated otherwise, rotations were determined in chloroform solution and ultraviolet absorption spectra in 95% ethanol solution. We are greatly indebted to the Srtas. Paquita Revaque and Maria Eugenia Frontana for the rotations and spectra, and to Srta. Amparo Barba of our Microanalytical Department for the analyses.

of the solvent and two recrystallizations from a mixture of chloroform and methanol gave 13 g. (25%) of the *p-nitrobenzoate* VIb with m.p. 204–206°, $[\alpha]_D^{20}$ − 53.4°. Further recrystallization from methanol-ethyl acetate afforded the analytical sample with m.p. 218–220°, $[\alpha]_D^{20}$ − 53°, u.v. maximum at 264 mμ, log ε 4.37 (chloroform).

Anal. Calc'd for $C_{33}H_{41}NO_4$: C, 76.86; H, 8.01; N, 2.71.

Found: C, 77.00; H, 8.13; N, 2.95.

Three grams of the *p*-nitrobenzoate VIb was refluxed for 30 minutes with 200 cc. of methanol and 3 g. of potassium hydroxide, diluted with water, acidified, and extracted with ether. Evaporation of the solvent and trituration with hexane afforded 2 g. (93%) of the *phenol* VIa, m.p. 110–115°. The analytical sample crystallized from dilute methanol as colorless needles, turning yellow on heating, m.p. 121–123°, $[\alpha]_D^{20}$ − 59.2°, u.v. maxima at 224 mμ (log ε 4.49), 266 mμ (log ε 3.96), and 304 mμ (log ε 3.21).

Anal. Calc'd for $C_{26}H_{38}O$: C, 85.18; H, 10.44.

Found: C, 84.92; H, 10.55.

Benzoylation of 0.5 g. of the phenol VIa in pyridine solution with benzoyl chloride at room temperature overnight produced 0.52 g. of the *benzoate* VIc, which crystallized from methanol-ether in two polymorphic forms, m.p. 138–140° or m.p. 128–130°, $[\alpha]_D^{20}$ − 43.7°, u.v. maxima at 230 mμ (log ε 4.49) and 262 mμ (log ε 4.03).

Anal. Calc'd for $C_{33}H_{42}O_2$: C, 84.20; H, 8.99.

Found: C, 84.33; H, 9.24.

The *acetate* VId crystallized from methanol-ether as colorless plates with m.p. 96–98°, $[\alpha]_D^{20}$ − 42°, u.v. maxima at 226 mμ (log ε 4.50) and 264 mμ (log ε 4.09).

Anal. Calc'd for $C_{28}H_{40}O_2$: C, 82.30; H, 9.86.

Found: C, 82.22; H, 10.09.

3-Hydroxy-19-nor-1,3,5-cholestatriene (VII). An ethyl acetate solution of 5 g. of the tetraene VIa was shaken with 0.5 g. of 5% palladium-on-charcoal catalyst (American Platinum Works, Newark, N. J.) in an atmosphere of hydrogen for 45 minutes at which time the hydrogen up-take corresponded to one mole. Filtration, evaporation of the solvent to dryness, and recrystallization from methanol yielded 4.2 g. (83%) of the phenol VIIa as needles with m. p. 113–114°, $[\alpha]_D^{20}$ ++74.9°, u.v. maximum at 284 mμ (log ε 3.20) and minimum at 250 mμ (log ε 2.30).

Anal. Calc'd for $C_{26}H_{40}O$: C, 84.71; H, 10.93.

Found: C, 84.59; H, 11.10.

The following derivatives of the phenol VIIa were prepared:

p-Nitrobenzoate VIIb (from ethyl acetate-methanol), m.p. 211–213°, $[\alpha]_D^{20}$ +56.4°.

Anal. Calc'd for $C_{33}H_{43}NO_4$: C, 76.56; H, 8.37.

Found: C, 76.67; H, 8.39.

Benzoate VIIc (from ether-methanol), small needles, m.p. 138–140°, $[\alpha]_D^{20}$ +50.5°.

Anal. Calc'd for $C_{33}H_{44}O_2$: C, 83.84; H, 9.38.

Found: C, 84.01; H, 9.34.

Acetate VIId (from ether-methanol), m.p. 93.5–95°, $[\alpha]_D^{20}$ +62°, u.v. maximum at 265 mμ (log ε 2.63) and minimum at 252 mμ (log ε 2.53).

Anal. Calc'd for $C_{28}H_{42}O_2$: C, 81.89; H, 10.30.

Found: C, 81.98; H, 10.15.

SUMMARY

Aromatization of a tetralin solution of 1,4,6-cholestatrien-3-one (V) at 700° produced 3-hydroxy-19-nor-1,3,5,6-cholestatetraene (VI), which on hydrogenation led to the phenol VII, an analog of cholesterol possessing an aromatic ring A. Both phenols were characterized by a number of derivatives.

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[CONTRIBUTION FROM AVERY LABORATORY OF THE UNIVERSITY OF NEBRASKA]

SYNTHESES OF SOME 3-PHENYL-3-*tert*-AMINO-1,2-PROPANEDIOLS

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Although several investigators have reported the preparation of 1-phenyl-2-amino-1,3-propanediols by reacting 1-phenyl-2-bromo-1,3-propanediol (I) with amines, no proof of the position of the amino group of the resulting diols was given (1, 2). Recently, Controulis, *et al.* showed that I gave 3-phenyl-3-amino-1,2-propanediol when treated with ammonia (3). It seemed possible that reaction of I with secondary amines may also have led to 3-phenyl-3-*tert*-amino-1,2-propanediols. It was thus interesting to reinvestigate such reactions.

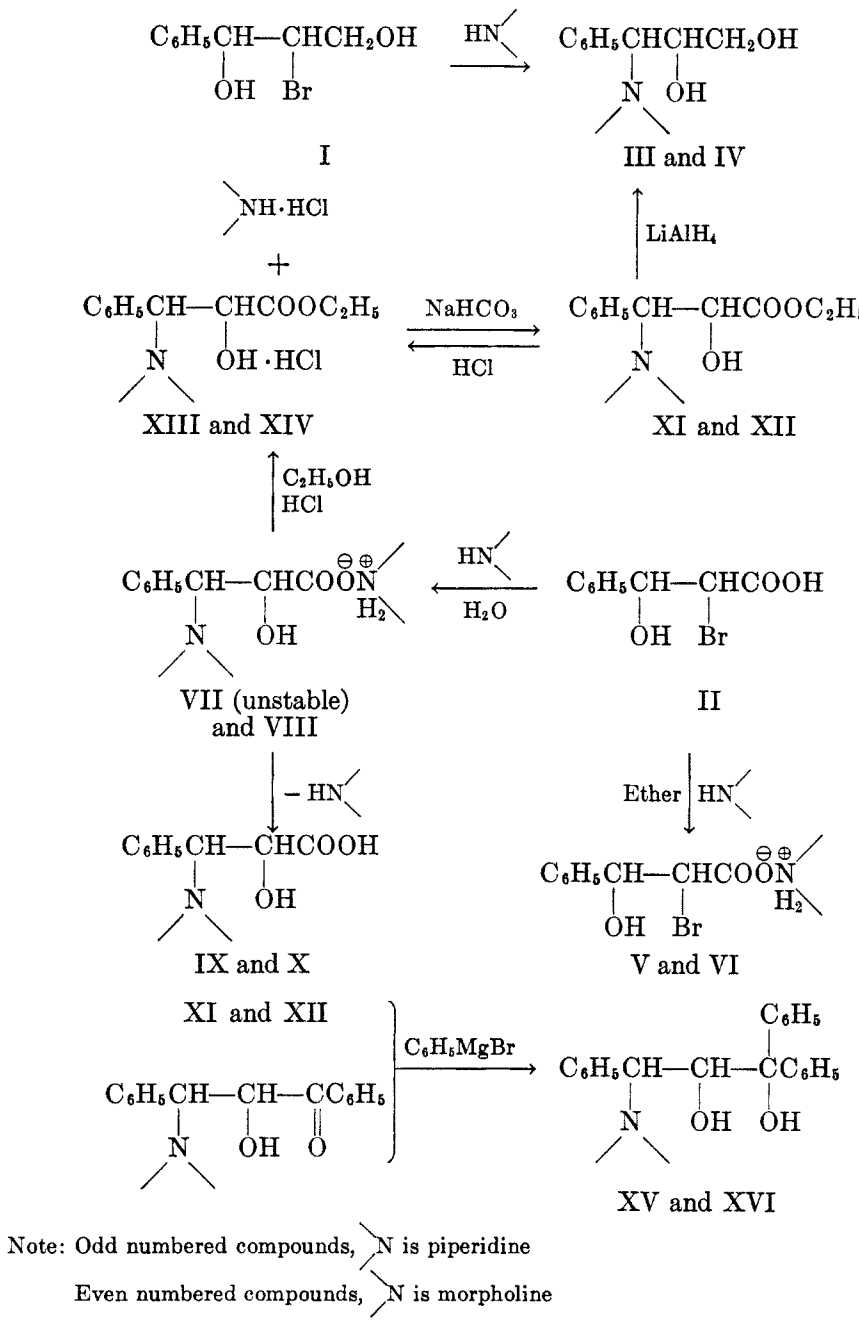
Another possible approach to the synthesis of 1-phenyl-2-*tert*-amino-1,3-propanediols would be through the reduction of α-amino-β-hydroxy-β-phenylpropionic acids by lithium aluminum hydride. Despite the fact that the literature had indicated that both α-amino and β-amino products were possible when α-bromo-β-hydroxy acids were treated with amines (4), the authors were interested in using α-bromo-β-hydroxy-β-phenylpropionic acid (II) (5) as a starting material in order to correlate these two schemes in their reaction mechanisms.

1-Phenyl-2-bromo-1,3-propanediol (I) was prepared in its solid form by using a slightly modified procedure of the early workers (3). On treatment of I with piperidine in water 3-phenyl-3-piperidino-1,2-propanediol (III) was obtained, associated with one mole of piperidine as solvent of crystallization. 3-Phenyl-3-morpholino-1,2-propanediol (IV) was prepared by a similar procedure in low yield.

α-Bromo-β-hydroxy-β-phenylpropionic acid (II) reacted with piperidine and morpholine in ether to give the corresponding amine salts (V and VI) of the starting acid. When II was treated with the amines in aqueous solution, the unstable piperidine salt (VII) of α-hydroxy-β-piperidino-β-phenylpropionic acid (IX) and the morpholine salt (VIII) of α-hydroxy-β-morpholino-β-phenylpropionic acid (X) were isolated. On drying at 100° VII lost piperidine readily to give the free acid (IX). On the other hand, salt VIII was quite stable. Previously Fourneau (6) had reported the preparation of acid IX by reacting piperidine with phenylglycidic ester, and had assigned the position of the amino group by referring to an early work of Erlenmeyer (7) who had assigned the structure from its method of synthesis as analogous to that for phenylisoserine. It seemed to us, however, that a melting point alone could not be the conclusive structural evidence in our investigation. The melting point of IX was found to vary widely by inserting the sample at different temperatures of the melting bath. Therefore, the location of the amino group was still doubtful until the latter part of this investigation.

[1] Abstracted in part from the Ph. D. thesis of Kwan-Chung Tsou, University of Nebraska Regents Fellow, 1948–1949, U. S. Public Health Grant Research Assistant, 1949–1950.

CHART ONE



Note: Odd numbered compounds, $\diagdown\!\!\diagup$N is piperidine

Even numbered compounds, $\diagdown\!\!\diagup$N is morpholine

Ethyl α-hydroxy-β-piperidino-β-phenylpropionate (XI) and ethyl α-hydroxy-β-morpholino-β-phenylpropionate (XII) were prepared as their hydrochlorides

by esterification of VII and VIII. Reduction of esters XI and XII by lithium aluminum hydride gave again the diols III and IV, respectively.

Nicolet and Shinn had observed that N-diethylaminoethanol, a tertiary hydroxyamine, was not affected by periodic acid (8). Later Leonard and Rebenstorf confirmed the same observation under more strenuous conditions (9). Using a procedure recommended by Siggia (10), we found that diol III consumed about two moles of periodic acid. It was felt, however, that this was not sufficient evidence on which to base the assignment of the amino group since no authentic 1-phenyl-2-*tert*-amino-1,3-propanediol was available for comparison. Hence, the final proof of structure of such diols has rested upon synthesis of the known 1,1,3-triphenyl-3-piperidino-1,2-propanediol (XV) from the reaction of ester XI with phenylmagnesium bromide; the structure of this diol has been established by Cromwell and Starks (11). As a comparison, 1,1,3-triphenyl-3-morpholino-1,2-propanediol (XVI) was synthesized by reaction of ester XII or α-hydroxy-β-morpholinobenzylacetophenone (12) with phenylmagnesium bromide. Such results necessarily confirmed the position of the piperidino group, as well as that of the morpholino group at the carbon holding the phenyl group both in the aminohydroxy esters and in the aminopropanediols. See Chart One for details.

It is thus probable that both starting bromohydrin compounds react *via* an epoxy intermediate followed by a nucleophilic attack of the amine molecule at the carbon atom holding the phenyl group. This carbon atom of the epoxy compound might be expected to accommodate a partial positive charge because of resonance interaction with the phenyl group.[2]

Acknowledgement. This investigation was supported in part by a research grant to one of us from the National Cancer Institute, U. S. Public Health Service.

EXPERIMENTAL[3]

1-Phenyl-2-bromo-1,3-propanediol (I). I was prepared by slightly modifying the procedure given by Controulis, *et al.* (3), using the same amounts of reagents. The addition took about 3½ hours, and at no time was the solution allowed to develop more than a slightly yellow color. The solution was decanted from some tarry material and evaporated under reduced pressure with gentle warming to remove ethanol. The aqueous residue was then saturated with sodium chloride, extracted first with two 50-ml. portions of petroleum ether (b.p. 30–60°), and then with three 150-ml. portions of ether. The combined ether extract was dried and evaporated under reduced pressure to a colorless oil which crystallized on addition of crystalline seeds of I. The yield of crude product was 22.0 g. (95%), m.p. 56–58°. Recrystallization twice from low-boiling petroleum ether (b.p. 30–50°) gave the analytical sample, m.p. 57–59°.

Anal. Calc'd for $C_9H_{11}BrO_2$: C, 46.77; H, 4.80.
Found: C, 46.89; H, 4.95.

The piperidine salt (V) *and the morpholine salt* (VI) *of α-bromo-β-hydroxy-β-phenylpropionic acid.* To 0.02 mole of α-bromo-β-hydroxy-β-phenylpropionic acid (II) (5) in 150

[2] The mechanism of the reaction of amines with epoxybenzylacetophenone leading to α-hydroxy-β-aminoketones has been investigated by Barker and Cromwell (to be published soon), and found to be a second order SN_2 reaction.

[3] Microanalyses for carbon, hydrogen, and nitrogen were made by the Clark Microanalytical Laboratory, Urbana, Ill.

ml. of dry ether was added 0.02 mole of piperidine or morpholine dropwise with stirring. The mixture was allowed to stand at room temperature for one hour and the precipitate was recrystallized from absolute ethanol to give V, m.p. 109–110°; or VI, m.p. 126–127°, in 90–95% yield.

Anal. Calc'd for $C_{14}H_{20}BrNO_3$ (V): C, 50.92; H, 6.11; N, 4.24.
Found: C, 50.60; H, 6.08; N, 3.96.

Anal. Calc'd for $C_{13}H_{18}BrNO_4$ (VI): C, 47.00; H, 5.46; N, 4.22.
Found: C, 47.05; H, 5.43; N, 4.05.

α-Hydroxy-β-piperidino-β-phenylpropionic acid (IX). A 16.2-g. sample of II was dissolved in a mixture of 40 ml. of piperidine and 30 ml. of water. The solution was allowed to stand at room temperature for two days. Evaporation under reduced pressure gave a solid residue which was recrystallized from 35 ml. of 90% ethanol to yield 17.0 g. of the unstable piperidine salt (VII) of IX, m.p. 174–176° (decomposed, and partially resolidified). On drying at 100°, VII lost piperidine to yield 12.7 g. (77%) of IX, m.p. 248–249° (dec.). Recrystallization twice from 95% ethanol containing a few drops of glacial acetic acid gave the pure sample which melted at 256° (dec.), when the melting-point tube was inserted at 244° and heated at the rate of 1° per minute. The melting point given by Fourneau (6) is 256°, and by Erlenmeyer, Jr. (7), 255°.

The morpholine salt of α-hydroxy-β-morpholino-β-phenylpropionic acid (VIII). To 4.9 g. of II in 10 ml. of water was added 5.2 g. of morpholine. The solution was allowed to stand at room temperature for one day. Evaporation under reduced pressure gave a solid residue which was recrystallized from 90% ethanol to yield 6.1 g. of a product, m.p. 160–172°. Recrystallization from the same solvent gave 5.8 g. of VIII, m.p. 178–180° (dec.) (85% yield). Recrystallization of VIII from ethanol containing a few drops of acetic acid and ether gave pure VIII unchanged, m.p. 179–180° (dec.).

Anal. Calc'd for $C_{17}H_{26}N_2O_5$: C, 60.33; H, 7.75; N, 8.28.
Found: C, 60.25; H, 7.62; N, 8.26.

An attempt to obtain the acid (X) was made by treating an ethanolic solution of VIII with an equimolar amount of dry hydrogen chloride. The isolated acid was found to be too hygroscopic to handle.

Ethyl α-hydroxy-β-piperidino-β-phenylpropionate (XI) *and ethyl α-hydroxy-β-morpholino-β-phenylpropionate* (XII). A 0.018-mole sample of VII or VIII was suspended in 100 ml. of absolute ethanol and dry hydrogen chloride passed in until the resulting solution was about to boil. On standing at room temperature for 24 hours, the solution was evaporated under reduced pressure to remove ethanol. The residue was treated with sodium bicarbonate solution, and the precipitate was removed. The yield of crude XI was 82%, m.p. 95–97°; that of XII, 58%, m.p. 95–97°. Pure samples of XI, m.p. 96–97.5°, and of XII, m.p. 96–97°, were obtained by recrystallization from ether and petroleum ether (b.p. 30–60°) mixtures.

Anal. Calc'd for $C_{16}H_{23}NO_3$ (XI): C, 69.29; H, 8.36; N, 5.05.
Found: C, 69.37; H, 8.40; N, 5.06.

Anal. Calc'd for $C_{15}H_{21}NO_4$ (XII): C, 64.49; H, 7.58; N, 5.02.
Found: C, 64.62; H. 7.55; N, 5.22.

The hydrochlorides of XI *and* XII. The hydrochlorides were prepared in dry ether solution using dry hydrogen chloride gas and recrystallized from absolute ethanol to give pure XIII, m.p. 196–197°; and pure XIV, m.p. 174–175°.

Anal. Calc'd for $C_{16}H_{24}ClNO_3$ (XIII): Cl, 11.30. Found: Cl, 11.42. Calc'd for $C_{15}H_{22}ClNO_4$ (XIV): C, 57.05; H, 7.02. Found: C, 56.94; H, 6.92.

SYNTHESES OF 3-PHENYL-3-*tert*-AMINO-1,2-PROPANEDIOLS

Method A. 3-Phenyl-3-piperidino-1,2-propanediol (III). A 12.0-g. (0.052 mole) sample of I was treated with 13.6 g. (0.16 mole) of piperidine in 40 ml. of water, with stirring. The mixture was allowed to stand at room temperature for 24 hours and in a refrigerator for two hours. The crystalline precipitate was removed, washed with two 5-ml. portions of water and dried; yield, 14.6 g., m.p. 80–90°. Recrystallization from ethyl acetate gave 10.8

g. of pure III containing one mole of piperidine (65% yield), m.p. 89.5–93°. Further recrystallization from ethyl acetate or chloroform did not change the melting point. This product was investigated to prove that it contained one mole of piperidine as solvent of crystallization:

A sample of the piperidinate was dried to constant weight at room temperature in a vacuum over phosphorus pentoxide.

Anal. Calc'd for $C_{14}H_{21}NO_2$ + 1 $C_5H_{11}N$: N, 8.74. Found: N, 8.52.

To 0.55 g. of the piperidinate (0.0017 mole) in 5 ml. of absolute ethanol was added 0.5 ml. of 3 *N* ethanolic hydrogen chloride (0.0015 mole). Ether was then added to this solution until the precipitation began. On standing at room temperature for two hours, 0.14 g. (0.0011 mole) of piperidine hydrochloride, m.p. 241–243°, was collected and washed with dry ether. A mixed melting point with authentic piperidine hydrochloride (m.p. 243–244°) showed no depression.

A 936.2-mg. sample of the piperidinate was dried at 70–75° *in vacuo* to constant weight. Loss of weight was 241.4 mg. (25.79%). Calc'd for piperidine in the piperidinate, 26.57%.

The dried sample melted at 93–95° and analyzed for pure III. Further recrystallization from ethyl acetate or chloroform did not alter the melting point.

Anal. Calc'd for $C_{14}H_{21}NO_2$: C, 71.45; H, 9.00; N, 5.95.

Found for III: C, 71.28; H, 8.78; N, 5.65.

3-Phenyl-3-morpholino-1,2-propanediol (IV). By using morpholine in a similar procedure to that described above, IV was obtained in 31% yield, m.p. 90–92°. The product was isolated by extracting the reaction mixture with ether. The pure sample, after recrystallizing twice from ethyl acetate, melted at 96–97°.

Anal. Calc'd for $C_{13}H_{19}NO_3$: C, 65.80; H, 8.07; N, 5.90.

Found: C, 65.76; H, 8.17; N, 5.99.

Method B. A 0.01-*M* dry ether solution of XI or XII was added to an ether solution of lithium aluminum hydride (0.01 *M*) with stirring. The mixture was heated gently under reflux for two hours and the excess reducing agent destroyed by the dropwise addition of water (5 ml.). The ether solution was separated by decantation, dried, and evaporated under reduced pressure to give the diol, III m.p. 94–96° (60% yield), or IV m.p. 90–92° (53% yield), respectively. The pure samples were also obtained by recrystallization from ethyl acetate or chloroform. In each case, a mixed melting point with the diol prepared as in *Method A*, showed no depression; whereas a mixed melting point with the starting ester showed 10 to 15 degrees depression.

1,1,3-Triphenyl-3-piperidino-1,2-propanediol (XV). A 2.77-g. sample of ester XI (0.01 mole) in 75 ml. of dry ether was added slowly to a Grignard solution prepared from 1.44 g. (0.06 atom) of magnesium and 9.42 g. (0.06 mole) of bromobenzene in 100 ml. of dry ether. The mixture was then heated gently under reflux for two hours and decomposed with ammonium chloride and ice. The ether layer was separated, washed with water and dried over calcium sulfate. Evaporation of this solution under reduced pressure gave a semi-solid residue which crystallized on the addition of 10 ml. of absolute ethanol; 2.5 g., m.p. 170–173° (65% yield). A mixture with a sample of XV prepared from the reaction of α-hydroxy-β-piperidinobenzylacetophenone and phenylmagnesium bromide (12), was found to melt at 172–174°.

1,1,3-Triphenyl-3-morpholino-1,2-propanediol (XVI). By using a similar procedure XVI was prepared in 83% yield, m.p. 185.5–189°, from ester XII. Recrystallization from absolute ethanol gave pure XVI, m.p. 192–193°.

Anal. Calc'd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99.

Found: C, 77.41; H, 7.20.

A well-pulverized sample of α-hydroxy-β-morpholinobenzylacetophenone (12) (0.01 mole) was reacted with 0.04 mole of phenylmagnesium bromide. The reaction mixture was treated and the product isolated as usual to give 0.7 g. of XVI, m.p. 190–192°, and 0.6 g. of the unreacted starting material, m.p. 154–156°, together with some unidentified oily products. A mixed melting point of XVI with the sample prepared from ester XII showed no depression.

SUMMARY

1. 1-Phenyl-2-bromo-1,3-propanediol has been found to react with the amines, morpholine and piperidine, to yield 3-phenyl-3-*tert*-amino-1,2-propanediols.

2. α-Bromo-β-hydroxy-β-phenylpropionic acid has been found to react with the same amines to give the α-hydroxy-β-amino-β-phenylpropionic acids. The β-morpholino acid was identified as its morpholine salt. The acids were converted to the corresponding ethyl α-hydroxy-β-amino-β-phenylpropionates. Reduction of such esters with lithium aluminum hydride gave the same diols as prepared by the aforementioned method.

3. The assignment of the position of the amino group in the above compounds to the carbon holding the phenyl group has been based upon the syntheses of the 1,1,3-triphenyl-3-*tert*-amino-1,2-propanediols through reaction of the ethyl α-hydroxy-β-amino-β-phenylpropionates with phenylmagnesium bromide. The structure of such diols has been established by Cromwell and Starks (11).

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

BEHAVIOR OF 10,11-UNDECYLENIC ACID ON AIR-OXIDATION AT 80°

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In contrast to naturally occurring acids, 10,11-undecylenic acid represents a relatively simple example of an unsaturated fatty acid. As such it is a nearly ideal subject for oxidation studies since reaction with oxygen would give rise to easily recognizable compounds as contrasted to the complex mixtures resulting, for example, from linoleic and linolenic acids. This investigation was undertaken to explain the changes occurring during thermal oxidation of undecylenic acid and the observed saponifiable component found in stored samples of this compound.

It has been well established that to a large extent oxygen attack during thermal oxidation of fatty material occurs at the double bond. Atherton and Hilditch (1) and Lewis and Quackenbush (2) have obtained evidence that peroxides formed at 20–40° are not identical with those formed at 100–120°. Presumably the peroxides formed at the lower temperatures are α-hydroperoxides as shown by Farmer and Sundrailingham (3). At elevated temperatures, it is possible that peroxide groups are formed directly at the double bond. In addition, ketohydroxy and hydroxy compounds have been observed and isolated from thermally-oxidized fatty materials. The formation of dihydroxystearic acid and epoxystearic acid from the reaction between methyl hydroperoxyoleate and oleic acid has been observed by Swift and Dollear (4). Gillam (5, 6, 7) has found that extensive formation of hydroxyl groups occurs during the auto-oxidation of oils. Furthermore, he found a significant increase in the free carboxyl content resulting from cleavage at the double bond and has reported, from analytical data, the presence of esters resulting from the reaction of these hydroxy and carboxy products.

Although several unsaturated aldehydes have been identified in auto-oxidized cottonseed oil (8), no evidence has been found for aldehyde production in thermally-oxidized fatty materials. This is not surprising since aldehydes would represent an intermediate oxidation state under such conditions.

A mechanism for direct oxygen attack at the double bond has been proposed by Skellon (9).

The results of the analyses for neutral equivalent, saponification equivalent, and iodine number for a group of samples of undecylenic acid which were stored under various conditions are given in Table I. These data indicate that a saponifiable component is present in stored commercial samples and also in those samples of pure or recently obtained commercial undecylenic acid which were exposed to air at elevated temperatures. However, in the presence of nitrogen only a slight indication for such a component was obtained. Furthermore, it is

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apparent from Table I that the decrease in the iodine number follows closely the increase in the neutral equivalent.

It was this indication of a saponifiable component in stored samples of undecylenic acid, and the fact that the same changes could be produced on pure acid by exposing it to air for comparatively short periods of time at 80°, that prompted this investigation. The work to be described shows that the reactions between air and undecylenic acid at 80° occur almost exclusively at the site of unsaturation and that formation of peroxides is of little significance within the limits of our observations. Molecular weight growth by esterification between carboxyl and epoxy groups and the formation of free carboxyl groups by oxidative cleavage accounts for most of the observed decrease in unsaturation.

The changes occurring on oxidation of undecylenic acid were induced by subjecting the acid at 80° in a constant-temperature oven to a continuous stream of dry, carbon dioxide-free air and withdrawing samples at periodic intervals for

TABLE I

ANALYSES OF UNDECYLENIC ACID SAMPLES

SAMPLE		NEUTRAL EQUIVALENT	SAPONIFICATION EQUIVALENT	IODINE NUMBER
Stored commercial (1–2 years old)	(A)	203.8	191.4	129.8
	(B)	202.0	188.8	133.0
	(C)	198.0	190.3	132.3
Recent commercial		195.7	192.0	129.8
	[a]	196.5	190.1	129.5
	[b]	222.0	180.5	105.9
Pure undecylenic acid		184.0	188.1	134.9
	[a]	184.8	187.1	136.9
	[b]	227.2	183.5	88.8

[a] Maintained for 17.5 days at 80° in a nitrogen atmosphere.
[b] Maintained for 17.5 days at 80° in air.

analysis. Analyses were made for unsaturation, peroxide, neutral equivalent and for the amount of carboxyl formed by oxidative cleavage. The latter values were determined by measuring the difference between the theoretical neutral equivalent for undecylenic acid and the saponification equivalent for the oxidized sample and were calculated as moles of sebacic acid formed per mole of undecylenic acid. It seemed likely that sebacic acid would account for the majority, if not all, of the carboxyl formed by oxidative cleavage since carbon dioxide was the only gaseous product detected and since sebacic acid was found in appreciable amounts in the oxidized undecylenic acid. The data obtained from these analyses are plotted in Fig. 1 on a mole *per* mole basis (*e.g.*, moles of unsaturation lost per mole of undecylenic acid present). Analyses for epoxide oxygen are not plotted since a maximum of only 1.5% calculated as epoxyhendecanoic acid was found after 44 hours.

Inspection of Fig. 1 shows that the three main reactions with oxygen at 80°

are decrease in unsaturation, scission at the double bond, and molecular weight growth. If the sum of the values for the latter two reactions are plotted, a curve is obtained which fits the unsaturation decrease curve reasonably well. From the small amount of peroxide and epoxide formed, it can be assumed that under the conditions of this experiment the contribution to the molecular weight and to unsaturation decrease from these factors is slight. It is interesting to note that the peroxide formed is rapidly destroyed by heating the oxidized acid sample under nitrogen. This behavior parallels that observed by Swift and Dollear (4) for the reaction between methyl hydroperoxyoleate and oleic acid. The relatively large amounts of carboxyl acidity developed appears to be due to direct oxygen attack at the double bond and seems to be rapid since neither peroxide nor epoxide is formed in sufficient quantity to account for it. Some reactions, although

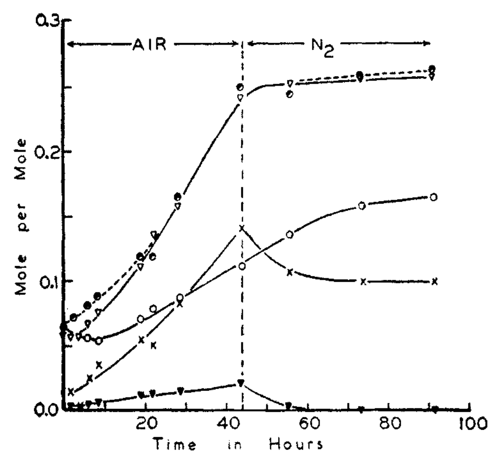
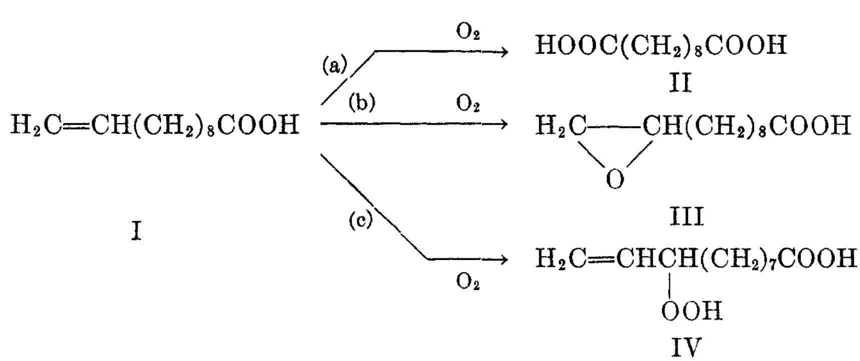


FIG. 1. COURSE OF THERMAL OXIDATION OF 10,11-UNDECYLENIC ACID. Open triangles indicate decrease in unsaturation; open circles, increase in neutral equivalent; crosses, sebacic acid content; closed triangles, peroxide content; half closed circles represent the summation of the sebacic acid content and the increase in neutral equivalent.

others are not excluded, which could be postulated for the observed behavior would be as follows:

1.



2. $$IV + I \rightarrow II + H_2C{=}CHCH(CH_2)_7COOH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad |$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad OH$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad\quad V$$

3. $$I + III \rightarrow HOOC(CH_2)_8CHCH_2OC(CH_2)_8CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |\qquad\quad ||$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad OH\qquad O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad VI$$

4. $$I + V \rightarrow HOOC(CH_2)_7CHO{-}{-}C(CH_2)_8CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\quad |\qquad\quad ||$$
$$\qquad\qquad\qquad\qquad\quad HC{=}CH_2\quad O$$
$$\qquad\qquad\qquad\qquad\qquad VII$$

5. $$I + VI \rightarrow HOOC(CH_2)_8CHCH_2OC(CH_2)_8CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad |\qquad\quad ||$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad OC(CH_2)_8CH{=}CH_2$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad ||$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\quad O$$
$$\qquad\qquad\qquad\qquad\qquad\qquad\qquad VIII$$

Although very little of VII and VIII would be anticipated, these reactions represent tbe most likely routes to the plausible esters, VI, VII and perhaps to some diester, VIII. The esters so produced would account for the increase in molecular weight and some of the decrease in unsaturation. Reaction between epoxide and carboxyl as in reaction 3 has been shown to go readily by Swern, Billen, and Eddy (10) and by Nicolet and Poulter (11) for 9,10-epoxystearic acid to give principally linear polymers. This same reaction was observed by the authors during several attempts to prepare 10,11-epoxyhendecanoic acid. Failure to detect appreciable amounts of epoxide in samples of thermally-oxidized undecylenic acid can be interpreted on the basis that reaction 3 is rapid in comparison to reaction 1 (b) and therefore the latter reaction is the rate-controlling step.

It seemed likely that IV might be an intermediate in the formation of III. Farmer and Sundrailingham (3) have demonstrated that the decomposition of α-hydroperoxide, either at elevated temperatures or by prolonged standing at lower temperatures, gave rise to epoxides. This would indicate that if peroxides were formed during thermal oxidation they would readily react, at elevated temperatures, with unsaturated centers to give secondary products such as ketols, epoxides, α-hydroxy acids, and carboxylic acids by addition to and scission of the double bond. In addition to these recognizable products, oxygenated polymers have also been observed. To obtain confirmatory evidence for the intermediate production of epoxide, a sample of methyl undecylenate was subjected to the same conditions of thermal air-oxidation as were used for the acid. Analyses were made for epoxide, unsaturation, and carboxyl. Results from this experiment are plotted in Fig. 2.

As expected for methyl undecylenate, epoxide oxygen was formed to a significant extent accompanied by cleavage and reduced unsaturation. With the exception of epoxide formation, the curves of Fig. 2 for methyl undecylenate resemble those for undecylenic acid in Fig. 1. As in the experiments with undecylenic acid, relatively small amounts of peroxide were found again showing a minor contribution to molecular weight increase and unsaturation decrease from this source. A high epoxide level would be expected in a low carboxyl environment, since reaction between these two groups would not occur. Appreciable cleavage is indicated by the curve for free methyl hydrogen sebacate. The presence of such carboxyl groups means that the amounts of epoxide and carboxyl found analytically are significantly lower than actually formed during oxidation. This is due

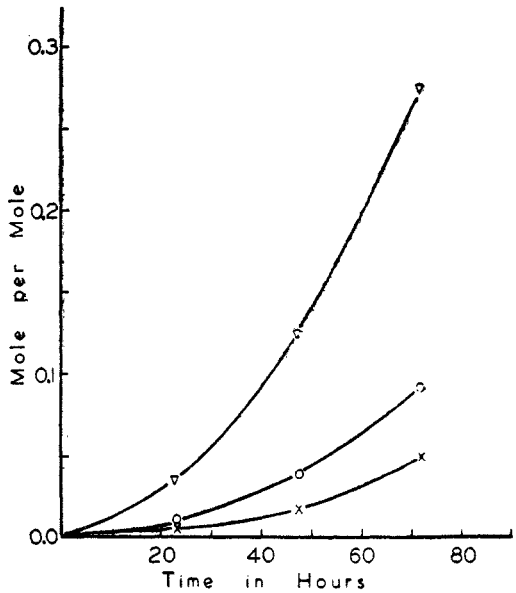


FIG. 2. COURSE OF THERMAL OXIDATION OF 10,11-METHYL UNDECYLENATE. Triangles indicate decrease in unsaturation; crosses, methyl hydrogen sebacate content; circles, epoxide content.

to the reaction of these groups with each other to give hydroxyl esters as in reaction 3 above. In agreement with this, the values for the methyl hydrogen sebacate curve in Fig. 2, when added to those for the epoxide curve, do not coincide with the unsaturation decrease curve.

As in the case of undecylenic acid, carbon dioxide was the only volatile oxidation product detected in the oxidation of methyl undecylenate. This also suggests that methyl hydrogen sebacate is one of the products of this oxidation. Additional proof that this half ester was the main product of oxidative cleavage was obtained in another experiment in which methyl undecylenate was thermally oxidized in the same way for 100 hours. After this time, the acidity as determined by titration with standard alkali and calculated as methyl hydrogen sebacate

amounted to 9.6%. This acid fraction was then extracted from the mixture with dilute aqueous alkali, which gave 8.9% of an oil having a neutral equivalent of 246 (theory for methyl hydrogen sebacate is 216). Saponification of this half ester gave sebacic acid. The data from this experiment and the results shown in Fig. 2 indicate that the reactions 1 (b) and 3 are highly probable. It cannot be established under these temperature conditions whether these are the actual routes taken, or whether as Farmer (3) suggests, peroxides are necessary to the formation of epoxides and scission at the double bond.

In order to establish further that the mechanism of the thermal oxidation of undecylenic acid involves reactions 1(b) and 3, the high-molecular weight com-

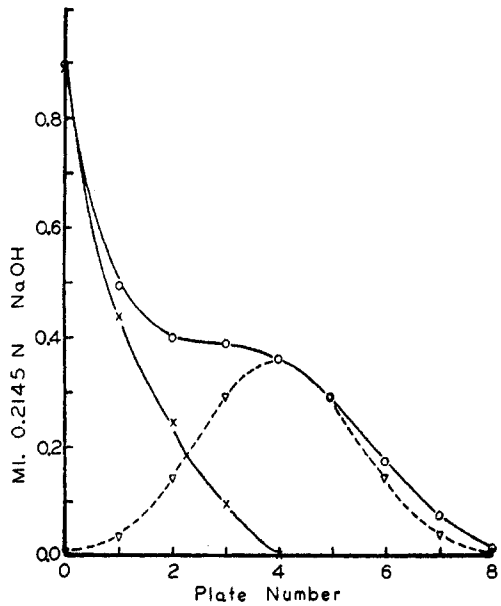


FIG. 3. DISTRIBUTION CURVE FOR FRACTION CONTAINING 10,11-DIHYDROXYHENDECANOIC ACID. Circles indicate the experimental distribution curve; triangles, a theoretical curve for a constant of unity; crosses, calculated curve for impurity present with dihydroxyhendecanoic acid.

ponent from an oxidized sample of this acid was isolated and analyzed. A sample of undecylenic acid which had been aerated at 80° for 7 days was extracted with petroleum ether. This operation, which is similar to that used by Szent-Györgyi (12) and Gillam (6), separated the oxidized undecylenic acid into soluble and insoluble fractions. The ether-insoluble fraction, amounting to 36% of the weight of oxidized sample taken, was found to be homogeneous to further extraction with petroleum ether and had a neutralization equivalent of 310 and an iodine number of 66. This petroleum ether extraction affected only a qualitative separation of the oxygenated material, since the neutral equivalent of the ether-soluble fraction was 264 (theory for undecylenic acid is 184).

The ether-insoluble fraction (neutral equivalent, 310) was saponified with

caustic, reacidified, and again extracted with petroleum ether. The ether-soluble fraction amounted to 33% of the sample and consisted almost entirely of undecylenic acid. The petroleum ether-insoluble fraction from the saponification was subjected to a nine-plate countercurrent distribution using the system ethyl ether/40% methanol-water. The results of this distribution are shown in Fig. 3. The material in plates 4 to 8 was shown from its neutralization equivalent, melting point, and mixed melting point to consist of nearly pure 10,11-dihydroxyhendecanoic acid. From the experimental curve in Fig. 3, the distribution coefficient of this compound in plates 4 to 8 was calculated and was found to be close to that observed for the pure dihydroxy acid. From the theoretical distribution curve, also shown in Fig. 3, it was deduced that dihydroxyhendecanoic acid would account for nearly 46% of the petroleum ether-insoluble fraction from the saponified material.

The remainder of the ether-insoluble fraction of the saponified material, which was in plates zero to three, was isolated as a viscous oil, and had the neutral equivalent 172 and iodine number 39. Negative tests for both epoxide and carbonyl groups were obtained and uncrystallizable oils were produced in several attempts to prepare ester derivatives. However, oxidation with alkaline potassium permanganate gave a mixture of dibasic acids which was shown to consist principally of azelaic and sebacic acids. These observations together with the solubility of the sample and the color change observed during the saponification step suggested that this fraction consisted of an aldol type condensation product which was produced from ketonic oxidation products during the saponification. This would require the formation of ketonic oxidation products from undecylenic acid, possibly through a heat-induced rearrangement of epoxide, as observed by Nicolet and Poulter for epoxystearic acid (11). Although the presence of carbonyl groups in the various fractions of oxidized undecylenic acid could not be detected by any of the standard reagents, it is possible that comparatively unreactive ketonic groups similar to those found in ketols were present. A similar anomaly has been noted by Gunstone and Hilditch (13). The behavior of this material closely resembles the polymeric residue from the catalytic air oxidation of methyl oleate encountered by Swern, *et al.* (14).

EXPERIMENTAL

PREPARATION OF MATERIALS

Undecylenic acid. Commerical acid was distilled and the fraction of b.p. 152–154° at 7.5 mm. was fractionally crystallized from petroleum ether. (All petroleum ether used was the 60–70° fraction.) The material melting at 24–25° was used as pure 10,11-undecylenic acid. Iodine number, 135; neutral equivalent, 184. (Theoretical values 138 and 184, respectively.) Commerical acid was used where indicated.

Methyl undecylenate. Commercial undecylenic acid was esterified by refluxing 100 g. of the acid with 500 ml. of methanol containing 2% of sulfuric acid for 6 hours. The fraction that distilled at 121.5–123° at 11.5 mm. was obtained in 81% yield and had the iodine number 125 and saponification equivalent 200. Theoretical values, 128 and 198, respectively.

10,11-Dihydroxyhendecanoic acid. The procedure of Findley, *et al.* (15) was followed using glacial acetic acid instead of 98–100% formic acid. An improvement over that used by Findley, *et al.* was found for recrystallizing this compound. The crude reaction product

was dissolved with vigorous stirring in the minimum amount of acetone and then filtered. Petroleum ether was added slowly to the appearance of permanent cloudiness. The solution was cooled to 0° and centrifuged. A fine powder was obtained which dried easily with little or no caking. After this crystallization, the product melted at 83–85° and had the neutral equivalent 214 (Theoretical, 218).

THERMAL OXIDATION OF UNDECYLENIC ACID

Commercial acid (25 g.) was placed in an 8″ Beckman tube which was fitted with a sintered-glass inlet tube and an outlet tube. This apparatus was held at 80° in a constant-temperature oven and dry, carbon dioxide-free air was passed through the sample at the rate of approximately 1.5 liters per hour. After 44 hours the air stream was exchanged for nitrogen for an additional 48 hours. Samples were withdrawn at intervals for analysis. The peroxide content was determined by the method of Wheeler (16). Iodine numbers were obtained by the Hanus method (17) and the epoxide content was determined as described by Swern, *et al.* (18). Neutral equivalents were obtained by titrating 200-mg. samples in 95% ethanol with standardized 0.2 *N* sodium hydroxide. Saponification equivalents were measured by refluxing weighed samples for 30 minutes with excess 0.5 *N* potassium hydroxide and back-titrating with standardized 0.2 *N* sulfuric acid.

The air, emerging from the sample, was passed through dilute aqueous barium hydroxide solution. A precipitate formed showing carbon dioxide present. Aliquots of the solution were acidified and titrated hot with standard permanganate. This test for formic acid was negative. An additional aliquot gave a negative test for formaldehyde when tested with chromotropic acid in concentrated sulfuric acid.

Another 100-g. sample of commercial undecylenic acid was subjected to the same oxidation treatment for a total of 7 days. This material (80 g.) was distilled rapidly at 1.5 mm. pressure and gave 14 g. which was shown to be pure undecylenic acid.

Petroleum ether-insoluble fraction. The residue of 65 g. from the above distillation was extracted in a separatory-funnel with three 100-ml. portions of petroleum ether. Forty-four grams of soluble material, neutral equivalent 264, and 21 g. of a yellow insoluble fraction, neutral equivalent 310 and iodine number 66, were obtained. An additional 7.5 g. of petroleum ether-insoluble material, neutral equivalent 307, was obtained by re-extracting the soluble fraction with three more 100-ml. portions of the solvent. The total insoluble fraction amounted to 36% of the original oxidized material, and was completely soluble in dilute sodium hydroxide, indicating the absence of any appreciable amount of neutral material in this fraction. Repeated solvent fractionation of this insoluble material with petroleum ether-ethyl ether mixtures did not appreciably change the neutral equivalent.

Undecylenic acid from petroleum ether-insoluble fraction. A 0.496-g. sample of the insoluble fraction was saponified with 5 ml. of 1 *N* alcoholic potassium hydroxide for one hour. This treatment caused the reaction mixture to turn orange-brown in color. After acidification with dilute hydrochloric acid, the mixture was extracted with three 30-ml. portions of petroleum ether. Removal of the solvent to constant weight gave 0.159 g. or 33% of an oil which solidified at 20°, had the neutral equivalent 187, and iodine number 118; the *p*-bromophenacyl derivative had m.p. 58–60°. Found for authenic *p-bromophenacyl undecylenate*, 59–60.5°.

10,11-Dihydroxyhendecanoic acid from petroleum ether-insoluble fraction. The material remaining after the extraction of the undecylenic acid in the previous step was taken up in three 30-ml. portions of ethyl ether. After drying to constant weight, the material weighed 0.328 g. and had the neutral equivalent 179 and iodine number 20.4. This material was submitted to a nine-plate countercurrent distribution employing the solvent system 40% methanol-water/ethyl ether. The transfers were made in 50-ml. separatory-funnels with the lower phase moving and 10 ml. of each solvent phase was used for each plate; 0.1231 g. of the ether-soluble fraction was distributed. The total plate contents after distribution were titrated with standardized 0.2 *N* sodium hydroxide. In this system the distribution

coefficient for pure 10,11-dihydroxyhendecanoic acid is 0.95 and the experimentally determined value from Fig. 3 is 1.0 as calculated by the method of Williamson and Craig (19). From the experimental curve it was calculated that the sample contained 46% 10,11-dihydroxyhendecanoic acid.

After titration the contents of plates 4 to 7 were combined and the ether, methanol, and most of the water was removed under a vacuum until a volume of 15 ml. remained. After acidification to litmus the solution was extracted with five 10-ml. portions of ethyl ether. After evaporating the ether extracts to dryness, 34 mg. of a white solid (m.p. 72–78°, neutral equivalent, 222) was obtained. A large scale countercurrent distribution was carried out in the same manner on 3.5 g. of the saponified fraction of the petroleum ether-insoluble material. In this case 100-ml. volumes of the solvent phases were used. Plates 4 to 7 gave after three crystallizations 0.55 g. of the same white material, m.p. 84–85°, mixed melting point with pure 10,11-dihydroxyhendecanoic acid gave no depression; the *p*-bromophenacyl ester had m.p. 103–105°. (Found for authenic 10,11-dihydroxyhendecanoic acid ester, m.p. 104–106°.)

Material in plates 0 and 1. The isolation method used for the material in Plates 4 to 7 was repeated on Plates 0 and 1. From the large scale distribution, 1.2 g. of material having the neutral equivalent 172 and iodine number 39 was obtained. No reaction was observed with periodic acid, sodium bisulfite, or 2,4-dinitrophenylhydrazine which indicated the absence of adjacent hydroxy, epoxy, and carbonyl groups. Oxidation of 1.0 g. of this fraction with alkaline potassium permanganate according to the directions given in Shriner and Fuson (20) gave a solid having the neutral equivalent 97. This solid was twice crystallized from water and yielded 0.2 g. of a crystalline material, m.p. 129–131°, mixed m.p. with sebacic acid gave no depression. An ether extraction of the mother liquor gave 0.48 g. of a solid which after three crystallizations from water had m.p. 93–99° and neutral equivalent, 90. Further recrystallization was impractical so the material was converted to the *p-bromophenacyl ester* (m.p. 130–132°); a mixed m.p. with authenic *p-bromophenacyl azelate* showed no depression.

THERMAL OXIDATION OF METHYL UNDECYLENATE

The ester (21 g.) was oxidized in the same way as was undecylenic acid. No nitrogen was used in this experiment. In addition to analyses for epoxide and unsaturation, the acidity developed during oxidation was determined by titration by standard alkali and calculated as methyl hydrogen sebacate.

A second sample of 10.5 g. was oxidized for 100 hours with air. After this time, an acidity which amounted to 9.6% when calculated as methyl hydrogen sebacate was developed. The oxidized ester was dissolved in 50 ml. of ethyl ether and extracted three times with 10-ml. portions of 5% sodium hydroxide. The alkaline extracts were combined, washed twice with ether, and acidified with dilute sulfuric acid. The insoluble oil formed was extracted with ethyl ether and when the ether was evaporated, 0.87 g. of an oil having the neutral equivalent 247 was obtained. (Theoretical neutral equivalent for methyl hydrogen sebacate is 216.) Saponification of 0.35 g. of this oil with excess potassium hydroxide gave 0.27 g. of a solid (m.p. 95–111°, neutral equivalent 111, *p*-bromophenacyl ester m.p. 144–146°, mixed m.p. with authenic *p-bromophenacyl sebacate* gave no depression).

Acknowledgment. The authors gratefully acknowledge the financial assistance of the J. H. Wallace Research Fund. Also, we wish to thank the Decyl Pharmacal Company for supplying some of the chemicals used in this investigation.

SUMMARY

Samples of 10,11-undecylenic acid which were oxidized at 80° in the presence of air showed a decrease in unsaturation, the presence of saponifiable material, an increase in carboxyl content, and small amounts of epoxides and peroxides.

Products resulting from this attack have been identified as sebacic acid, 10,11-dihydroxyhendecanoic acid, and some polymeric material.

The sebacic acid arises from oxidative cleavage at the double bond.

The 10,11-dihydroxyhendecanoic acid, present in the oxidized undecylenic acid as high-molecular weight ester, apparently resulted from the reaction of epoxide and carboxyl groups.

The polymeric material was isolated after saponification of the high-molecular weight ester fraction. This material may have arisen from aldol type condensations of keto oxidation products.

The presence of very little peroxide in oxidized undecylenic acid suggests that this type of compound is either not formed or if produced, it must react readily to give other oxidation products.

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CORRECTIONS AND ADDITIONS

Ammoniatriacetic acid (*"triglycine"*). The use of the term "triglycine" (1) to represent glycine-N,N-diacetic acid, $N(CH_2COOH)_3$, (I) has been criticised (2) on the basis that it has been widely used as the name of the tripeptide: $H_2NCH_2CONHCH_2CONHCH_2COOH$ (II). A preliminary search of Beilstein and of Chemical Abstracts revealed no such usage, although diglycylglycine is employed in place of glycylglycylglycine for this tripeptide, and triglycylglycine seems to be preferred as a more convenient form in place of glycylglycylglycylglycine. In current literature the term triglycine has been employed for the polypeptide by a number of workers (3, 4). On the other hand triglycine has been used previously for the amino acid (I) (5).

To avoid the ambiguity that has thus resulted the authors suggest the name ammoniatriacetic acid for the chelating agent (I) in question. In view of the analogous and widely-used term ethylenediaminetetraacetic acid, this is considered more meaningful than the previously employed names: Nitrilotriacetic acid, trimethylamine-α, α', α''-tricarboxylic acid, triglycolamic acid, and triglycine.

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After publication of this paper, Dr. Gauthier advised us of his results, abstracted only in highly condensed form (1), which agree with ours. His rather extensive work (2) was evidently carried out and published simultaneously with ours (3). It consists in the preparation of pure *cis*- and *trans*-4-*n*-propylcyclohexanols, the corresponding ketone, and numerous derivatives of these substances. Constants determined for the pure ketone and the isomeric alcohols agree with those reported by us. Dr. Gauthier has also observed the hydrogenolysis reaction which accompanies the hydrogenation of the nucleus or the carbonyl group. His crude alcohol mixtures, like ours, contained impurities as judged by their physical constants.

(1) *Chem. Abstr.*, **40**, 3732, 4362, 4364 (1946).
(2) GAUTHIER, *Ann. chim. phys.*, **20**, 581 (1945); *Compt. rend.*, **217**, 28 (1943); **218**, 595, 650 (1944).
(3) UNGNADE AND LUDUTSKY, *J. Org. Chem.*, **10**, 620 (1945).

"An Improved Synthesis of DL-Glyceraldehyde," William F. Gresham and William E. Grigsby, *J. Org. Chem.*, **14**, 1103 (1949). Add "Contribution from the

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"N-2-Pyridylalkanolamines and Esters," Nathan Weiner and Irving Allan Kaye, *J. Org. Chem.*, **14,** 868 (1949). Page 871, Table III, compound Id A, the *picrate*, $C_{27}H_{23}N_5O$ should read $C_{27}H_{23}N_5O_9$; compound Ie A, the *picrate*, $C_{29}H_{25}N_5O_1$ should read $C_{29}H_{25}N_5O_{11}$.