[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ON 1,2 AND 1,4 ADDITION.[1] IV. NITROGEN TETROXIDE AND ISOBUTYLENE

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Ssidorenko[2] found that nitrogen tetroxide acted upon isobutylene in ether solution to yield a small amount of the so-called bis-(isobutylene nitrosate), $[(CH_3)_2C(ONO_2)C(NO)H_2]_2$(I) and, as the main product, a blue liquid, which gave a low yield of isobutylenediamine on reduction. Ipatieff[3] showed that the dimeric product (I) and potassium cyanide yielded potassium nitrate and β-cyanoisobutyraldoxime.* These products, analogous to those previously obtained by Wallach[4] from the corresponding isopentane derivative, established the structure of nitric ester I. We have confirmed this structure: sodium nitrate and α-nitroso-β-phenylsulfidoisobutane $[(CH_3)_2C(SC_6H_5)CH_2(NO)]$ are formed quantitatively on treating the nitric ester with sodium thiophenolate, and catalytic reduction yielded ammonia and β-hydroxyisobutylamine. But the composition of the blue oil is uncertain. Ssidorenko[2] obtained only a small yield of isobutylenediamine in the reduction, and Strack and Fanselow[5] could not experimentally confirm the result. This difference in experimental results led us to re-investigate the reaction and we have also endeavored to determine the chemical character of the main, complex, oily reaction product.

Pure nitrogen tetroxide (prepared from lead nitrate), distilled into a cold ether solution of isobutylene, yielded a bluish-green solution, from which nitric ester I did not separate. In petroleum ether the nitric ester appeared in variable yields (0 to 13.7 per cent.) and, although the

[1] Previous papers: (*a*) MICHAEL AND WEINER, *J. Am. Chem. Soc.*, **59**, 744 (1937); (*b*) MICHAEL AND CARLSON, *ibid.*, **59**, 843 (1937); (*c*) MICHAEL AND CARLSON, J. ORG. CHEM., **4**, 169 (1939). The mechanism of the tetroxide addition has been discussed in 1*b*.

[2] SSIDORENKO, *Zentr.*, **1907, I**, 399.

[3] IPATIEFF, *ibid.*, **1901, II**, 1201.

* The compounds named in this paper belong to the butyl series and are termed in accordance. These names are simpler and easier to connect with chemical structure than those founded upon the Geneva nomenclature, which unnecessarily complicates the chemical terminology of butyl and amyl derivatives. (A. M.)

[4] WALLACH, *Ann.*, **241**, 296 (1888).

[5] STRACK AND FANSELOW, *J. physiol. Chem.*, **180**, 153 (1928).

experimental conditions were reproduced as far as possible, consistent results could not be obtained. The results of typical experiments are given in Table I (see under Experimental). The nitric ester separated from the crude reaction product in experiment 7 in a yield of only 0.1 per cent., but, after the volatile portion of the product had been distilled at low pressure, the residual non-volatile oil deposited 6.2 per cent. of the ester. From the crude products in experiments 8 and 9, the dimeric nitric ester separated in yields of 6 and 7 per cent., respectively, but the filtrates deposited more of the ester on longer standing (total yields are given in Table I). These results show that the nitroso-nitric ester derivative of isobutane, in contrast to the corresponding derivative of isopentane,[1b] is slowly and incompletely deposited from the crude reaction product. However, under similar conditions, the oily product formed in ether solution did not deposit the nitric ester, even after removal, at low pressure, of the easily volatile blue oil. Under no conditions could appreciable amounts of the ester be isolated from the products formed in ether solution (experiments 1–6). Accordingly, the nitroso-nitric ester of isobutane, as of isopentane, appears in higher yields in petroleum ether than in ether solution; the maximum yield of the isopentane derivative was 28 per cent.,[1b] while the highest yield of the isobutane product was 13.7 per cent.

From the pasty reaction products formed in the absence of solvents (experiments 10–13), the bis-(nitric ester) was isolated in yields (7–12 per cent.) approximately the same as those obtained in petroleum ether (6–12 per cent.). While the yields of nitric ester I under comparable conditions (experiments 12 and 13) differed by 2 per cent., a change in temperature of 68° altered the yields only 4.6 per cent., (experiments 10 and 13), which shows that the course of reaction varies only slightly with moderate changes in temperature.

Nitrogen tetroxide, volatilized slowly at room temperature into a current of gaseous isobutylene, reacted with evolution of heat; the addition was accompanied by oxidation, as was shown by the presence of carbon dioxide in the effluent gas. No solid separated from the green oil obtained with the tetroxide at ordinary temperature in experiment 14. The nature of this green liquid could not be determined; reduction with zinc and acetic acid gave an inappreciable yield of basic product, which apparently consisted largely of hydroxylamine. At first, crystals were formed on the walls of the reaction tube, when the tetroxide was passed slowly through a tube heated to 210° and then into a current of isobutylene diluted with nitrogen, but a green oil also appeared, which soon dissolved the crystals initially deposited on the glass surface. From the green solution only a very small amount of nitric ester I could be isolated and, because considerable oxidation had occurred, the oily product was not examined.

TABLE I

PREPARATION OF ADDITION PRODUCTS

EXPT. No.	1[a]	2[b]	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]	10[j]	11[k]	12[l]	13[m]	14[n]
N_2O_4, g.	9	20.2	21.1	16.1	15.9	15.5	20	20.8	20.3	20.2	15.9	22.2	20.1	13.4
Isobutylene, g.	13.4	18.9	16.9	13.6	21.5	27.0	17	16	19.6	33.1	27.7	20.7	27.4	Excess
Solvent, cc.														
Ether	100	65	60	60	60	60								
Petrol							60	60	60					
Time, mins.		50	90	60	60	60	45	120	135	40	60	90	75	240
Temp., °C.	−10	−8	−12	−5	−9	−8	−7	−5	−5	−80	−10	−8	−12	40
Product, g.														
Bis-nitrate (I)								2	2.3	2.4	1.2	3.6	3.9	
Liquid (A)	14.0	34	31.1	26.1	28.0	27.2	32	26.8	26.0	22.8	24.9		28.8	24.6
Calc'd Yield	14.5	32.5	34.0	25.9	25.6	25.0	32.2	33.5	32.7	32.5	25.6	35.7	32.4	21.6
Dist. gave, g.														
Blue dist. (B)		9.8		11.7	15.0	11.4	3.5							
Residue (C)		22.8		12.9	11.0	13.8								
% Bis-nitrate							6.2	10.5	12.2	7.4	8.6	10	12	

[a] Zinc dust (12 g.) was added to 5 g. of A in 50 cc. of glacial acetic acid, excess acid was distilled *in vacuo*, the residue was made basic and then steam-distilled: the distillate required 15 cc. of *N* hydrochloric acid for neutralization, and, accordingly, contained, at maximum, 0.7 g. of isobutylenediamine. A similar reduction was made with zinc and hydrochloric acid and the steam-distillate required 6 cc. of *N* hydrochloric acid for neutralization; the neutral solution, evaporated to dryness *in vacuo*, gave 0.1 g. of unidentified solid.

[b] Oil B deposited no solid during 3 days at room temperature; 2 g. of B, added to a solution prepared from 0.5 g. of sodium, 20 cc. of methyl alcohol and 3 g. of thiophenol, gave no inorganic salt and, as the only identified organic product, 1 g. of diphenyl disulfide.

A portion of B (5.1 g.) was solidified at −80°; the centrifuged mixture yielded 3.4 g. of blue solid, which, crystallized from an ether-petrol solution at −80°, gave 2 g. of white solid. Washed with ether at room temperature, the solid turned blue and fused to a wax, which, pressed on tile, gave 0.05 g. of the bis-nitroso-nitro derivative of isobutane, m.p. 80–82°.

[c] A solution of 5 g. of C in 50 cc. of ether was extracted at 0° with a solution of 7 g. of sodium hydroxide in 75 cc. of water, and the aqueous solution was shaken with small portions of benzoyl chloride until acidic: the product (0.7 g.) was gummy and could not be identified.

Five grams of C and 7 g. of potassium cyanide in 50 cc. of methyl alcohol gave, during 24 hours, 4.6 g. of insoluble salts: solvent was distilled *in vacuo* from the filtrate, the residue was acidified and gave 2 g. of oily product which decomposed at room temperature.

[d] Oil C (mol. wt. calc'd for $C_4H_8N_2O_4$, 148; found 188.7) decomposed when distilled at low pressure (bath temperature, 50°).

[e] Oil C decomposed at low pressure (bath-temperature, 50°): 8.5 g. of crude C, treated with 12 g. of dimethylaniline, gave 4.5 g. of oily product (b.p. 155–165°), which could not be identified.

[f] Two grams of B, added to a solution prepared from 0.6 g. of sodium, 20 cc. of methyl alcohol and 3 g. of thiophenol, gave no inorganic salt and the organic product (1.1 g.) gave 0.6 g. of diphenyl disulfide as the only identifiable product.

[g] Oil A deposited 0.05 g. of impure nitric ester I, m.p. 102°. At low pressure, the filtrate evolved gas rapidly for 4 hours; when evolution of gas ceased, distillation

gave: (*1*) 3.5 g. of blue distillate and (*2*) a green residual oil, which deposited 2 g. of nitric ester I (m.p. 110–111°; mol. wt. calc'd for $C_4H_8N_2O_4$, 296; found 292). The filtrate (16.6 g. of green oil) could not be distilled at low pressure: 3 g. of the oil, added to a solution prepared from 1 g. of sodium, 25 cc. of methyl alcohol and 7 g. of thiophenol, gave 0.8 g. of inorganic salt (found Na, 29.7; mixture contained 42% of $NaNO_3$ and 58% of $NaNO_2$) and 2.6 g. of oil, from which 0.9 g. of diphenyl disulfide was isolated as the only identifiable product.

[h] Oil A deposited 1.5 g. of nitric ester I: the filtrate (21.8 g.) decomposed during low-pressure distillation.

[i] Oil A deposited 1.7 g. of nitric ester I: the filtrate (21 g.) was steam-distilled and gave: (*1*) 5.8 g. of blue and (*2*) 1.1 g. of green distillate; leaving 5.4 g. of viscous oil, which was not examined.

Oil *1*, added to a solution prepared from 1.8 g. of sodium, 30 cc. of methyl alcohol and 8.7 g. of thiophenol, gave 0.8 g. of inorganic salt (found Na, 30.57; 30.51%; mixture contained 55% of $NaNO_3$ and 45% of $NaNO_2$) and 4.4 g. of oil, which yielded 3.7 g. of distillate (*3*), b.p. 145–170° at 5 mm., leaving 0.3 g. of residue.

Chromic anhydride (1.5 g.) was added slowly to a solution of 1 g. of *3* in 15 cc. of hot glacial acetic acid; the solution was poured into ice-water and yielded 0.5 g. of product, m.p. 85–89°, from which 0.05 g. of diphenyl disulfone, m.p. 193–194°, and 0.2 g. of β-phenylsulfonyl-α-nitroisobutane, m.p. 89–90°, were isolated.

A solution of 2.7 g. of *3* in 20 cc. of glacial acetic acid was treated with 15 g. of 30% hydrogen peroxide in 25 cc. of acetic anhydride and, until the vigorous reaction subsided, the mixture was maintained at 35–40°. The mixture, kept at room temperature overnight, and poured into ice-water, gave 0.7 g. of β-phenylsulfonyl-α-nitroisobutane; m.p. 89–90° (*Anal.* Calc'd for $C_{10}H_{13}NO_4S$: C, 49.45; H, 5.35; N, 5.76; S, 13.15. Found C, 49.43; H, 5.44; N, 5.72; S, 13.60).

[j] The pasty reaction product was diluted with ether: the solid was removed by filtration, but began to decompose and was immediately suspended in ether at −80° and again filtered. The bis-(nitric ester) (I), centrifuged from a methyl alcohol suspension, melted at 117–118°. Solvent was distilled *in vacuo* from the ether filtrates; the residual oils, 12.8 g. and 10 g., respectively, decomposed violently within 3 minutes after isolation.

[k] Oil A, during 60 hours, deposited only a trace of solid. A solution of 20 g. of A in 50 cc. of glacial acetic acid, containing platinum oxide catalyst, absorbed 170 cc. of hydrogen during 6 hours. Catalyst was filtered off, the filtrate added to water; the oily product (13.7 g.) deposited 1 g. of nitric ester I.

[l] The reaction mixture was stored at 0° for 10 hours and the bis-nitric ester (I) filtered off: the filtrate (23.1 g. of green oil) decomposed rapidly.

[m] The reaction mixture was stored at 0° for 36 hours, ether was added, nitric ester I was removed by filtration; the solvent, distilled from the filtrate, left 28.8 g. of green oil. At low pressure, the oil (27 g.) gave: (*1*) 3.8 g. of blue distillate and and (*2*) 22.7 g. of green residual oil, which solidified to a glass at −80°. A solution of 17.7 g. of *2* in 50 cc. of glacial acetic acid containing platinum oxide catalyst absorbed only 10 cc. of hydrogen during 12 hours.

[n] The excess isobutylene contained carbon dioxide, and water appeared in oil A. An ether solution of A was washed with water, dried and the solvent distilled, gave 15.7 g. of green oil (*1*). One gram of dimethylaniline and 0.5 g. of *1* gave only an oily product. Five grams of *1*, reduced with 5 g. of zinc in 25 cc. of acetic acid, gave 0.2 g. of product as the hydrochloride, which gave a positive test for hydroxylamine by the Bamberger method. A solution of 3.7 g. of *1* in 3 vols. of ether, treated with 5 g. of anhydrous potassium carbonate and 5 g. of benzoyl chloride, gave 5 g. of red oil, which, as it decomposed on distillation, could not be identified.

The oil, which was separated from the pasty product in experiment 10, decomposed rapidly while still below room temperature. In experiment 12, too, the green oily product, although formed at −8°, decomposed violently after nitric ester I had been removed by filtration. Yet, the product formed under similar conditions in experiment 13 was stable and could be distilled at low pressure. It yieded an easily volatile blue, and a much less volatile green, viscous oil, which, like the crude product of experiment 11, could not be reduced catalytically.

Decomposition of the green liquid formed in petroleum ether solution in experiment 7 was brisk at room temperature; the liquid, contained in an all-glass distilling apparatus, evolved gas so rapidly for four hours that a pressure below 5 mm. could not be maintained. When the evolution of gas had ceased, distillation at low pressure separated the residue into a volatile blue, and a non-volatile green, oil, which, after separation of nitric ester I, was treated with sodium thiophenolate. The products, a mixture of sodium nitrate and nitrite and diphenyl disulfide, gave no insight into the composition of the oily addition product. During steam-distillation, about one-half of the oil from experiment 9 decomposed with evolution of brown fumes; the volatilized green, mobile oil yielded with sodium thiophenolate a mixture of sodium nitrate and nitrite and an organic product, which, on oxidation, gave β-phenylsulfonyl-α-nitro-isobutane. The sulfone was undoubtedly formed from the corresponding thio-ether, which, although the source is not definitely established,† probably was formed from α,β-dinitroisobutane; accordingly, the latter compound constituted at least 3 per cent of the crude addition product.

Although the liquid product formed in petroleum ether solution, or without solvent, decomposed easily, the product obtained in ether solution, could be distilled at low pressure, and yielded a volatile, blue, and a non-volatile, green oil. With sodium thiophenolate, the blue distillate (experiment 2) gave diphenyl disulfide as the only identifiable product, which gave no insight into the composition of the blue oil. However, this oil solidified at −80° to a blue mass, from which the adhering oil was centrifuged. The solid was crystallized from an ether-petroleum ether solution at −80° and gave a white solid, which, when washed with a few drops of ether at room temperature, changed to a waxy substance. From this wax a small amount of the poorly named, bis-(isobutylene pseudonitrosite), *i.e.*, $[(CH_3)_2C(NO_2)C(NO)H_2]_2$ (III), was isolated. The appearance of this product indicated that some nitrogen tetroxide had been reduced to the trioxide before the addition.

Catalytic reduction of the distilled blue oil in experiment 4 (Table II)

† The thio-ether may be derived from the nitro-nitrous or the nitroso-nitrous ester derivative of isobutane. The mechanism of the formation of the sulfide is not known, see 1*c*, footnote 11.

TABLE II

CATALYTIC REDUCTION OF ADDITION PRODUCTS

PRODUCT REDUCED			H_2 ABSORBED		PRODUCTS		
Oil	From expt.	g.	l.	Time, hrs.	NH_4Cl, g.	Fractions, g.	B.p., °C.
A	3[a]	31.1	14.1	24.1	5.1	1 Ether 2 3.3 3 0.7 4 2.9 5 1.8	35.2–35.5 Mainly ether Up to 140 140–160 180–200
B	4[b]	11.7	7.06	56	1.4	1 Ether 2 1.7 3 4.8	34–35.5 40–115 (mainly ether) 115–155
B	5[c]	15	10.2	71	1.8	1 Ether 2 3.7 3 5.8	34.5–35.3 60–100 (mainly at 60) 100–160 (mainly at 145–160)
B	6[d]	9.1	6.3	58	0.6	1 Ether 2 1.9 3 4.1	34.5–35.3 40–50 (mainly ether) 140–160 (mainly 150)
C	6[e]	13.8	9.2	85	3.1	1 Ether 2 1.1 3 3.2	34.8–35.3 Up to 60 (mainly ether) 145–195
Bis-nitrate I	7[f]	6.7	5.5	30	1.5	1 Ether 2 1.4 3 2.2 4 Residue	 Up to 145 145-155 (mainly at 152)

[a] Catalyst was removed by filtration; gaseous hydrogen chloride was bubbled into the filtrate; solvent was distilled *in vacuo*; an aqueous solution of the residue was extracted with ether (1.5 g. of unidentified oil, b.p. 90–92° at 20 mm. was extracted); the aqueous solution was evaporated to dryness *in vacuo*, and the residue, boiled in secondary butyl alcohol, dissolved 5.1 g. of ammonium chloride. Solvent was distilled *in vacuo* from the filtrate; the syrupy residue (11.7 g.) was made basic at 0°, and the ether extract was fractionated. Fraction 4 was refractionated and gave: (*6*) 1 g., b.p. up to 140°; (*7*) 1 g., b.p. 140–145° (mainly at 145°); (*8*) 0.5 g., b.p. 145–160°.

With *p*-nitrobenzoyl chloride (0.5 g.), 0.2 g. of *6* gave 0.7 g. of unidentified oil.

A portion of *7* (0.6 g.), with 3 g. of potassium hydroxide and 3 g. of toluenesulfonyl chloride, gave 1.2 g. of toluenesulfonyldiisobutylamide; m.p. 110–111°. (*Anal.* Calc'd for $C_{15}H_{25}NO_2S$: C, 63.55; H, 8.8; N, 4.95; S, 11.3. Found: C, 63.75; H, 8.95; N, 5.14; S, 10.95), identical with an authentic specimen. Diisobutylamine (0.5 g.; Kahlbaum preparation, b.p. 136–138°) gave 0.8 g. of the toluenesulfonamide, m.p. 110–111°.

[b] The syrupy hydrochloride extracted with boiling secondary butyl alcohol, yielded 0.6 g. of ammonium chloride: total amount isolated, 1.4 g. Distillate *1* and gaseous hydrogen chloride gave 0.3 g. of a solid hydrochloride; *2* gave 0.3 g. The combined salts and *p*-nitrobenzoylchloride gave 1.3 g. of crude product, yielding 1 g. of the *p*-nitrobenzoate of isobutylamine; m.p., 117–118°. (*Anal.* Calc'd for $C_{11}H_{14}N_2O_3$: C, 59.45; H, 6.3; N, 12.6. Found: C, 59.49; H, 6.07; N, 12.68).

An ether solution of *3* and gaseous hydrogen chloride gave a syrupy product (*4*): 0.5 g. of *4* and 0.9 g. of benzoyl chloride gave 0.6 g. of crude product, from which 0.15 g. of the pure benzoate of β-hydroxyisobutylamine (m.p. 104–105°; the benzoate, which did not depress the m.p. of *5*, was isolated. A portion of *4* (6.2 g.) was basidified, and the mixture was extracted with ether. The dried solution gave: (*5*) an ether distillate; (*6*) 2.1 g., b.p. 35–120° (mainly ether) and (*7*) 3.4 g., b.p. 120–150°. Combined *5* and *6* gave, with gaseous hydrogen chloride, less than 0.1 g. of a solid precipitate.

A portion of *7* (0.5 g.), 0.9 g. of sodium carbonate and 2.1 g. of *p*-nitrobenzoyl chloride, gave a product, which was fractionally crystallized from acetone, and gave 0.6 g. of *p*-nitrobenzoic anhydride; m.p. 192–193°. (*Anal.* Calc'd for $C_{14}H_8N_2O_7$: C, 53.15; H, 2.53; N, 8.86. Found: C, 53.10; H, 2.47; N, 9.27) and 0.7 g. of the *p*-nitrobenzoate of β-hydroxyisobutylamine; m.p. 137–138°. (*Anal.* Calc'd for $C_{11}H_{14}N_2O_4$: C, 55.45; H, 5.87; N, 11.75. Found: C, 55.57; H, 6.11; N, 11.76). The same yield (0.7 g.) of the *p*-nitrobenzoate of the amino alcohol (m.p. 137–138°) was obtained when 0.5 g. of *7* was treated with one molecular equivalent (1.1 g.) of the acid chloride.

[c] Fraction *1* and gaseous hydrogen chloride gave 1.2 g. of hydrochloride (*4*): 0.5 of *4* and 0.9 g. of *p*-nitrobenzoyl chloride gave 1.1 g. of the *p*-nitrobenzoate of isobutylamine, m.p. 117–118°. With 0.9 g. of benzoyl chloride, 0.7 g. of *4* gave an oil from which 0.3 g. of the benzoate of isobutylamine, m.p. 56°, was isolated [WINANS AND ADKINS, J. Am. Chem. Soc., **55,** 2051 (1935), state that the benzoate melts at 55°; ASANO AND KANEMATSU, *Zentr.*, **1931, II,** 1867, report 57°].

Fraction *2* and gaseous hydrogen chloride gave 0.6 g. of a solid, which, with 1.1 g. of *p*-nitrobenzoyl chloride, yielded 1.2 g. of oil, from which 0.7 g. of the *p*-nitrobenzoate of isobutylamine, m.p. 115–117°, was isolated.

Fraction *3* contained no appreciable amount of isobutylenediamine (*Anal.* Calc'd for $C_4H_{12}N_2$; $C_4H_{11}NO$: N, 31.8; 15.7. Found: N, 13.73).

A portion of *3* (0.5 g.) and 1.1 g. of *p*-nitrobenzoyl chloride gave 1 g. of crude product, which yielded 0.8 g. of pure *p*-nitrobenzoate of 2-hydroxyisobutylamine, m.p. 137–138°. With benzoyl chloride (0.8 g.), 0.5 g. of *3* gave 0.8 g. of crude product, which solidified almost completely, but, on recrystallization, yielded only 0.3 g. of pure benzoate of β-hydroxyisobutylamine (*5*); m.p. 104–105°. (*Anal.* Calc'd for $C_{11}H_{15}NO_2$: C, 68.4; H, 7.8; N, 7.25. Found: C, 68.12; H, 7.64; N, 6.92). A portion of *3* (0.5 g.) and 1.1 g. of toluenesulfonyl chloride gave 0.3 g. of toluenesulfonyldiisobutylamide, m.p. 108–109°, identical with that described in experiment 3.

[d] Fraction *3* was dissolved in 5 cc. of ether, and, on refractionation, gave: (*4*) 2.4 g., b.p. up to 120° and (*5*) 3.7 g., b.p. 145–160° (mainly at 150–152°).

Combined *1* and *2* gave, with gaseous hydrogen chloride, 0.9 g. of hydrochloride: 0.5 g. of the salt and 1.3 g. of *p*-nitrobenzoyl chloride gave 1.4 g. of crude *p*-nitrobenzoate of isobutylamine, from which 1 g. of the pure product, m.p. 116–117°, was isolated by fractional crystallization.

Fraction *4* and gaseous hydrogen chloride gave 0.2 g. of hydrochloride, which, with 0.4 g. of *p*-nitrobenzoyl chloride, gave 0.25 g. of pure *p*-nitrobenzoate of isobutylamine, m.p. 116°.

A portion of *5* (0.5 g.) and 1 g. of *p*-nitrobenzoyl chloride gave 1.3 g. of crude product, which yielded 1.1 g. of the *p*-nitrobenzoate of 2-hydroxyisobutylamine, m.p. 137–138°.

[e] Fraction *1* and gaseous hydrogen chloride gave 0.6 g. of a hydrochloride; fraction *2* gave 0.1 g. of solid. The combined salts (0.7 g.) and 1.9 g. of *p*-nitrobenzoyl chloride gave 1.1 g. of the *p*-nitrobenzoate of isobutylamine, m.p. 116–118°.

A portion of *3* (0.5 g.) and 2.1 g. of *p*-nitrobenzoyl chloride gave 0.8 g. of oily product which could not be crystallized. Analysis indicated that *3* was impure diisobutylamine (*Anal.* Calc'd for $C_8H_{19}N$: C, 74.5; H, 14.75; N, 10.85. Found: C, 72.81, 72.79; H, 14.08, 14.15; N, 10.70, 10.80). Camphorsulfonic acid (0.9 g.) and 0.5 g. of *3* gave a product which was fractionally crystallized from acetic ester and gave 0.5 g. of pure camphorsulfonate of diisobutylamine (*4*); m.p. 185° (*Anal.* Calc'd for $C_{18}H_{35}NO_4S$: C, 59.8; H, 9.7; N, 3.88. Found: C, 60.08; H, 10.0; N, 3.67). A portion of *4* (0.16 g.), added to a mixture of 0.1 g. of potassium hydroxide and 0.08 g. of *p*-toluenesulfonyl chloride in 7 cc. of water, gave (*5*) 0.09 g. of crude, *p*-toluenesulfonamide of diisobutylamine, m.p. 108–109°.

Diisobutylamine (0.5 g.; Kahlbaum preparation, b.p. 136–138°) and 0.9 g. of camphorsulfonic acid in 30 cc. of hot acetic ester gave (*6*) 1.2 g. of the camphorsulfonate of diisobutylamine; m.p. 185° (*Anal.* Calc'd for $C_{18}H_{35}NO_4S$: C, 59.8; H, 9.7; N, 3.88; S, 8.86. Found: C, 59.78; H, 9.77; N, 3.81; S, 9.11), identical with *4*. A hot solution of 0.3 g. of *6* and 0.1 g. of potassium hydroxide in 7 cc. of water, treated with 0.16 g. of *p*-toluenesulfonyl chloride, gave (*7*) 0.2 g. of crude toluenesulfonamide of diisobutylamine, m.p. 108–109°. This crude product did not depress the melting point of the toluenesulfonamide of experiment 3.

[f] Fraction *1* and gaseous hydrogen chloride gave 0.8 g. of a syrupy hydrochloride, which, with *p*-nitrobenzoyl chloride, gave 0.9 g. of crude product, yielding 0.7 g. of pure *p*-nitrobenzoate of β-hydroxyisobutylamine, m.p. 137°.

A portion of *3* (0.5 g.) gave, with *p*-nitrobenzoyl chloride, 1.2 g. of the *p*-nitrobenzoate of β-hydroxyisobutylamine, m.p. 138°.

Residue *4* was distilled over a free flame, and gave 0.7 g. of viscous distillate which, with *p*-nitrobenzoyl chloride, gave 1 g. of an unidentified oil.

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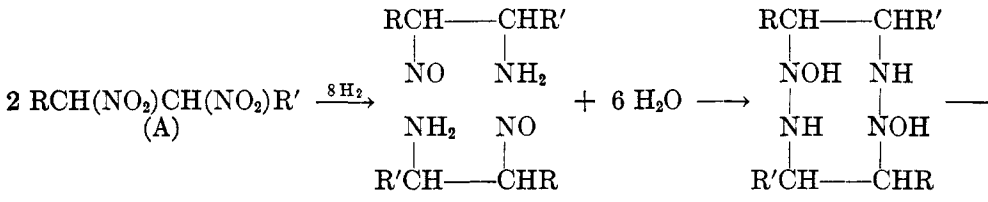
yielded ammonia, isobutylamine and β-hydroxyisobutylamine (IV). Similar results were obtained in experiments 5 and 6, but the relative yields of these products varied considerably. The yield of isobutylamine, probably formed largely from nitroisobutene, indicated that the blue liquids contained about 5, 10, and 12.6 per cent. of nitroisobutene, respectively, in experiments 4, 5 and 6. The divergence in the yields showed that the composition of the volatile addition product varied, but the differences may be partially attributed to the experimental difficulties involved in isolating and separating the reduction products. In experiment 5, the yield of ammonia is practically equivalent to that of the amino alcohol (IV); in 4 the yield slightly exceeded that of the amino alcohol, while the latter exceeded that of ammonia in experiment 6. This discrepancy in yields may be due to the difficulty of separating the products; the appearance of ammonia and the amino alcohol in approximately equimolecular amounts (experiments 4 and 5) suggests that these products

were derived from the α-nitro-β-nitrous ester derivative of isobutane, $(CH_3)_2C(ONO)C(NO_2)H_2$ (V). Although amino alcohol IV may have been formed from nitric ester I, or the corresponding nitroso-nitrous ester, $(CH_3)_2C(ONO)C(NO)H_2$ (VI), the first product could not be detected in the distilled blue oil. The bis-(nitric ester) (I) and sodium thiophenolate yielded sodium nitrate quantitatively, but the salt was not formed from the mercaptide and the distilled blue oils in experiments 2, 5, 6 and 7 (Table I) and the presence of an appreciable amount of nitroso-compound VI in the addition products, formed in a dilute, cold solution, seems improbable. Accordingly, nitrous ester V was probably the source of the amino alcohol; the yield of the latter product indicated that the crude addition products in experiments 4, 5 and 6 contained 16, 25, and 23 per cent., respectively, of this nitrous ester.

Isobutylenediamine could not be detected in the high-boiling product obtained by reduction of the distilled blue oil. The yield of crude *p*-nitrobenzoate of β-hydroxyisobutylamine in experiment 5 showed that the amino alcohol represented at least 75 per cent. of the high-boiling reduction product; this result and the analyses of the crude amino alcohol show that an appreciable amount of isobutylenediamine could not have been present. Nor was the diamine formed by catalytic reduction of the non-volatile green product; an oil which consisted mainly of monomeric addition products, as was shown by a molecular-weight determination (experiment 4) (mol. wt. calc'd for $C_4H_8N_2O_4$, 148; found, 188.7). Reduction of the non-volatile, green oil (experiment 6) gave ammonia, isobutylamine and a high-boiling liquid, which, although a complete purification was not realized, gave values on analysis corresponding closely to $C_8H_{19}N$. The amine was characterized as a secondary base by the insolubility of its acyl derivatives in alkali and was identified through the camphorsulfonate as diisobutylamine. Small amounts of this secondary amine were apparently present in the basic liquids obtained on reduction of the volatile blue products, but the yields were low and isolation succeeded only in experiment 5. The secondary base constituted 40–50 per cent. of the basic products obtained by reducing the crude blue oil in experiment 3 and at least 42 per cent. of the amines in experiment 6. The amine is formed from a slightly volatile addition product, and α,β-dinitroisobutane appears to be the source. Undoubtedly, the latter product was only incompletely separated from the more volatile oils by low-pressure distillation; accordingly, the yields of diisobutylamine obtained on reducing the distilled blue oils should have varied with the extent of separation of the volatile from the less volatile products. While the yield of the *p*-nitrobenzoate of β-hydroxyisobutylamine in experiment 5 indicated that the crude, high-boiling reduction product (fraction 3,

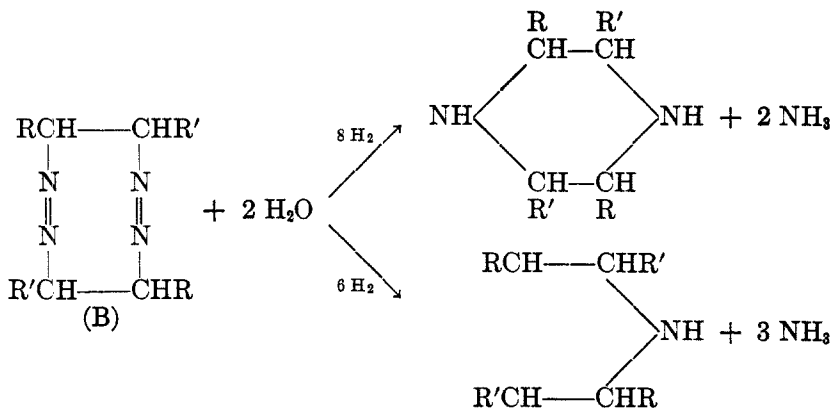
Table II) contained 75 per cent. of amino alcohol IV, the corresponding liquids in experiments 4 and 6 gave the *p*-nitrobenzoate in yields of 52 and 97 per cent., respectively. Accordingly, since the concentration of diisobutylamine in the reduction products in experiments 5 and 6 was relatively low, failure to isolate the base in experiment 6 may be attributed to the difficulty of separating the reduction products and their acyl derivatives. However, with a decrease in the yield of amino alcohol IV in experiment 4, no increase in the yield of the secondary amine was observed, nor could another basic product be isolated. The reason for this discrepancy in the relative yields of the reduction products is not clear. However, assuming that the diisobutylamine was formed from α,β-dinitroisobutane, the results would indicate that the latter compound constituted at least 17 and 12 per cent., respectively, of the crude addition products in experiments 3 and 6.

The formation of piperazine derivatives has been observed in the reduction of certain addition products of nitrogen tetroxide and alkenes,[6] and Demjanoff,[7] on reducing the product formed by the action of nitrogen pentoxide upon trimethylethylene, apparently obtained a secondary amine, although the yield was so low that positive identification could not be made. However, since no secondary amine appeared in the reduction of the products formed by the action of "nitrous fumes" upon trimethylethylene,[1c] the formation of diisobutylamine was not expected. This secondary amine is probably derived from α,β-dinitroisobutane (II), through reactions related to those through which certain vicinal dinitro compounds yield piperazines. At a certain stage of the reduction a nitroso-amino derivative of the alkane may appear and, if the fully and partially reduced groups can interact, the intermolecular reaction of two molecules may lead to a labile, tetranitrogen octacyclic derivative, which, upon further reduction, may yield a stable piperazine, or a secondary, aliphatic amine, according to the following formulations:



[6] DEMJANOFF [*Bull. soc. chim.*, **22**, 549 (1899); *Bull. Acad. Sci. USSR.*, **7**, 1123 (1931)] showed that the product formed by the action of nitrogen tetroxide upon butene-2 yielded a piperazine derivative when reduced with metal and acid. WIELAND [*Ann.*, **424**, 75 (1921)] found that, irrespective of the method of reduction, *sym*-diphenyldinitroethane yielded tetraphenylpiperazine.

[7] DEMJANOFF, *Annales de l'Institut Agronomique de Moscow*, **4**, 155 (1899).



Possibly derivative A may also yield a primary amine, and the appearance of isobutylamine in the above reductions would then be attributed to the reduction of α,β-dinitroisobutane; however, as the dinitro compound is only slightly volatile, the isobutylamine obtained by reducing the distilled, blue oils must have been formed largely from nitroisobutene. Whether reduction of the dinitro derivative A takes one or the other course undoubtedly depends upon the nature of the groups R and R'; α,β-dinitroisopentane gave the corresponding diamine in a yield of 87 per cent.,[1c] while dinitroisobutane gave mainly diisobutylamine.[8]

Indirect determinations of the yields of dinitro derivative III indicate that the crude addition products in experiments 9, 3, and 6 contained 3, 21, and 12 per cent., respectively, of the dinitro compound, but these estimated values are probably much lower than the actual yields and may approach 30–50 per cent. Other methods of determining the composition of the oily addition products were tried: although the oil dissolved almost completely in dilute alkali, treatment of the solution with benzoyl chloride gave only a small yield of insoluble, oily product (experiments 2 and 14); dimethylaniline apparently not only eliminated nitrous acid, but also underwent oxidation; potassium cyanide yielded products which decomposed very easily, and could not be identified (experiment 2); the non-volatile addition product and sodium thiophenolate gave mixtures, or very small yields, of inorganic salts and diphenyl disulfide as the only identified organic product (experiment 7). On reduction with metal and acid, the crude and the non-volatile green addition products (experiments 1 and 14) gave inappreciable yields of basic products. Although the chemical composition of the crude addition product could not be

[8] WINANS AND ADKINS [*J. Am. Chem. Soc.*, **55**, 2051 (1935)] observed the formation of this secondary base on reduction of isobutyraldimine (polymer), and attributed the formation to the elimination of ammonia in the condensation of the imino and amino derivatives postulated as intermediate reduction products.

definitely determined, the results indicate that nitroisobutane constituted about 10 per cent. of the crude product, that the α-nitro-β-nitrous ester and the α,β-dinitro derivatives of isobutane are the main constituents, and that the former compound probably represents about one-half of the addition product.

EXPERIMENTAL

General procedure.—Isobutylene, prepared by heating tertiary butyl alcohol with 10% hydrochloric acid, was passed through a trap and two large U-tubes, filled with potassium hydroxide pellets and cooled to 0°. The gas was then passed, at room temperature, through a tower charged with potassium hydroxide pellets, and was condensed in an all-glass ampoule, which was then sealed. The weighed, cooled ampoule was opened, and the butene was distilled slowly through a suitably arranged tube connected with the cooled reaction flask. Anhydrous nitrogen tetroxide, prepared from dry lead nitrate[1b], was similarly distilled into the reaction flask, arranged as previously described[1b]. The reactants were mixed in an all-glass system of concentric nozzles[1b] in the gas-phase reactions. Solvents were dried with phosphoric anhydride and distilled.

The solvent was distilled from the reaction product at reduced pressure after the crystalline bis-(nitric ester) (I), when present, had been removed by filtration. In experiments 10–13, made without solvent, the reaction products were diluted with ether, the bis-(nitric ester) (I) was removed by filtration, and the filtrates were treated as described in the notes to Table I. Low-pressure distillations were made in an all-glass apparatus at the pressure of a mercury vapor pump. A summary of typical experiments is given in Table I.

Action of sodium thiophenolate on nitric ester I.—Three grams of the nitric ester, added to a solution prepared from 0.7 g. of sodium, 25 cc. of ethyl alcohol and 3.6 g. of thiophenol, gave 1.6 g. of sodium nitrate (*Anal.* Calc'd for $NaNO_3$; Na, 27.06. Found: 26.96) and 4.2 g. of organic product, m.p. 80–84°, which yielded 3.8 g. of pure α-nitroso-β-phenylsulfidoisobutane; m.p. 86–87°.

Anal. Calc'd for $C_{10}H_{13}NOS$: C, 61.5; H, 6.66; N, 7.17; S, 16.4.
Found: C, 61.7; H, 6.66; N, 6.95; S, 16.04.

Catalytic reductions.—The products were reduced in glacial acetic acid (50 cc.) in the usual manner, using platinum oxide catalyst with hydrogen only slightly above atmospheric pressure. Catalyst was removed by filtration, and hydrogen chloride was bubbled into the filtrate. The precipitated ammonium chloride was removed by filtration (except in experiments 3 and 4, see footnotes), solvent was distilled from the filtrate *in vacuo*, the residue was made basic, and the mixture was extracted with ether. The dried ether solution was fractionated as shown in Table II. The basic product, or its hydrochloride, was acylated in the usual way, using benzoyl, *p*-nitrobenzoyl, or *p*-toluenesulfonyl chloride. The results are summarized in Table II.

SUMMARY

1. The action of nitrogen tetroxide on isobutylene has been investigated under varied experimental conditions.

2. In our experiments, the bis-(α,β-nitroso-nitric ester) derivative of isobutane did not separate from the addition product formed in ether

solution. Without solvent, liquid isobutene gave the bis-(nitric ester) in yields of 7–12 per cent.; in petroleum ether the yields varied more considerably (0–13 per cent.), although the experimental conditions were reproduced as far as possible.

3. The course of the reaction does not vary appreciably with moderate changes in low temperatures; the yields of the bis-(nitric ester) were 12 and 7.4 per cent., respectively, at $-12°$ and $-80°$.

4. Nitrogen tetroxide formed mainly oily products with gaseous isobutene; they were not examined because pronounced oxidation had occurred. Those formed in petroleum ether solution also readily decomposed and could not be separated into component parts. On the other hand, the liquid product formed in ether solution was relatively stable and could be distilled at low pressure.

5. The product formed in petroleum ether solution yielded with sodium thiophenolate a mixture of sodium nitrate and nitrite and an organic product, which gave β-phenylsulfonyl-α-nitroisobutane on oxidation. Although the thio-ether corresponding to this sulfone was probably formed from α,β-dinitroisobutane, that compound could not be isolated, nor could the corresponding diamine be obtained by catalytic reduction of the crude, or the distilled, addition product formed in the ether solution.

6. Isobutylamine was formed on catalytic reduction of the crude, and the distilled, addition product. This amine was probably formed mainly from nitroisobutene and from α,β-dinitroisobutane, through a series of reactions, which also yielded diisobutylamine.

7. Ammonia and β-hydroxyisobutylamine appeared in practically equimolecular proportion on reduction of the distilled blue oil; it is probable that these products were formed from the same compound, *viz.*, the α,β-nitro-nitrous ester derivative of isobutane.

8. Based on the yields of the reduction products, α-nitroisobutene constituted 5–12 per cent. of the crude addition product, and the α,β-nitro-nitrous ester derivative of isobutane represented 16–23 per cent. Assuming that the isolated diisobutylamine was formed from α,β-dinitroisobutane, the latter compound constituted at least 12 per cent. of the crude addition product.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

ON 1,2- AND 1,4-ADDITION.[1] V. NITROGEN TETROXIDE AND TETRAMETHYLETHYLENE

ARTHUR MICHAEL AND G. H. CARLSON

In an investigation on the addition of nitrogen tetroxide to tetramethylethylene, Demjanoff (1) obtained the crystalline, nitro-nitric ester, $(CH_3)_2C(ONO_2)C(NO_2)(CH_3)_2$ (I), a blue oil and, also, a bluish solid. The latter was considered to be the nitroso-nitric ester, $(CH_3)_2C(ONO_2)$-$C(NO)(CH_3)_2$ (II); because it was blue and, like the corresponding nitro ester I (2), it yielded 2-amino-2,3-dimethylbutanol-3 on reduction. On the other hand, Schmidt (3) concluded from his experimental results that the dinitrous ester, $(CH_3)_2C(ONO)C(ONO)(CH_3)_2$ (III), was formed as the main, and the dinitro compound, $(CH_3)_2C(NO_2)C(NO_2)(CH_3)_2$ (IV), as the minor product in the addition of nitrogen tetroxide, or "nitrous fumes," to the alkene in ether solution. The dinitro compound (IV) was obtained in a very low yield and was imperfectly investigated, but the structure of the dinitrous ester (III) was considered definitely established, as only ammonia was formed on reduction and, on hydrolysis with alkali, sodium nitrite appeared in practically quantitative yield. However, the other possible product, pinacol, was not isolated; indeed, no attempt was made to determine the nature of the organic product. In view of these divergent experimental results, Demjanoff and Ssidorenko (4) examined the action of "nitrous fumes" upon the alkene, and the results largely confirmed Demjanoff's earlier work. However, the bluish solid, previously believed to be nitroso-nitric ester (II), was completely purified and, in agreement with Schmidt, was identified, by reduction to tetramethylethylenediamine, as the dinitro compound (IV). Besides the dinitro compound (IV) and nitro-nitric ester (I), Demjanoff and Ssidorenko (4) isolated a third, crystalline solid (V), which was considered an inseparable mixture of nitro-nitric ester (I) and dinitro compound (IV). This conclusion was supported by analytical data, and by the formation of 2-amino-2,3-dimethylbutanol-3 and tetramethylethylenediamine on reduction. In this, as in the previous investigation, the formation of the dinitrous ester (III) could not be detected, yet Schmidt's result is generally accepted in the literature. Because of these conflicting statements, the action of nitrogen tetroxide on tetramethylethylene has been re-investigated.

[1] Previous papers; (a) MICHAEL AND WEINER, *J. Am. Chem. Soc.*, **59**, 744 (1937); (b) MICHAEL AND CARLSON, *ibid.*, **59**, 843 (1937); (c) *J. Org. Chem.*, **4**, 169 (1939); **5**, 1 (1940).

Practically constant yields (19.5–22%) of 2,3-dinitro-2,3-dimethylbutane (IV) were obtained on treating tetramethylethylene with nitrogen tetroxide in ether solution (Table I, experiments 1–3), but the addition of gaseous tetroxide without solvent (experiments 4–5), or in petroleum ether solution (experiment 6), gave only small yields of the compound. Although a perfect separation of the components of the blue oil (experiments 4–6) could not be realized, our results show that the nitric ester of 2-nitro-2,3-dimethylbutanol-3 (I) constituted a considerable part of the reaction product. This nitric ester readily formed a double compound with the dinitro compound (IV) to yield a fairly soluble, crystalline substance; from a similar compound formed with diphenyldisulfide (experiment 4), the nitric ester component could be recovered only after the disulfide had been destructively oxidized. Since nitric ester (I) appeared in a relatively high yield only under the oxidizing action of the tetroxide (experiments 4–6), the disappearance of dinitro compound (IV) in these experiments may be attributed to a conversion to double compound (V). Nitrogen tetroxide appears to unite with tetramethylethylene under all experimental conditions to yield some dinitro compound (IV), but, although this product is relatively insoluble in organic solvents, isolation was only possible when the amount of nitric ester (I) present in the reaction mixture was insufficient for the complete conversion of the dinitro derivative into double compound (V).

Deep blue reaction products were formed (experiments 1–3 and 6) in the presence of and, also, in the absence of solvents (experiments 4–5), when the alkene was used in excess of the molecular proportion of the tetroxide. The blue substance, either the nitroso-nitric ester (II) or, for reasons mentioned below, the nitroso-nitro derivative $(CH_3)_2C(NO)C(NO_2)(CH_3)_2$, (VI), could not be isolated. While these products, like the nitrosyl chloride and bromide addition compounds of tetramethylethylene (5), are undoubtedly monomolecular, the nitrogen trioxide and tetroxide products, unlike the halogen compounds, failed to crystallize from the crude reaction product and a separation by distillation could not be realized. However, at a low temperature, the crude, and the distilled, blue oil solidified almost completely, but centrifuging the mixture at $-80°$ (experiment 6), or with an ether-petrol mixture as diluent (experiment 4), did not effect a complete separation of the solid from the oily product. The crude, and the distilled, blue oils were not acted upon by sodium methoxide or thiophenylate in the cold (experiments 1 and 6), but, in sealed tubes at 100°, mixtures of sodium nitrate and sodium nitrite were formed; with the mercaptide, a practically quantitative conversion to diphenyldisulfide occurred (experiments 4 and 6) and only a small amount of an oil appeared as a by-product. Although inert towards aniline, the nearly colorless oil in experiment 8, like the blue oils of other experiments, rapidly polymerized

phenylisocyanate, but yielded no addition compound. The chemical nature of the oily products could not be established.

In experiments 7–9, tetramethylethylene, dissolved in ether, was treated with approximately three molecular equivalents of nitrogen tetroxide. The white, crystalline solid, which appeared at first in the blue reaction mixture, redissolved as the excess of the tetroxide was added and a pale green solution was formed. After removal of the solvent at reduced pressure, a practically colorless product was obtained, which solidified almost completely. However, separation of the small amount of adhering oil by filtration (experiment 7), or by centrifuging a suspension of the oily product in methyl alcohol at 0° (experiment 9), involved loss of considerable material; purification by steam-distillation was unsatisfactory because much of the product was decomposed. Analysis of the crystalline product (experiment 7) indicated that it was composed of 18% of the dinitro and 82% of the nitro-nitric ester derivative of tetramethylethane. Fractional crystallization did not change the properties of the solid, nor could it be separated into its components by sublimation at low pressure. On catalytic reduction, the sublimed product yielded ammonia, 2-amino-2,3-dimethylbutanol-3 and tetramethylethylenediamine. The diamine was precipitated practically quantitatively as the dihydrochloride on treating an acetic acid solution of the reduction product with hydrogen chloride; the yield indicated that the double compound (V) contained 22% of 2,3-dinitro-2,3-dimethylbutane, while the analytical data showed 18%. The semi-quantitative reduction and the analytical results are in fair agreement and establish the composition of V.

Under the oxidizing action of an excess of the tetroxide (experiments 7–9), product V appeared in a relatively high yield, but, under conditions tending to minimize the oxidative action, *viz.*, using ether as diluent and the alkene in excess, mainly the free dinitro compound was isolated (experiments 1–3). Although the tetroxide was used in an approximately equimolar proportion to the alkene in experiments 4 and 5, made without solvent, the yield of the double compound V was appreciable; it also constituted a large part of the reaction product formed in petroleum ether solution (experiment 6). These results lead to the conclusion that nitric ester (I), though formed under all conditions, appears only under oxidative conditions in amounts sufficient to combine with all of the dinitro compound (IV), which, probably, is mainly formed by direct addition of the tetroxide to the alkene. The reaction products in experiments 1–3 contained about 20% of the dinitro derivative (IV); the latter compound was completely incorporated into double compound (V) under the oxidative conditions of experiments 7–9. In view of the composition of V,

these results indicate that the crude reaction product, when formed under sub-oxidative conditions, (experiments 1–3), contained at least 60% of nitroso-nitric ester (II), which, under favorable conditions, was oxidized to the corresponding nitro-nitric ester (I) and used in forming double compound (V) (experiments 4–9). Accordingly, the appearance of the dinitrous ester (III) as the main reaction product, as reported by Schmidt (3), is very improbable.

Immediately after preparation, 83% of the reaction product in experiment 4 was volatile at low pressure, but, 15–20 hours later, the distilled oil, which had been kept at −80°, yielded 57% of a very slowly volatile oil, from which nitric ester I was isolated in a yield of 46%. Refractionations of the reaction product in experiment 5 gave green, oily residues, from which nitric ester (I) and double compound (V) were isolated. These results indicate that the easily volatile, blue product, probably nitroso-nitric ester (II), or the nitroso-nitro compound (VI), underwent an autoxidation. The blue oil became discolored spontaneously, with apparent conversion of blue nitroso- to colorless, oxidized products, since corresponding reduction products could not be detected. However, the gradual separation of the more slowly from the easily volatile oils in experiments 4 and 5 may be attributed to an incomplete separation of these products by a single distillation, rather than to a slow chemical change of easily volatile into less volatile products. The isolated, pure products, even the high-melting dinitro compound (IV), sublimed readily at low pressure, but the liquid and the solid products have nearly the same vapor pressure and, therefore, a semi-quantitative separation of the reaction products by distillation was impossible. Separation of the products by crystallization entailed considerable loss of material. Accordingly, the relative yields of the primarily-formed reaction products could not be determined even approximately, and our experiments do not definitely establish the mode of formation of nitro-nitric ester (I).

Nitrogen tetroxide may act upon the easily oxidizable tetramethylethylene with formation of the corresponding alkylene oxide, which may unite with the tetroxide to yield nitro-nitric ester (I). However, the appearance of this ester, as was suggested by Demjanoff (4, 6), may also be attributed to oxidation of nitroso-nitric ester (II), which is probably formed primarily in the action of nitrogen tetroxide upon the alkene. Since nitro-nitric ester (I) appeared in a comparatively high yield in experiments 4–6, notwithstanding that the tetroxide and the alkene were used in approximately equivalent amounts, the primarily formed nitroso-nitric ester must undergo oxidation facilely and its conversion to the nitro-nitric ester undoubtedly proceeds concurrently with the addition of the tetroxide to the alkene.

Therefore, under the conditions of the above experiments, products formed from nitrogen trioxide[2] should appear; although such products could not be isolated, detection may have failed, owing to the difficulty of separating the components of the liquid reaction mixtures.

Like Demjanoff and Ssidorenko (4), whose experimental results have been fully confirmed, we found that a deep blue reaction product was formed when nitrogen tetroxide was added to the alkene in an equivalent, or a slightly lower, amount. Since Schmidt (3) did not notice a blue coloration, the appearance of dinitrous ester (III) in his product might be attributed to the use of the tetroxide in excess, but in experiments 7–9, in which nearly three molecular equivalents of the tetroxide was gradually added, a deep blue color appeared at first and was then only slowly discharged. From the nearly colorless solutions, no dinitrous ester (III) could be isolated and, with anhydrous nitrogen tetroxide, Schmidt's compound (III) could be obtained neither under mildly (experiments 1 and 2), nor strongly oxidative conditions (experiments 7–9); nor was this product isolated in experiment 3, in which the tetroxide was not dried with phosphoric anhydride. A trace of moisture did not noticeably alter the course of the reaction and under no conditions could the formation of this anomalous compound be confirmed.

EXPERIMENTAL

General procedure.—Tetramethylethylene dibromide was prepared by bubbling hydrogen bromide into pinacol hydrate (40 g.) at 0° until the solution fumed strongly. After 12–15 hours, the precipitated dibromide (27–29 g.) was filtered and washed with methyl alcohol; the combined filtrates from two preparations yielded 5.4 g. of an unidentified, lachrymatory bromine product[3] and 7 g. of pinacolone. The dibromide (40 g.) was reduced according to Thiele's (7) method and yielded 6–9 g. of tetramethylethylene, b.p. 73°.

Nitrogen tetroxide, prepared from anhydrous lead nitrate, was dried with phosphoric anhydride, condensed in a glass ampoule and then distilled into the reaction flask (experiments 4–6). In experiments 1–3, a weighed amount of the tetroxide was absorbed in ether, cooled to −20°, and the solution was added to the alkene; the tetroxide was not dried in experiment 3. The lead nitrate was decomposed slowly in experiments 7–9 and the evolved, cooled gas was passed directly into the alkene solution.

The solid reaction products were filtered, solvents removed from the filtrates and the liquid products were then treated as described in the footnotes to Table I. A mercury vapor pump was used for low pressure distillations.

Catalytic reduction.—The solid substance was dissolved in 25 cc. of glacial acetic

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[2] With tetramethylethylene, as with isopentene-2[1c] and isobutene, the trioxide should yield a nitroso-nitro addition compound, $(CH_3)_2C(NO_2)C(NO)(CH_3)_2$ (VI), which the oxidizing action of the tetroxide may convert to the dinitro compound (IV).

[3] KONDAKOFF [*J. pr. Chem.*, **54**, 429 (1896)], using hydrochloric acid, observed the formation of an analogous product.

TABLE I

EXPERIMENT NUMBER	1[a]	2	3[c]	4[d]	5[e]	6[f]	7[g]	8[h]	9[i]
Tetramethylethylene, g.	4	5.5	5.5	10	11	10	3	3	3
Nitrogen Tetroxide, g.	4	4.8	5.1	10.8	9.3	10.1	9	10.8	9
Solvent cc. Ether	25	30	30				10	30	30
Petrol						30			
Temp., °C.	−18	−20	−16	−10	−10	−14	−20	−18	−15
Time, mins.	30	10	20	70	90	40	20	17	30
Product, g. Solid (S)	1	1.8	1.1		0.02	0.1	3.8		
M.p., °C.	210–211	208–210	208–210			209–210	100–102		
Liquid (A)	6.9	7.3	8.2	20.1	20.2		1.9	6.7	6.1
Calc'd Yield, g.	7.6	9.2	9.7	20.7	17.8				
Dist. gave Blue dist. (B), g.				17.1		17.7			
Green, res. (C), g.				2.5		1.8			
% Dinitro compound	19.8	19.6	22						

In the footnotes, nitro-nitric ester (I), the dinitro- (IV) and the double compound (V) are represented, respectively, by D, E and F.

[a] Oil A, diluted with 5 cc. of petrol, deposited 0.5 g. of impure E, m.p. 195–205°. A suspension of E (0.2 g.) in 25 cc. of NaOH (0.1045 *N*) was heated in a sealed tube at 100° for 2 hours. The cooled mixture required 21.9 cc., and a control solution (25 cc.) 22.3 cc., of HCl (0.1169 *N*): the recovered E (0.2 g.) melted at 205–208°.

Two grams of A, treated with 0.3 g. of Na in 15 cc. of methyl alcohol gave no inorganic salt; solvent was distilled off *in vacuo*, the residue (0.7 g.) was acidified and yielded 0.01 g. of impure E, m.p. 200°, as the only identifiable product.

One gram of A, in 15 cc. of methyl alcohol containing platinum oxide catalyst, absorbed no hydrogen during 3 hours.

[c] Solid S was filtered off, the filtrate washed with water and sodium carbonate solution, dried and the solvent removed *in vacuo*. Oil A deposited 0.7 g. of blue solid (*1*), m.p. 160°: a portion of *1*, recrystallized from ether, gave E, m.p. 208–210°. A portion of crude *1*, exposed on tile for 12 hours, melted at 185–190°. The oil

separated from *1* was diluted with petrol and, during 24 hours, deposited 0.3 g. of E, which was crystallized from ether and then melted at 210–211°.

[d] Oil C solidified. The solid, recrystallized from ether at −80°, gave 1.1 g. of D, m.p. 88°: low pressure sublimation did not alter the m.p.

Oil B solidified at −80°. An ether solution of B, cooled to −80°, deposited a blue solid (*1*); solvent was distilled *in vacuo* from the decanted, ether solution. The residual oil (*2*) began to decompose at 2 mm. (bath-temperature 45°), but was rapidly cooled and a portion (3 g.), treated with a solution of 0.8 g. of Na in 25 cc. of methyl alcohol and 4 g. of thiophenol, gave 0.3 g. of inorganic salt (a mixture of sodium nitrate and nitrite; Found: Na, 31.6%) and 1.2 g. of diphenyldisulfide.

Solid *1* fused at about −50°; the blue liquid (7–8 g.) was distilled at low pressure and gave (*3*) 2.2 g. of blue distillate and (*4*) 4.6 g. of green, residual oil, which, crystallized from ether at −25°, gave 2.1 g. of D, m.p. 87°. Solvent was distilled from the filtrate and the residue, crystallized from methyl alcohol at −20°, gave D, m.p. 87°. When sublimed at low pressure, D melted at 88–89°. *Anal.* Calc'd for $C_6H_{12}N_2O_5$: C, 37.5; H, 6.3; N, 14.58. Found: C, 37.73; H, 6.07; N, 14.1. Mol. wt.: Calc'd: 192. Found: 179.

Two grams of D and a hot methyl alcohol solution of 1.4 g. of sodium thiophenylate gave no inorganic salt; solvent was distilled, the residue was extracted with ether and the extract yielded (*5*) 1.5 g. of a double compound of nitric ester (I) and diphenyldisulfide, m.p. 64–65°, which, sublimed at low pressure, melted at 64–65°. A portion of *5* (0.5 g.) was treated with 0.5 g. of chromic anhydride in 15 cc. of hot glacial acetic acid; the solution, poured into water, yielded a solid, which was sublimed and gave 0.3 g. of D, m.p. 88–89°.

[e] Oil A deposited no solid during 24 hours. At low pressure, A gave (*1*) a blue distillate and (*2*) 5.6 g. of greenish, residual oil. Crystallized from methyl alcohol at −80°, *2* gave 2 g. of a solid, from which, by low pressure sublimation, 1 g. of F, m.p. 100–103°, and 1 g. of a mixture of D and F, m.p. 90–95°, were obtained.

Oil *1*, distilled at low pressure, gave: (*3*) 5.2 g. of blue distillate and (*4*) 3.6 g. of greenish, residual oil, which solidified partially at −80° and yielded (*5*) 1.5 g. of a solid. On fractional sublimation, *5* gave (*6*) 0.8 g. of D, m.p. 88–89° and (*7*) 0.7 g. of impure D, m.p. 85–87°. Combined *6* and *7*, after resublimation, gave 1.2 g. of D, m.p. 86–87°, which was used for catalytic reduction (experiment 2, Table II). Refractionation of *3* gave (*8*) 1.4 g. of blue distillate and (*9*) 1.7 g. of residual oil, from which, by crystallization at −80° and sublimation of the crude solid at low pressure, 0.6 g. of impure D, m.p. 80–85°, was isolated.

[f] Solid S was filtered off, solvent distilled *in vacuo* from the filtrate and the residual oil distilled at low pressure (bath-temperature 20°). Oil C solidified; the product D was crystallized from ether at −25° and then sublimed at low pressure, m.p. 88–89°.

Oil B could not be separated into its components by distillation; the liquid (15.7 g.), diluted with 5 cc. of ether and cooled to −80°, deposited (*1*) 12.6 g. of a blue solid, which was separated by centrifuging at −80°. Solid *1* melted (at about −50°) to a blue oil (*2*), which, during 36 hours, deposited 1 g. of impure D, m.p. 75–77°; the solid was pressed on tile and then melted at 83–84°.

Three grams of *2* and a solution of 0.4 g. of sodium and 1.9 g. of thiophenol in 25 cc. of methyl alcohol, heated for 1 hour at 100°, gave 1.3 g. of inorganic salt (a mixture of sodium nitrate and nitrite, Found: Na, 29.2%) and 2 g. of oil, which yielded 1.6 g. of diphenyldisulfide.

[g] Crude S, recrystallized from an ether-petrol mixture, gave 3.5 g. of F, m.p. 100–102°. *Anal.* Found: C, 37.99, 38.34, 38.02; H, 5.58, 7.02, 6.04. Oil A solidified, but could not be purified. A solution of 0.5 g. of F and 0.6 g. of sodium in 25 cc.

of methyl alcohol was boiled, solvent was distilled from the clear solution, the residue was extracted with ether and from the extract 0.4 g. of unchanged F, m.p. 100–101°, was recovered.

[h] After 24 hours, the reaction mixture was washed with water, dried and the solvent distilled *in vacuo*. Oil A distilled very slowly at low pressure. A portion of A (4.1 g.) was steam-distilled; the volatilized oil (1.7 g.) and 2 g. of aniline gave no solid product.

[i] After 24 hours, the green, ether solution of the reaction product was poured into water, washed with sodium carbonate solution, dried and the solvent distilled *in vacuo*. Oil A solidified, but most of the solid fused in an attempt to separate oily product by filtration; the filtrate was solidified and the oil separated by centrifuging at 0°. The combined, isolated solids were recrystallized from methyl alcohol at 0°; the mixture, centrifuged at 0°, gave 1.8 g. of F, m.p. 104–105°.

TABLE II

EXPERIMENT	PRODUCT REDUCED		H_2 ABSORBED		PRODUCTS g.		
		g.	Cc.	Min.	NH_4Cl	Diamine di-HCl	Syrupy hydrochloride
1[a]	E	2.8	2155	2895		2.4	
2[b]	D	1.2	1005	2595	0.25		
3[c]	F	2.5	2055	3935			1.9

Letters D, E and F designate the same compounds as in Table I.

[a] After removal of the dihydrochloride, less than 0.1 g. of oily product was isolated from the acetic acid solution. A portion of the dihydrochloride (0.5 g.) and 1 g. of *p*-nitrobenzoyl chloride gave 1 g. of di-nitrobenzoate of tetramethylethylenediamine, m.p. 213–214°. *Anal.* Calc'd for $C_{20}H_{22}N_4O_6$: C, 58.00; H, 5.25; N, 13.55. Found: C, 57.93; H, 5.22; N, 13.81.

[b] The weight of the syrupy hydrochloride was not determined; the syrup and 1.2 g. of *p*-nitrobenzoyl chloride gave 0.2 g. of *p*-nitrobenzamide and an oil, from which 0.7 g. of the *p*-nitrobenzoate of 2-amino-2,3-dimethylbutanol-3, m.p. 137°, was isolated. After crystallization from benzene, the nitrobenzoate melted at 139°. *Anal.* Calc'd for $C_{13}H_{18}N_2O_4$: C, 58.6; H, 6.77; N, 10.55. Found: C, 58.75; H, 6.63; N, 10.74.

[c] The precipitated hydrochlorides (*1*) (0.9 g.) and 3.1 g. of *p*-nitrobenzoyl chloride gave 1 g. of impure di-*p*-nitrobenzoate of tetramethylethylenediamine, m.p. 203–210°, which, crystallized from benzene, gave (*2*) 0.6 g. of pure dinitrobenzoate, m.p. 211–212°, and (*3*) 0.4 g. of slightly impure product, m.p. 210°: accordingly, *1* contained 0.4 g. of ammonium chloride.

The syrupy hydrochloride (1.9 g.), which was isolated from the acetic acid solution of the reduction product, gave, with 2.5 g. of *p*-nitrobenzoyl chloride, 1 g. of solid (*4*) and 1.8 g. of oil (*5*), which, diluted with ether, deposited 0.9 g. of solid (*6*), m.p. 130°. Fractional crystallization of *4* gave 0.1 g. of *p*-nitrobenzamide, m.p. 198°, and (*7*) 0.7 g. of solid, m.p. 130°. Two forms of crystals were present in *6* and *7*, which could not be separated by crystallization. After two extractions with hot water and crystallization of the insoluble product from benzene, the combined solids (*6* and *7*) gave 0.6 g. of pure *p*-nitrobenzoate of 2-amino-2,3-dimethylbutanol-3, m.p. 139°, and 0.3 g. of impure product, m.p. 130–133°. The aqueous extracts yielded 0.2 g. of slightly impure nitrobenzoate of the amino alcohol, m.p. 136–137°.

acid (15 cc. of acid used in 2) and reduced in the usual manner, using platinum oxide catalyst and hydrogen slightly above atmospheric pressure. Catalyst was removed by filtration, hydrogen chloride bubbled into the filtrate and the precipitate was separated by filtration. The solvent was distilled *in vacuo* and the residue treated as described in the footnotes to Table II.

SUMMARY

1. The action of nitrogen tetroxide on tetramethylethylene has been examined under varied experimental conditions.

2. Practically constant yields (19.6–22%) of 2,3-dinitro-2,3-dimethylbutane are formed in ether solution; addition of gaseous tetroxide to the alkene without solvent, or in petroleum ether solution, gave only low yields of the dinitro compound.

3. The nitric ester of 2-nitro-2,3-dimethylbutanol-3 appears to be formed in variable amounts under all the examined, experimental conditions. In the absence of solvent and under strong oxidative conditions, the yield of the nitric ester is considerable. The nitric ester readily unites with 2,3-dinitro-2,3-dimethylbutane to form a double compound. Under the oxidizing action of an excess of the tetroxide, all of the dinitro compound is incorporated into this double compound. Accordingly, isolation of the dinitro compound is realized only under conditions tending to depress the oxidizing action of the tetroxide and the yield of the nitro-nitric ester. The composition of the double compound was deduced from the analytical data and from the relative amounts of the basic products obtained by catalytic reduction; *viz.*, ammonia, 2-amino-2,3-dimethylbutanol-3 and tetramethylethylenediamine.

4. The formation of the nitric ester of 2-nitro-2,3-dimethylbutanol-3 is discussed. The possibility is suggested that nitrogen tetroxide may oxidize tetramethylethylene to the corresponding oxide and then act upon the latter to yield the nitro-nitric ester. However, it is more probable that the nitro-nitric ester is formed by oxidation of the corresponding nitroso-nitric ester, which probably is formed primarily by direct addition of the tetroxide to the alkene.

5. With the alkene in excess and ether as diluent, 2,3-dinitro-2,3-dimethylbutane was obtained in yields of about 20%. Under the oxidizing action of excess tetroxide, all of the dinitro derivative appeared combined, as a double compound, with the nitric ester of 2-nitro-2,3-dimethylbutanol-3. These results, and the composition of the double compounds, indicate that the crude reaction product, formed with the reactants in approximately equivalent molecular amounts, consisted mainly of the dinitro derivative and the nitric ester of 2-nitroso-2,3-dimethylbutanol-3 and that the latter ester, under the oxidizing action of the tetroxide, was converted to the corresponding nitro-nitric ester, which combined with the dinitro derivative to the double compound.

6. Our results confirm those of Demjanoff and Ssidorenko. In agreement, the appearance of Schmidt's dinitrous ester could not be observed; until the precise conditions leading to the formation of this product are established, it should be omitted from the list of known organic compounds.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF NORTH CAROLINA]

SULFUR STUDIES. XV. THE SYNTHESIS OF ALKANESULFONIC ACIDS AND CERTAIN DERIVATIVES*

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Of the various methods which have been used for the preparation of alkanesulfonic acids, perhaps the method most widely used is that of oxidizing mercaptans or disulfides to the corresponding sulfonic acids. Although the Hemilian modification of the Strecker reaction[1] has been used extensively with the lower members of the series, thus far no member above *n*-pentanesulfonic acid has been prepared by the Hemilian method.[2] Even when the latter method was used, in some cases no yields were reported, while in others there was no general agreement between the various authors.

This work was undertaken to determine whether sulfonic acids above *n*-pentane- could be prepared by the Hemilian method and, if so, whether the method could be justified by the yields and purity of product. It also seemed desirable to investigate the factors which might cause the discrepancies in the yields of those members reported.

The general procedure involved in the Hemilian method is that of heating a given quantity of an alkyl halide with an excess of ammonium sulfite. Since the reaction products have similar solubilities in water and in the common solvents, it is difficult to separate the ammonium alkanesulfonate from the ammonium bromide. They are best separated by converting them into their corresponding barium salts, whereupon the barium bromide can be rather easily extracted from the barium alkanesulfonate with absolute ethanol.

Since there are a number of variable factors involved during the preparation and purification of the barium alkanesulfonates by this method, it is quite likely that wide discrepancies in yields would result unless suitable precautions are taken.

The water-solubilizing property of the sulfonic group is well known,

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[1] STRECKER, *Ann.*, **148**, 90 (1868).

[2] HEMILIAN, *ibid.*, **168**, 145 (1873).

hence it is to be expected that, in separating the barium sulfonate from the barium bromide during the purification, considerable amount of barium alkylsulfonate may be lost with the bromide extraction. This is to be expected particularly with the lower members of the series where the percentage of carbon is low. Furthermore, since the reaction mixture consists of two liquid phases, the alkyl bromide and the aqueous ammonium sulfite phases, the conditions for an optimum reaction would be greatly enhanced by employing a more concentrated solution of the sulfite than has hitherto been employed. Also the rather low thermal stability of the ammonium sulfite and the extreme volatility of the lower alkyl halides are factors which must be considered in this reaction. The length of time which the reactants were heated is also a factor, although this has been shown by Bost and Williams[3] not to be as important as the temperature during the induction period.

It was found by Bost and Williams, and in later more thorough studies by us, that the best yields of barium alkanesulfonate are obtained when one mole of alkyl halide is allowed to react with two moles of ammonium sulfite. The most suitable concentration of sulfite is that obtained when the salt is dissolved in an equal weight of distilled water.

EXPERIMENTAL

The alkyl halide, distilled water, and the ammonium sulfite are placed in a one-liter, three-necked flask fitted with a stirrer, a thermometer which is set so that the bulb dips into the reaction mixture, and an efficient reflux condenser. The mixture is heated on a steam bath, below the refluxing point of the alkyl halide, for three or four hours, after which time the heat is increased until a gentle refluxing sets in. The heating is continued for thirty or forty hours for the preparation of the barium salts of *n*-hexane- and *n*-heptanesulfonic acids. Even after heating for one hundred hours the reaction was found to be incomplete in the case of the reaction of *n*-heptyl bromide with ammonium sulfite.

At the end of the heating period the mixture is diluted with three volumes of distilled water, and one-half of a mole of barium hydroxide is added. The mixture is heated over a hot-plate, with constant stirring, until ammonia is no longer evolved. It is then filtered to remove the barium sulfite. It is suggested that the barium hydroxide be added in two portions, each followed by a filtration, so that there will be no trouble from bumping during the heating. The excess barium hydroxide is removed as barium carbonate by passing a slow current of carbon dioxide into the solution as long as any precipitate is formed, after which the mixture is heated to boiling and the barium carbonate is removed by filtration. The solution now contains the barium salt of the sulfonic acid and the barium halide. In the cases of barium methane, ethane, and propane-1 sulfonates the solution is taken to dryness over a steam plate and most of the halide removed by a continuous extraction with absolute alcohol using a Sohxlet apparatus. The halide is reduced to a trace by continuous extraction for a period of twenty-four hours; however, some of the barium sulfonate is lost in this process due to a slight solubility in alcohol. To

[3] W. W. WILLIAMS, Doctoral Dissertation, University of North Carolina, 1936.

remove the last trace of the halide the barium alkane sulfonate is fractionally recrystallized from 80% alcohol. In the cases of barium butane sulfonate-1 and higher members the material separates on concentration of the reaction mixture and is purified from the last trace of halide by fractional recrystallization from distilled water. The yields of the first seven barium alkane sulfonates prepared using the above modification of the Hemilian method are given in Table I.

TABLE I

BARIUM *n*-ALKANESULFONATES

RADICAL	HALOGEN	YIELD	% Ba		WATER OF CRYST'N (MOLES)	M.P. PHENYLHYDRAZONIUM SALT, °C.
			Calc'd	Obs'd		
CH_3	I	81.6	38.91	38.62	1.5	193–194 (dec.)
C_2H_5	I	83.0	36.84	36.87	1.0	182.8
C_3H_7 (*n*)	Br	89.0	34.27	34.31	1.0	204.5 (dec.)
C_4H_9 (*n*)	Br	86.5	32.03	32.27	1.0	114–115
C_5H_{11} (*n*)	Br	82.0	30.07	30.14	1.0	108–108.2
C_6H_{13} (*n*)	Br	68.7	28.33	28.38	1.0	101–101.6
C_7H_{15} (*n*)	Br	70.0	26.78	26.72	1.0	100–100.5

TABLE II

n-ALKYLSULFONYL-*p*-TOLUIDIDES

ALKYL GROUP	M.P., °C.	% SULFUR		% YIELD
		Calc'd	Obs'd	
Methyl	102.0–102.7	17.33	17.36	66.7
Ethyl	80.0–80.5	16.10	16.13	45.0
n-Propyl	67.0–67.8	15.06	15.34	49.5
n-Butyl	74.2–75.2	14.12	14.28	58.4
n-Amyl	48.4–49.4	13.39	13.46	56.0
n-ALKYLSULFONYL-*p*-PHENETIDIDES				
Methyl	126.5–127.4	14.90	14.73	54.5
Ethyl	80.4–81	13.99	13.87	38.4
n-Propyl	101.0–101.5	13.18	13.21	61.0
n-Butyl	78.2–79.0	12.47	12.41	48.5
n-Amyl	69.0–70.0	11.83	11.95	34.5

Since the barium alkanesulfonates do not melt, a convenient method for determining their purity and identity is the method of Latimer and Bost[4] in which the free sulfonic acid is allowed to form the phenylhydrazonium salt.

The free sulfonic acids will undergo the Hell-Volhard-Zelinsky reaction giving the corresponding α-bromosulfonyl bromides. The α-bromosulfonyl bromides are light-yellow liquids which show considerable tendency to lose hydrogen bromide on distillation. These will be reported in detail in a later communication.

[4] LATIMER AND BOST, *J. Am. Chem. Soc.*, **59**, 2500 (1937).

As the next step in this investigation it was thought advisable to study the introduction of the *n*-alkylsulfonyl group into various aromatic amines. Since the alkylsulfonyl chlorides react more readily and do not have the extreme hygroscopic nature possessed by the free alkanesulfonic acids, it was found to be more practical to use the alkylsulfonyl chlorides rather than attempt to use the free sulfonic acids,

TABLE III

METHANESULFONIC ACID DERIVATIVES

COMPOUND	M.P., °C.	% SULFUR		% YIELD
		Calc'd	Obs'd	
o-Benzoxyphenyl methanesulfonate..	92–93	10.97	11.04	56
β-Naphthyl methanesulfonate.....	103.5–104.5	14.44	14.39	50

TABLE IV

ANTIPYRETIC ACTION

PRODUCT	TEST ANIMAL	NO. OF ANIMALS USED	MINIMAL EFFECTIVE DOSE	
			In mgm. per kgm.	In millimoles per kgm.
Methylsulfonyl-*p*-phenetidide.....	Rat	10	15[a]	70.5
n-Propylsulfonyl-*p*-phenetidide.....	Rat	10	20[a]	92.4
Methylsulfonyl-*p*-toluidide.....	Rat	10	10	49.7
	Rabbit	3	100	540.0
n-Propylsulfonyl-*p*-toluidide.....	Rat	10	16[a]	69.7
Phenacetine.....	Rat	10	12.5	70.0
	Rabbit	3	50.0	280.0

[a] These doses caused a slight hyperpyrexia instead of hypothermia.

TABLE V

TOXICITY TESTS

PRODUCT	TEST ANIMAL	NO. OF ANIMALS USED	APPROXIMATE LD_{50}	
			In mgm. per kgm.	In millimoles per kgm.
Methylsulfonyl-*p*-toluidide.....	Mice	17	300.0	1620.0
Phenacetine.....	Mice	18	70.0	280.0

in the reactions with the amines. There are two different methods by which the *n*-alkylsulfonyl chlorides may be prepared: (1) by the action of phosphorus pentachloride or thionyl chloride on the barium n-alkane sulfonate, or (2) by the method of Sprague and Johnson[5] which consists of the action of gaseous chlorine on an

[5] SPRAGUE AND JOHNSON, *ibid.*, **58**, 1348 (1936).

aqueous solution of the *n*-alkylthiouronium chloride. The lower cost of the starting materials and the saving in time afforded by the second method make it the most feasible method to use in preparing the *n*-alkylsulfonyl chlorides.

The first amines to be treated with the sulfonyl chlorides were *p*-toluidine and *p*-phenetidine. They were allowed to react with a series of five sulfonyl chlorides from methyl- to *n*-amylsulfonyl chloride.

These compounds are best prepared by the action of a slight excess of the sulfonyl chloride on a pyridine solution of the amine. The reaction mixture is poured into ice and water, and the tan crystalline product which is formed is collected by filtration. This crude product is put into solution in cold 5 per cent. sodium hydroxide and precipitated by the addition of hydrochloric acid. The resulting precipitate, usually white or light-grey in color, is recrystallized from 95 per cent. alcohol, decolorizing if necessary. The product separates as white needles. Two recrystallizations are usually sufficient to obtain a constant melting point. In general these compounds are soluble in sodium carbonate and sodium bicarbonate solutions, very soluble in alcohol, and only slightly soluble in water.

In Table III will be found data on other derivatives of alkanesulfonic acids which were prepared in this work.

The action of the sulfonyl chlorides on urea, salicylic acid, methyl salicylate and dibutylaminopropyl alcohol has been studied but the results were not encouraging.

The *n*-alkylsulfonyl-*p*-toluidides and *n*-alkylsulfonyl-*p*-phenetidides were checked for chemotherapeutic action by the Eli Lilly and Co., to whom grateful acknowledgment is made. They were found to afford no protection to mice infected with Pneumococcus Type I, Type II, Puerto Rican Strain #8 Influenza Virus, or Staphylococcus. One compound, methylsulfonyl-*p*-toluidide, showed antipyretic action which, however, was not constant between rats and rabbits.

SUMMARY

1. *n*-Alkanesulfonic acids containing as many as seven carbon atoms can be made in good and consistent yields by the Hemilian modification of the Strecker reaction.

2. An improved method of isolation and purification of the barium *n*-alkanesulfonates has been developed.

3. The *n*-alkylsulfonyl-*p*-phenetidides and -*p*-toluidides from methyl- through *n*-amyl- have been prepared, and their chemotherapeutic and antipyretic action studied.

[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE RATE OF DISSOCIATION OF PENTAARYLETHANES*

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In a previous paper[1] it was demonstrated that pentaarylethanes undergo reversible dissociation into free radicals, the position of equilibrium being nearly entirely in favor of the pentaarylethane.

$$R_3C-CHR_2 \rightleftarrows R_3C- + R_2CH-$$

From studies on the reaction of oxygen with solutions of the pentaarylethanes, it was concluded that the rate of oxygen absorption was a measure of the rate of dissociation of the pentaarylethane. It was found that at 100° pentaphenylethane dissociates into the triphenylmethyl and diphenylmethyl radicals approximately as rapidly as hexaphenylethane dissociates at 0°. From the velocity constants from the dissociation of pentaphenylethane at different temperatures, the energy of activation of the dissociation process was calculated to be 27.6 kcal., a value 50 per cent. greater than the corresponding value for hexaphenylethane.

If the rate of reaction with oxygen is actually a measure of the rate of dissociation of the pentaarylethane, then substantially the same rate of reaction should be observed with other reagents capable of reacting rapidly with the radicals formed on dissociation, and it was highly desirable that this point be tested. Accordingly, we decided to explore another reaction of this type, and we chose iodine as the reagent, since it is well-known that triarylmethyl radicals react rapidly with iodine as well as with oxygen. Preliminary experiments showed that at temperatures of 70–100° solutions of pentaphenylethane absorbed iodine, and the reaction appeared to be suitable for development as another method of determining the rates of dissociation.

For the reaction we employed a solution of iodine in a suitable solvent which contained some ethanol and pyridine, a mixture similar to that used by Ziegler, Ewald, and Orth[2] in their studies on the rate of dissociation of hexaarylethanes. The ethanol served to convert the triphenylmethyl iodide to triphenylmethyl ethyl ether as fast as it was formed; it was

* From the ph.D. dissertation of Gerald Osborn.

[1] BACHMANN AND WISELOGLE, J. ORG. CHEM., **1**, 354 (1936).

[2] ZIEGLER, EWALD, AND ORTH, *Ann.*, **479**, 277 (1930).

necessary to do this since the reaction of triphenylmethyl and iodine to give triphenylmethyl iodide is reversible. Pyridine was added to combine with the hydrogen iodide which is formed in the reaction giving the ether; this was done in order to prevent a reaction between the free radicals and the hydrogen iodide.

It was found that in the presence of ethanol and pyridine the radicals formed by dissociation of pentaphenylethane reacted with practically the theoretical amount of iodine; the final products proved to be triphenylmethyl ethyl ether and diphenylmethylpyridinium iodide. From this result it was apparent that the diphenylmethyl iodide formed by the union of the diphenylmethyl radical and iodine combined with the pyridine to give a quaternary salt in preference to forming an ether by reaction with the ethanol. The following equations indicate the reactions that take place when pentaphenylethane is employed.

$$(C_6H_5)_3C{-}CH(C_6H_5)_2 \rightleftarrows (C_6H_5)_3C{-} + (C_6H_5)_2CH{-}$$

$$2(C_6H_5)_3C{-} + I_2 \rightleftarrows 2(C_6H_5)_3CI$$

$$2(C_6H_5)_2CH{-} + I_2 \rightarrow 2(C_6H_5)_2CHI$$

$$(C_6H_5)_3CI + C_2H_5OH \rightarrow (C_6H_5)_3COC_2H_5 + HI$$

$$HI + C_5H_5N \rightarrow C_5H_5NHI$$

$$(C_6H_5)_2CHI + C_5H_5N \rightarrow C_5H_5N\begin{matrix} I \\ \diagup \\ \\ \diagdown \\ CH(C_6H_5)_2 \end{matrix}$$

Since it was necessary to work at a temperature of 80° or higher in order to have an appreciably rapid reaction, the choice of solvent was limited to those having boiling points above 100° when working at atmospheric pressure. Another requirement of the solvent was that it must not react with any of the compounds present in the reagent mixture. It was found that *o*-dichlorobenzene, bromobenzene, xylene, and α-bromonaphthalene were satisfactory solvents, while ethylene dibromide, anisole, and cyanobenzene were unsuitable. The rate of iodine absorption was determined by adding a weighed sample of the pentaarylethane to a measured volume of a solution of iodine in a solvent containing ethanol and pyridine. The reaction mixture was kept in a constant-temperature bath for a definite interval of time, then removed quickly and chilled. An excess of standard sodium thiosulfate solution was added to the mixture, and the excess was titrated with a standard solution of iodine. At a given temperature a series of samples identical in weight were run for different intervals of time, and an absorption-time curve was then plotted, from which the rate constant was determined.

In agreement with the results obtained on oxygen absorption, the rate-controlling step proved to be a reaction of the first order, corresponding to the unimolecular process of dissociation. Letting $Z = x/a$, the fraction of pentaphenylethane reacting, the equation for the first order reaction may be written:

$$k = \frac{-2.3}{t} \log (1 - Z)$$

Z was calculated as the ratio of the actual absorption of iodine to the theoretical absorption. When $-\log (1 - Z)$ was plotted against t, straight lines were obtained (Fig. 1); the slopes of the lines multiplied by 2.3 gave the velocity constants k. The data given in Table I show the

TABLE I

TYPICAL DATA OBTAINED IN REPRESENTATIVE EXPERIMENT

Wt. pentaphenylethane in each run, 0.1025 g.
o-Dichlorobenzene, 89.3%; pyridine, 4.7%; ethanol, 6.0%.
Theoretical absorption of 0.1 *N* iodine, 5 cc.
Temp., 94.9°.

TIME, MIN.	0.1 *N* IODINE ABSORBED, CC.	$-\log(1 - Z)$	Z FOUND	Z^* CALC'D[a]	DIFF.
1.0	0.31	0.0278	0.062	0.061	+0.001
2.0	0.56	0.0516	0.112	0.115	−0.003
3.0	0.90	0.0856	0.180	0.166	+0.014
4.0	1.07	0.1046	0.214	0.215	−0.001
5.0	1.33	0.1343	0.266	0.278	−0.012
6.1	1.54	0.1600	0.308	0.309	−0.001
8.0	1.95	0.2147	0.390	0.384	+0.006

[a] Z^* calc'd is from the rate constant, 0.605, obtained from the curve (upper line, Fig. 1).

agreement between the actual results and those calculated on the basis of a first order reaction. The rate constant was found to be independent of the volume of solvent or concentration of iodine, as the results recorded in Table II indicate.

In Table III is presented a comparison of the velocity constants and half-life periods ($t_{\frac{1}{2}}$) for pentaphenylethane as determined by the iodine reaction and by the oxygen reaction. In both reactions *o*-dichlorobenzene was used as the solvent; however, pyridine and alcohol were present in the iodine reaction, while pyrogallol was present in the oxygen reaction. With due consideration for this difference, there is agreement between the two sets of values. A further comparison is obtained in the values of the energy of activation determined by the two reactions.

The energy of activation of the dissociation process was determined by

plotting $-\log k$ against $1/T$ in the customary manner (Fig. 2) and multiplying the slope of the line by $2.3R$. From the curves a value of 27.1 kcal. was obtained for the energy of activation by the iodine reaction, which is in good agreement with the value 27.6 kcal. obtained by the oxygen method.

TABLE II

EFFECT OF VARYING CONCENTRATIONS OF REAGENTS

Temp. 94.9°; solvent, *o*-dichlorobenzene

CONC. IODINE	CONC. PENTAPHENYLETHANE	RATE CONSTANT k
0.10 N	0.050 molar	0.0603
0.10	0.025	0.0605
0.05	0.025	0.0602

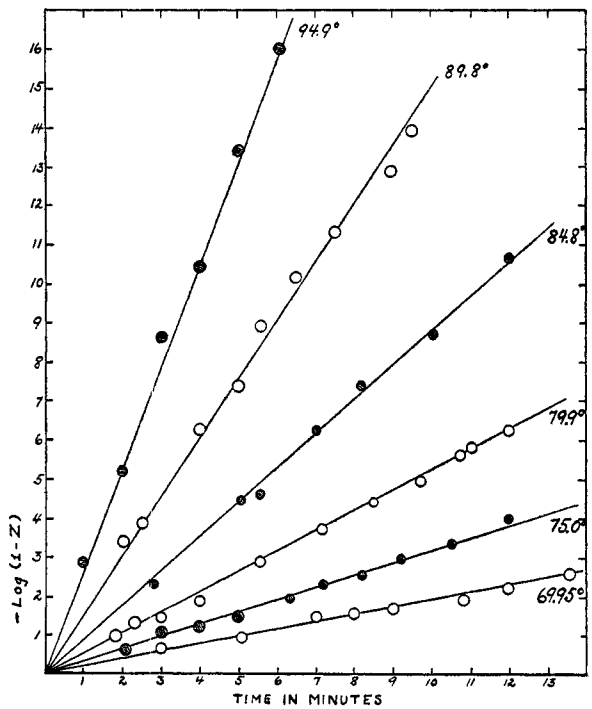


FIGURE 1.—IODINE ABSORPTION BY PENTAPHENYLETHANE IN *o*-DICHLOROBENZENE
Z = fraction of pentaphenylethane reacting

The rate of dissociation of pentaphenylethane was determined not only in *o*-dichlorobenzene but also in xylene, bromobenzene, and α-bromonaphthalene. Although the specific rate constants varied in the different solvents, as is seen in Table IV, the value for the energy of activation

remained fairly constant, the average of the values obtained in the four solvents being 28.0 kcal.

With the successful development of a rapid and convenient method of measuring the rate of dissociation of a pentaarylethane, we were in a position to determine the effect of a series of aryl groups on the rate of dissociation. This was accomplished by measuring the rate of dissociation

TABLE III

RATE CONSTANTS AND HALF-LIFE PERIODS

Iodine reaction

Temp., °C.	69.95	75.00	79.90	84.80	89.80	94.90
k	.0042	.0075	.0122	.0205	.0339	.0605
t (min.)	165	92	56.7	33.8	20.4	11.4

Oxygen reaction

Temp., °C.	79.85	84.70	89.55	94.40	99.30	104.15
k	.0163	.0274	.0462	.0765	.1260	.2010
t (min.)	42.5	25.3	15.0	9.06	5.50	3.44

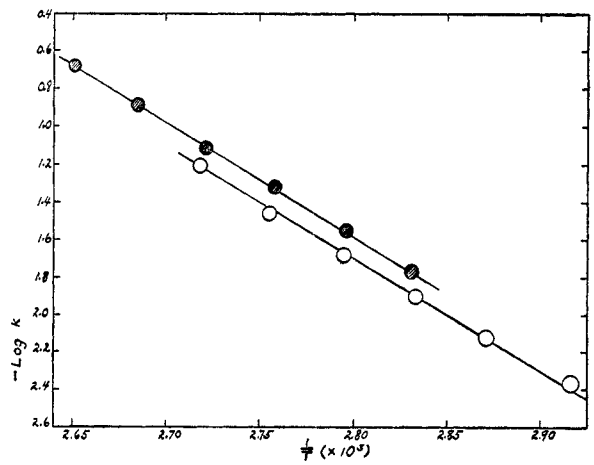


FIGURE 2.—Open circles: iodine reaction; E = 27.1 kcal. Shaded circles: oxygen reaction; E = 27.6 kcal.

of seven pentaarylethanes at the same temperature (80°) and in the same solvent. These pentaarylethanes all had the same general formula $(C_6H_5)_3C-CH(C_6H_5)R$ differing from one another only in the one group R. In Table V are shown the rate constants and half-life periods of the pentaarylethanes as determined by the iodine reaction. It is seen that the 9-phenanthryl, α-naphthyl and 2-fluoryl groups are most effective in

promoting a rapid dissociation, the *p*-biphenyl and *p*-anisyl groups have an intermediate effect, while the *p*-tolyl and phenyl groups are least effective. Work is now in progress to determine the effect of other groups

TABLE IV

ENERGY OF ACTIVATION OF PENTAPHENYLETHANE

SOLVENT		70°	75°	80°	85°	90°	95°	*E* (kcal.)
o-Dichloro-benzene	*k*	.0043	.0075	.0124	.0209	.0341	.0607	27.1
	$t_{\frac{1}{2}}$	161	92.4	56.0	33.2	20.3	11.4	
Xylene	*k*			.0111	.0198	.0345	.0575	28.1
	$t_{\frac{1}{2}}$			62.3	34.4	20.1	12.1	
Bromobenzene	*k*			.0108	.0216	.0361	.0575	28.5
	$t_{\frac{1}{2}}$			64.2	32.1	19.2	12.1	
α-Bromonaph-thalene	*k*			.0123	.0225	.0407	.0690	28.4
	$t_{\frac{1}{2}}$			56.3	30.8	17.0	10.05	

TABLE V

RATE CONSTANTS OF PENTAARYLETHANES

$(C_6H_5)_3C—CH(C_6H_5)R$

Temp., 80°

GROUP, *R*	*k*	HALF-LIFE, MIN.
Phenyl	0.0124	56.0
p-Tolyl	0.0131	52.8
p-Anisyl	0.0166	41.8
p-Biphenyl	0.0241	28.8
2-Fluoryl	0.0404	17.2
α-Naphthyl	0.0437	15.9
9-Phenanthryl	0.0506	13.7

TABLE VI

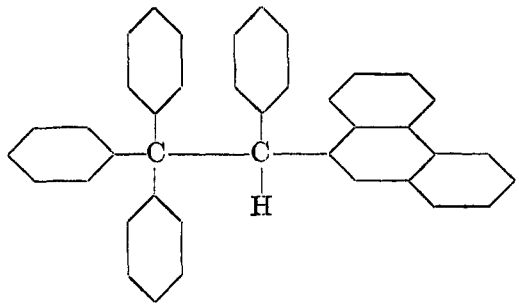
RATE CONSTANTS AND HALF-LIFE PERIODS OF 1,1,1,2-TETRAPHENYL-2-(9′-PHENANTHRYL)ETHANE

o-Dichlorobenzene, 89.5%; pyridine, 4.7%; ethanol, 5.8%

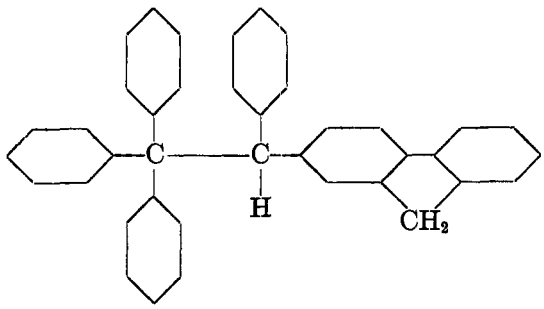
Temp., °C	65	70	75	80	85
k	.0094	.0154	.0308	.0506	.0828
t	73.7	45.0	22.5	13.7	8.4

in the molecule. When more data are at hand it will be apparent whether there is any correspondence between the effect of the groups in increasing the rate of dissociation of pentaarylethanes and in promoting the extent of dissociation of hexaarylethanes.

Two of the pentaarylethanes, 1,1,1,2-tetraphenyl-2-(9′-phenanthryl)-ethane (I) and 1,1,1,2-tetraphenyl-2-(2′-fluoryl)ethane (II), are new; they were prepared by interaction of triphenylmethylsodium and the appropriate diarylmethyl chloride.



I



II

In view of the marked effect of the 9-phenanthryl group on the rate of dissociation of the pentaarylethane molecule, we determined the energy of activation of the dissociation process for 1,1,1,2-tetraphenyl-2-(9′-phenanthryl)ethane. Table VI shows the values of the rate constants and the half-life periods for this pentaarylethane in *o*-dichlorobenzene. The energy of activation was found to be 26.6 kcal., a value similar to that observed for pentaphenylethane.

EXPERIMENTAL

Phenyl-2-fluorylcarbinol.—Following the directions of Bachmann[3], 5.4 g. of 2-benzoylfluorene[4] was reduced by 60 g. of 2 per cent. sodium amalgam and 2.5 cc. of absolute alcohol in 25 cc. of anhydrous ether and 25 cc. of dry benzene. During the thirty minutes of shaking the solution became deep-blue and finally pale-green in color. The yield of recrystallized carbinol was 5.1 g. (94%); m.p. 113–114.5°. Ray and Levine[5] reported a somewhat lower yield (82%), but slightly higher melting

[3] Bachmann, *J. Am. Chem. Soc.*, **55**, 770 (1933).
[4] Bachmann and Barton, J. Org. Chem., **3**, 300 (1938).
[5] Ray and Levine, *Ibid.*, **2**, 273 (1937).

point (116°), for the carbinol obtained by reduction of the ketone by zinc dust and alcoholic ammonia or potassium hydroxide. The ketone gives a yellow color and the carbinol gives a deep-red color with concentrated sulfuric acid.

Phenyl-2-fluorylchloromethane.—A solution of 4.8 g. of phenyl-2-fluorylcarbinol in 50 cc. of benzene containing 2.5 g. of anhydrous calcium chloride was saturated with hydrogen chloride at 0°. After standing for twelve hours, the solution was filtered, and the benzene was evaporated under reduced pressure. Recrystallization of the residue from petroleum ether gave 4.6 g. (88%) of colorless crystals of the chloride; m.p. 122.5–123.5° (Ray and Levine, 122°).

Phenyl-2-fluorylbromomethane.—To a solution of 6 g. of phenyl-2-fluorylcarbinol in 6 cc. of benzene was added 2.5 cc. of acetyl bromide; the solution was warmed to its boiling point and then cooled. Upon addition of petroleum ether (60–70°), 6.7 g. (91%) of colorless crystals of the bromide precipitated; m.p. 128–129°. Ray and Levine[5] obtained a 50% yield of the bromide melting at 118–119° by the action of hydrogen bromide on the carbinol.

1,1,1,2-Tetraphenyl-2-(2'-fluoryl)ethane (*II*).—A solution of triphenylmethylsodium was prepared from 2.79 g. of triphenylchloromethane and coupled with 2.91 g. of phenyl-2-fluorylchloromethane according to the procedure described previously[1]. Recrystallization of the product from benzene gave 2.45 g. (49%) of fine, colorless crystals of the pentaarylethane. The compound melts at 152–162° in air and at 164–168° in nitrogen to an orange-colored liquid.

Anal. Calc'd for $C_{38}H_{30}$: C, 93.9; H, 6.1.
Found: C, 93.4; H, 6.0.

Nearly the same yield of pentaarylethane was obtained when phenyl-2-fluorylbromomethane was employed in place of the chloride.

The structure of the pentaarylethane was proved by cleavage by hydrogen iodide into triphenylmethane and 2-benzylfluorene. A mixture of 0.1 g. of iodine, 0.3 g. of red phosphorus, 0.2 cc. of water and 10 cc. of acetic acid was warmed for ten minutes; after addition of 0.25 g. of the pentaarylethane the mixture was refluxed for one hour in an atmosphere of nitrogen. The solution was filtered, and the filtrate was poured into a solution of sodium carbonate containing some sodium bisulfite. The products were extracted with benzene, the benzene solution was dried and then concentrated to a small volume. From the solution 90 mg. of triphenylmethane crystallized. By evaporation of the filtrate and solution of the residue in 30 cc. of hot alcohol and cooling, 55 mg. of 2-benzylfluorene was isolated in the form of colorless leaflets. The 2-benzylfluorene was found to exist in two forms; the crystals first melted at 94–95°, the melt solidified and remelted at 104–105.5°. The dimorphic state explains the wide range of melting points, varying from 99° to 106°, previously reported for this compound.

A sample of 2-benzylfluorene was prepared for comparison in the following manner. To 0.25 g. of phenyl-2-fluorylcarbinol was added 0.3 g. of red phosphorus, 0.1 g. of iodine, 0.2 cc. of water and 10 cc. of acetic acid. The mixture was refluxed for one hour and then worked up in the manner described for the cleavage reaction; yield, 0.19 g. (80%); m.p. 94–95°; 104–105.5°. When this material was mixed with the 2-benzylfluorene obtained in the cleavage reaction, the melting points remained unchanged.

Phenyl-9-phenanthrylcarbinol.—Eleven and three-tenths grams of 9-benzoylphenanthrene[6] and 50 cc. of anhydrous isopropyl alcohol were added to the aluminum isopropoxide solution prepared from 1 g. of aluminum wire and 20 cc. of anhydrous

[6] BACHMANN AND KLOETZEL, *Ibid.*, **2**, 363 (1937).

isopropyl alcohol according to the procedure of Lund[7]. The mixture was heated on a steam bath so that the acetone formed in the reaction was distilled off slowly with the isopropyl alcohol. When no more acetone could be detected in the distillate by means of 2,4-dinitrophenylhydrazine, the isopropyl alcohol was removed under reduced pressure, and the residue was treated with ice-cold dilute sulfuric acid. Recrystallization of the dried product from benzene-petroleum ether gave 10.6 g. (93%) of colorless crystals of the carbinol; m.p. 139–140°. The product was identical with the carbonol prepared by interaction of 9-phenanthrylmagnesium bromide and benzaldehyde[8].

Phenyl-9-phenanthrylchloromethane.—A cold solution of 8.52 g. of phenyl-9-phenanthrylcarbinol in 70 cc. of dry benzene containing 3 g. of anhydrous calcium chloride was saturated with hydrogen chloride. After twelve hours at room temperature the benzene solution yielded 7.7 g. (85%) of fine, colorless needles of phenyl-9-phenanthrylchloromethane; m.p. 114–116°.

Anal. Calc'd for $C_{21}H_{15}Cl$: Cl, 11.7. Found: Cl, 11.6.

Phenyl-9-phenanthrylbromomethane.—A mixture of 5.9 g. of phenyl-9-phenanthrylcarbinol and 2.4 cc. of acetyl bromide was heated on a steam bath for one-half hour. The acetic acid was removed under reduced pressure, and the residual oil was dissolved in a mixture of warm benzene and ligroïn. On cooling, 6.87 g. (95%) of the bromide crystallized in clusters of colorless plates; m.p. 115–116°.

Anal. Calc'd for $C_{21}H_{15}Br$: Br, 23.0. Found: Br, 22.6.

1,1,1,2-Tetraphenyl-2-(9'-phenanthryl)ethane (*I*).—This pentaarylethane was obtained in 80% yield by reacting a solution of 3.03 g. (0.01 mole) of phenyl-9-phenanthrylchloromethane in 5 cc. of benzene with an ice-cold solution of triphenylmethylsodium (0.01 mole) in the customary manner[1]. After recrystallization from benzene the compound melted at 176–188° in air and at 190–193° in nitrogen to a reddish-orange liquid.

Anal. Calc'd for $C_{40}H_{30}$: C, 94.1; H, 5.9.
Found: C, 93.8; H, 5.7.

A 0.25-g. sample of the pentaarylethane was cleaved by hydrogen iodide according to the procedure described for the 2-fluoryl derivative. The mixture of the two methanes, triphenylmethane and 9-benzylphenanthrene, was dissolved in 4 cc. of 90–100° petroleum ether; on being cooled slightly the solution deposited 45 mg. of 9-benzylphenanthrene; m.p. 155–156°, alone and when mixed with an authentic specimen. The filtrate was evaporated and the residue dissolved in hot benzene; from the solution 55 mg. of triphenylmethane crystallized.

Reaction between pentaphenylethane and iodine.—A solution of 0.4 g. of pentaphenylethane, 0.2 g. of iodine, 1 cc. of absolute alcohol, 1 cc. of pyridine, and 10 cc. of benzene was refluxed on a steam bath. After two and one-half hours the iodine color had practically disappeared. On cooling, 0.48 g. of yellow crystals precipitated; by recrystallization from water 0.37 g. of diphenylmethylpyridinium iodide was obtained as yellow prisms. The salt had no definite melting point; it decomposed between 162° and 194°.

Anal. Calc'd for $C_{18}H_{16}NI$: I, 34.0. Found: I, 33.9.

The benzene filtrate from the diphenylmethylpyridinium iodide was evaporated, and the residue was dissolved in hot petroleum ether. After removal of 40 mg. of precipitated pentaphenylethane, the solution was concentrated and cooled, whereupon 0.26 g. of triphenylmethyl ethyl ether crystallized.

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[7] LUND, *Ber.*, **70**, 1520 (1937).

[8] BACHMANN, *J. Am. Chem. Soc.*, **56**, 1366 (1934).

Diphenylmethylpyridinium iodide.—To a solution of 5 g. of sodium iodide in 50 cc. of acetone was added 10 cc. of an acetone solution of 3.14 g. of diphenylbromomethane. After one hour the sodium bromide was removed by filtration, and 10 cc. of pyridine was added to the clear solution of diphenyliodomethane. After twelve hours the acetone and pyridine were removed in a current of air, and the solid residue was recrystallized from hot water, yielding 3.9 g. (89%) of diphenylpyridinium iodide as yellow prisms; m.p. 162–194° with decomposition.

Anal. Calc'd for $C_{18}H_{16}NI$: I, 34.0. Found: I, 33.9.

Rate measurements.—The pentaarylethanes were dried for several hours in high vacuum at 80–100°; the purity of the samples was established by analysis for carbon and hydrogen. The iodine solution was made up by adding *o*-dichlorobenzene (or other solvent) to a solution of 6.5 g. of iodine in 32.5 cc. of pyridine until the total volume was 500 cc. The samples (0.1025 g. each) of pentaphenylethane were weighed into glass vials, 12 mm. deep and 8 mm. in diameter, having flat bottoms. Ten cubic centimeters of the iodine solution and 1 cc. of absolute alcohol were placed in a 125-cc. Erlenmeyer flask bearing a glass stopper. The flask was suspended in a water bath kept at the desired temperature to within 0.05°. The vial containing the sample of pentaphenylethane was then lowered in an upright position into the Erlenmeyer flask by means of forceps and allowed to float on the surface of the organic solution of iodine. The flask after being stoppered loosely was allowed to reach the temperature of the bath, for which ten minutes proved to be sufficient. The vial was then tipped over by swirling the flask, a stop-watch being started at this time; the pentaphenylethane dissolved very rapidly. When the desired interval of time had elapsed, the flask was removed quickly from the bath and immersed in ice-water, the watch being stopped at this point.

Ten cubic centimeters of sodium thiosulfate solution, slightly stronger than 0.1 *N* (strong enough to react with all the iodine originally present in the organic solution), was added, 50 cc. of water was used to rinse down the sides of the flask, and the excess of sodium thiosulfate was titrated with a standardized 0.1 *N* solution of iodine in potassium iodide and water. From the volume of this standard iodine solution needed to give the end-point with starch was subtracted the volume of iodine solution required to give the end-point to a blank. The latter was run with all of the reagents present except the pentaphenylethane in exactly the same manner as the regular run. The difference was the volume of 0.1 *N* iodine which reacted with the radicals formed by dissociation of the pentaphenylethane. It is apparent that the strength of only the aqueous solution of iodine must be known accurately. The other pentaarylethanes were run in the same manner.

The presence of an appreciable amount of the diarylmethyl-pyridinium iodide in the water solution interfered with the end-point; for this reason the reactions were not allowed to proceed to any great extent. It is believed that the results which were obtained are in error by no more than 5 per cent.

SUMMARY

Solutions of pentaarylethanes readily absorb iodine at 70–100° in the presence of ethanol and pyridine. It has been shown that the reaction proceeds through the intermediate formation of free radicals produced by dissociation of the pentaarylethane. The products that are formed under these conditions are triarylmethyl ethyl ethers and diarylmethylpyridinium iodides.

A rapid and convenient method was developed for determining the rate of dissociation of pentaarylethanes.

The energy of activation for the dissociation of pentaphenylethane was determined in four different solvents. The energy of activation for the dissociation of 1,1,1,2-tetraphenyl-2-(9′-phenanthryl)ethane was also determined.

The rate of dissociation at 80° of seven different pentaarylethanes was measured. From the results a comparison of the effect of seven aryl groups on the rate of dissociation was obtained.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE REDUCTION OF 1,2,3-BENZOTRIAZOLE AND ITS *N*-METHYL DERIVATIVES BY SODIUM IN LIQUID AMMONIA

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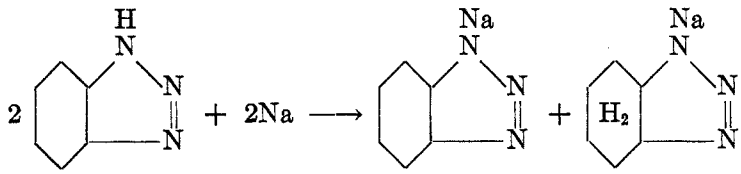
INTRODUCTION

In the course of a series of experiments on the salt-forming power of the 1,2,3-triazoles, 1,2,3-benzotriazole was treated with sodium in liquid ammonia. It was thought that the hydrogen of the heterocyclic nucleus would be displaced by sodium with the formation of hydrogen gas. Experiments demonstrated, however, that sodium reacts with 1,2,3-benzotriazole in a 1:1 ratio without the liberation of hydrogen. Subsequent experiments indicated that the benzene nucleus is hydrogenated probably to a dihydro-1,2,3,-benzotriazole so that the reaction may be formulated



Moreover, sodium is entirely ineffective in converting a larger portion of the 1,2,3-benzotriazole to the dihydro compound. Here is a definite case where "nascent" (presumably atomic) hydrogen is a more effective reducing (hydrogenating) agent than the ammonated electron ($Na + xNH_3 \rightleftharpoons Na^+ + \epsilon^- \cdot xNH_3$)[1]

The literature records cases (*1*) where the theoretical amount of hydrogen has not been obtained in the reaction of an ammonia solution of sodium with compounds containing replaceable hydrogen,[2] and (*2*) where it has been postulated that nascent hydrogen is responsible, in whole or in part, for the products obtained by sodium reductions in ammonia.[3] In most instances of this kind, complete quantitative data is unavailable, and in

[1] For a review of solutions of metals in liquid ammonia see FERNELIUS AND WATT, *Chem. Reviews*, **20**, 195–258 (1937).

[2] FERNELIUS AND WATT, *loc. cit.*, pp. 217, 222, 246.

[3] FERNELIUS AND WATT, *loc. cit.*, pp. 232, 240, 244–5.

no instance has such a reaction been studied thoroughly. Wooster and Godfrey[4] have observed that the system Na—NH_3—H_2O reduces toluene whereas the systems Na—NH_3 and Na—NH_3—NH_4^+ are totally ineffective. Consequently, they recommend that water not be used to destroy the excess of sodium customarily employed for reductions in liquid ammonia but instead that ammonium salts or an ammonolysis catalyst (*e.g.*, iron) be used. The results of the work described here leave some doubt as to the reliability of this suggestion.

Other investigators[5] have shown that an ammonia solution of nitroguanidine is readily reduced to aminoguanidine by sodium in the presence of ammonium chloride whereas sodium alone yields an indefinite mixture. It is not clear from the published reports whether the failure to obtain 100 per cent. yields of aminoguanidine is to be attributed to side reactions or to the generation of *insufficient* hydrogen to effect complete reduction. To settle the question it would be necessary to determine what fraction of the total hydrogen generated is retained by the compound undergoing reduction.

EXPERIMENTAL

Preparation of 1,2,3-benzotriazole.—This substance was prepared by a slight modification of the method described by Fieser and Martin.[6] The acetyl derivative of 1,2,3-benzotriazole was conveniently deacetylated by solution in liquid ammonia at −33°. After evaporation of the ammonia, the residue was dissolved in water, the solution was neutralized with acetic acid, and the benzotriazole allowed to crystallize; m.p. 98.5°. The average yield was 95%, starting with the purified acetate.

Anal. Calc'd for $C_6H_5N_3$: N, 35.3. Found: N, 35.2, 35.3.

Preparation of the N-methyl derivatives.—The 1- and 2-methyl derivatives of benzotriazole were prepared by the methylation of benzotriazole with dimethyl sulfate and sodium hydroxide according to the method of Krollpfeiffer, Rosenberg and Mühlhausen[7] and also by methylation with diazomethane in ethyl alcohol. The yield in the first method was approximately 37% of 1-methyl-1,2,3-benzotriazole (m.p. 65°) and 25% of 2-methyl-2,1,3-benzotriazole, (105–7°/15 mm.). The second method resulted in a 15% yield of the 1-methyl and a 51% yield of the 2-methyl derivative.

Apparatus.—The apparatus used in this work was a modified form of the closed system described by Johnson and Fernelius[8] which provided for (*1*) condensation of ammonia (usually about 150 ml.), (*2*) stirring of the solution by means of a current of gaseous ammonia, (*3*) addition of a known weight of sample, (*4*) alternate addition of weighable quantities of alkali metal and ammonium salt without opening

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[4] WOOSTER AND GODFREY, *J. Am. Chem. Soc.*, **59**, 596 (1937).

[5] FULLER, LIEBER, AND SMITH, *J. Am. Chem. Soc.*, **59**, 1150 (1937).

[6] FIESER, AND MARTIN, *ibid.*, **57**, 1838 (1935).

[7] KROLLPFEIFFER, ROSENBERG, AND MÜHLHAUSEN, *Ann.*, **515**, 124 (1935).

[8] JOHNSON AND FERNELIUS, *J. Chem. Educ.*, **6**, 444–447 (1929).

of the system to the air, (*5*) quantitative collection of gases evolved during reaction, and (*6*) complete removal of ammonia prior to the working up of the product.

1,2,3-Benzotriazole and sodium.—1,2,3-Benzotriazole dissolved in liquid ammonia (very soluble) reacted rapidly with sodium without the evolution of gas. The solution remained clear until approximately 0.82 gram atom of sodium had been added when it became yellow. This color intensified upon further reaction and was orange-yellow near the end-point (dark-green, due to the blue color of dissolved sodium). The average of five runs gave a ratio of 1.05:1.00 for gram atoms of sodium/moles of triazole. Excess of sodium over this ratio resulted in no further reaction over a period of four hours.

The yellow product remaining after evaporation of the ammonia was readily soluble in water. Upon neutralization with hydrochloric acid a yellow-brown precipitate formed, which darkened rapidly in contact with air. Further addition of acid dissolved the precipitate to form a dark-red solution. With small quantities of material it was not possible to isolate a pure compound, but with 0.1 mole of triazole a dark-red precipitate was obtained by working at 0° with the minimum amount of water and treatment with aqua regia. After filtering and thorough washing with ether, the red material melted sharply at 137–137.6°. It was extremely soluble in water, ethanol, and acetone, but only slightly soluble in ether, ligroïn, and chloroform. Yield: 5 g. from 10 g. (0.083 moles) of 1,2,3-benzotriazole.[9]

Exhaustive ether extraction of the solution remaining after the precipitation of the above material together with the washings, yielded a residue which upon solution in hot water, charcoal clarification, and crystallization melted at 98.5° and showed no depression in melting point when mixed with 1,2,3-benzotriazole. Yield: 4.768 g., or 47.5% of the original triazole.

1,2,3-Benzotriazole, sodium, and ammonium bromide.—After addition of sodium to a solution of 1,2,3-benzotriazole until the end-point was reached, the reaction mixture was treated alternately with sodium and ammonium bromide until a considerable quantity of hydrogen gas had been liberated (this usually represented a fivefold excess of sodium over the amount required for the initial end-point). During the early stages of the titration, the neutral solution was yellow. This color, which could be discharged by excess ammonium bromide, disappeared entirely near the end of the reaction. The weight of ammonium bromide required to just discharge the blue color of the excess sodium was exactly equivalent to this excess but the amount of gaseous hydrogen collected was always less than that which would be equivalent to the excess sodium:

Gram atoms Na	0.0858	0.0909	0.1017
Moles triazole	0.0142	0.0152	0.0171
Gram atoms H_2 collected	0.0286	0.0272	0.0322
Gram atoms H_2 taken up	0.0430	0.0485	0.0524
Gram atoms N_2 collected		0.0034	0.0029
H/mole	3.01	3.19	3.06

It was found advisable to add a considerable excess of ammonium bromide at the *end* of the reaction so that the aqueous solution later obtained would not be strongly basic.

The presence of *o*-phenylenediamine in the reaction products was shown by forming, in separate runs, the phenazine derivative with phenanthraquinone and

[9] FIELDS (unpublished observations) has studied a number of reactions of this substance with the object of determining its structure. Since permanganate oxidation yields the 4,5-dicarboxylic acid of 1,2,3-triazole, it is very doubtful that the triazole nucleus has been hydrogenated.

the dibenzenesulfonyl derivative with benzenesulfonyl chloride. The dibenzo [*a*, *c*] phenazine melted at 204–6°. The dibenzenesulfonyl derivative melted at 190–191.5°. Neither derivative showed any depression of melting point with authentic samples. In further runs, the dibenzoyl derivative was prepared, d. 305°; yields 48%, 43%.

Sodium 1,2,3-benzotriazolate, sodium, and ammonium bromide.—The soluble sodium salt of 1,2,3-benzotriazole was prepared by the reaction between excess sodium amide and the triazole. This salt did not discharge the color of a sodium solution even on long standing. On alternately treating such solutions with ammonium bromide and sodium the following results were obtained:

Gram atoms Na	0.1420	0.1546
Moles triazole	0.0161	0.0176
Gram atoms H_2 collected	0.0489	0.0544
Gram atoms H_2 taken up	0.0931	0.1002
H/mole	5.78	5.69
Yield: *N,N'*-Dibenzoyl-*o*-phenylene diamine	3.94 g. (77%)	5.01 g. (89%)

Hydrogenation of 1,2,3-benzotriazole in basic solution.—1,2,3-Benzotriazole was dissolved in liquid ammonia and sufficient potassium added to produce a permanent blue color (no gas evolved). Excess potassium was then added, together with an iron wire to catalyze the reaction between potassium and ammonia. Hydrogen was evolved at a moderate rate and the solution became yellow-red in an hour.

Gram atoms K	0.1113	0.1003
Moles triazole	0.0154	0.0139
Gram atoms H_2 collected	0.0717	0.0631
Gram atoms H_2 taken up	0.0242	0.0233
H/mole	1.57	1.67
Yield: *N,N'*-dibenzoyl-*o*-phenylene diamine	0.14 g.	0.21 g.

2-Methyl-1,2,3-benzotriazole, sodium, and ammonium bromide.—A liquid ammonia solution of the 2-methyltriazole did not decolorize sodium. Ammonium bromide and sodium were then added alternately until a considerable volume of hydrogen had been collected. No gas was liberated until 5.65 equivalents had been generated. During the early stages of the titration, the neutral solution was yellow. This color which could be discharged by excess ammonium bromide disappeared entirely near the end of the reaction.

Gram atoms Na	0.1061	0.0979
Moles triazole	0.0149	0.0125
Gram atoms H_2 collected	0.0185	0.0254
Gram atoms H_2 taken up	0.0876	0.0725
H/mole	5.87	5.80
Yield: dibenzo [*a*,*c*] phenazine	2.98 g. (73%)	3.06 g. (89%)

1-Methyl-1,2,3-benzotriazole, sodium, and ammonium bromide.—A suspension of the 1-methyltriazole did not discharge the color of dissolved sodium. The mixture was then treated alternately with ammonium bromide and sodium until a considerable volume of gas had been collected. The solution at the end-point was red-orange.

	1	2
Gram atoms Na	0.0675	0.0927
Moles triazole	0.0113	0.0104
Gram atoms H_2 collected	0.0159	0.0400
Gram atoms H_2 taken up	0.0516	0.0527
Gram atoms N_2 collected	0.0079	0.0096
H/mole	4.56	5.06

The product from reaction 1 was converted to the dibenzoyl derivative (light-tan) and recrystallized three times from 95% ethanol (white), m.p. 152.8–153.8°.

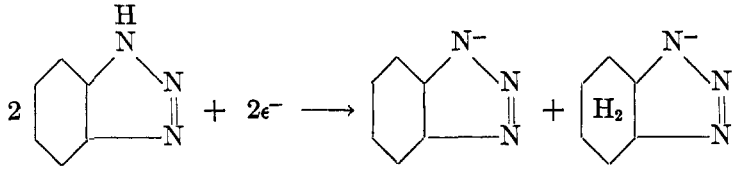
*Anal.** Calc'd for $C_{21}H_{18}N_2O_2$: C, 76.3; H, 5.5; N, 8.5
Found: C, 75.9; 75.9; H, 5.4, 5.5; N, 9.0, 9.3.

The product from reaction 2 was converted to the dibenzenesulfonyl derivative and recrystallized four times from 95% ethanol (colorless needles), m.p. 156–157°.†

Anal.‡ Calc'd for $C_{18}H_{18}S_2O_4N_2$: C, 56.7; H, 4.5.
Found: C, 57.2, 57.1; H, 4.4, 4.5.

DISCUSSION

The reactions described above demonstrate that hydrogen is not evolved in the reaction between a liquid-ammonia solution of 1,2,3-benzotriazole and sodium. Half of the 1,2,3-benzotriazole may be recovered at the end of the reaction; the other half is apparently reduced to an unstable dihydrobenzotriazole.[10]

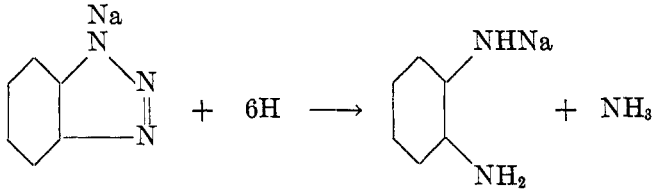


The above mixture of salts, sodium 1,2,3-benzotriazolate alone, and the 1- and 2-methyl derivatives of benzotriazole are not affected by a sodium solution.

The generation of hydrogen by the interaction of sodium and the ammonium ion,

$$NH_4^+ + \epsilon^- \rightarrow NH_3 + H,$$

reduces sodium 1,2,3-benzotriazolate and the 2-methyl derivative to *o*-phenylenediamine,

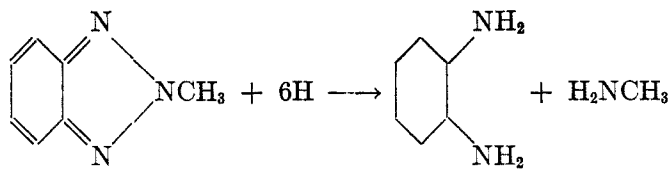


* Microanalysis by H. S. Clark.

† Apparently the dibenzoyl and dibenzenesulfonyl derivatives of *N*-methyl-*o*-phenylene diamine have not been described in the literature.

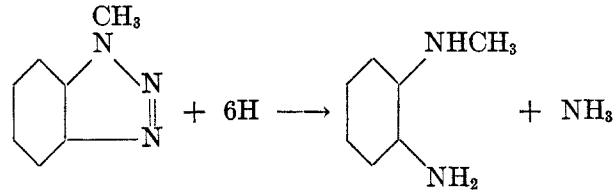
‡ Microanalysis by J. H. Walker.

[10] FRIES, GUTERBOCK, AND KÜHN, *Ann.*, **511**, 214 (1934), state (without giving experimental details) that they have investigated the catalytic hydrogenation of 1,2,3-benzotriazole. With a palladium or platinum catalyst they obtained tetrahydro-1,2,3-benzotriazole; with a nickel catalyst, *o*-phenylenediamine and ammonia.



Although the uptake of hydrogen approaches six atoms in both cases, this value was never realized in practice probably because (*1*) the hydrogenation is accompanied by some splitting of the ring as evidenced by the presence of nitrogen in the gases collected and (*2*) the hydrogenation of the last portion of the triazoles is inefficient because of the low concentration. Since the uptake of hydrogen in the case of an equimolecular mixture of the sodium salts of 1,2,3-benzotriazole and its dihydro derivative is only slightly in excess of 3 atoms, it appears that the dihydro compound resists further reduction.

The hydrogenation of 1-methyl-1,2,3-benzotriazole is complicated by its insolubility and the marked splitting of the ring. In practice an uptake of 5 atoms of hydrogen has been obtained, but not 6 as would be expected,



The hydrogenation of 1,2,3-benzotriazole in basic solution where the hydrogen is liberated by the reaction,

$$K \rightleftharpoons K^+ + \epsilon^-; \quad NH_3 + \epsilon^- \xrightarrow{\text{Fe catalyst}} NH_2^- + H,$$

is by no means as effective as hydrogenation with sodium and ammonium ion. This difference may be due to (*1*) the greater basicity of the solution, (*2*) the fact that hydrogen is liberated only at the surface of the iron, or (*3*) the possibility that iron promotes the combination of hydrogen atoms, $2\ H \rightarrow H_2$. There seems to be no obvious reason why the hydrogen liberated from 1,2,3-benzotriazole and that from the ammonium ion should reduce the benzene ring in the first case and the heterocyclic ring in the latter.

Reduction by electrons vs. *hydrogenation.*—There are two widely accepted theories as to the mechanism of the reduction of organic substances by active metals. One view regards the active hydrogen formed by the reactions of the metal with a solvent as the effective agent. According

to the other view organometallic compounds are first formed which are solvolyzed giving rise to the hydrogenated product.[11] Studies in liquid ammonia have brought to light a number of instances of this latter type of reduction. It is now evident that active hydrogen may also play an important rôle and that the effects of the two mechanisms may be separately evaluated, at least for the substances involved in these studies. The question is really one of the relative ease of addition of electrons and of hydrogen atoms. The triazole nucleus is stable toward electrons but is broken down by hydrogen atoms.

Destruction of excess sodium following a reduction.—The usual practice in using an ammonia solution of sodium as a reducing agent is that of adding an excess of metal and later destroying this excess by treatment with water or an ammonium salt. Since reduction may take place both before and after the addition of ammonium salt, it is desirable to know which is involved, or if both are. In case active hydrogen is effective, yields may be increased, or more extensive reduction obtained by providing those conditions which will yield an ample amount of such hydrogen. As an example, dibenzothiophene is converted to the dihydro derivative by sodium in liquid ammonia,[12] but is more completely reduced with excess sodium and ammonium bromide.[13]

The subject of reductions in ammonia presents another aspect. Suppose one wishes to obtain only the reduction due to the electron and not that due to active hydrogen. Suppose, further that it is desirable for speed, completeness, etc. to have an excess of sodium present initially. If the use of water, ammonium salts, and even ammonolysis catalysts, introduces complications, how may this excess metal be destroyed without liberating hydrogen or introducing other complications? Sodium nitrate reacts with three atoms of sodium without the evolution of any gas.[14] The probable reaction is:

$$NaNO_3 + 3Na + NH_3 \rightarrow Na_2NO_2 + NaOH + NaNH_2.^{15}$$

Preliminary studies indicate that sodium nitrate may be used safely and effectively to destroy excess sodium, provided the disodium nitrite so formed, is decomposed by ammonium salts before the evaporation of the ammonia. Advantage may also be taken of the fact that mercury, in

[11] For literature references see WOOSTER AND GODFREY, *J. Am. Chem. Soc.*, **59**, 596 (1937).

[12] GILMAN AND JACOBY, J. ORG. CHEM., **3**, 116 (1938).

[13] CAPPEL AND FERNELIUS, unpublished observations.

[14] BURGESS AND HOLDEN, *J. Am. Chem. Soc.*, **59**, 461 (1937).

[15] For formation and properties of Na_2NO_2 see MAXTED, *J. Chem. Soc.*, **111**, 1016 (1917); ZINTL AND KOHN, *Ber.*, **61**, 189 (1928).

contact with an ammonia solution of a metal, removes the metal from ammonia.[16]

Further studies on the relative reducing tendencies of the electron and active hydrogen are in progress.

We are indebted to Mr. Karl E. Blumenberg for help with the gas analyses involved in this work.

SUMMARY

1. 1,2,3-Benzotriazole reacts with sodium in ammonia solution to form equimolecular quantities of the sodium salts of 1,2,3-benzotriazole and its dihydro derivative. Active hydrogen ($NH_4^+ + \epsilon^-$) reduces the former salt to *o*-phenylenediamine but not the latter.

2. An ammonia solution of sodium does not react with 1-methyl- or 2-methylbenzotriazole, nor with the sodium salts of 1,2,3-benzo- and dihydro-1,2,3-benzotriazole.

3. Active hydrogen ($NH_4^+ + \epsilon^-$) reduces 2-methyl-2,1,3-benzotriazole to *o*-phenylenediamine and 1-methyl-1,2,3-benzotriazole to *N*-methyl-*o*-phenylenediamine.

4. Hydrogen generated by the interaction of potassium and liquid ammonia in the presence of iron is relatively ineffective in reducing potassium, 1,2,3-benzotriazolate to *o*-phenylenediamine.

5. The bearing of these results on the general subject of reductions in liquid ammonia is discussed.

[16] BERGSTROM, *J. Am. Chem. Soc.*, **45**, 2791 (1923).

[CONTRIBUTION FROM THE BUREAU OF ENTOMOLOGY AND PLANT QUARANTINE, U. S. DEPARTMENT OF AGRICULTURE]

ALLENES. II. THE PREPARATION OF 1-CYCLOHEXYL-2,3-PENTADIENE

FRED ACREE, JR., AND F. B. LAFORGE

Received July 26, 1939

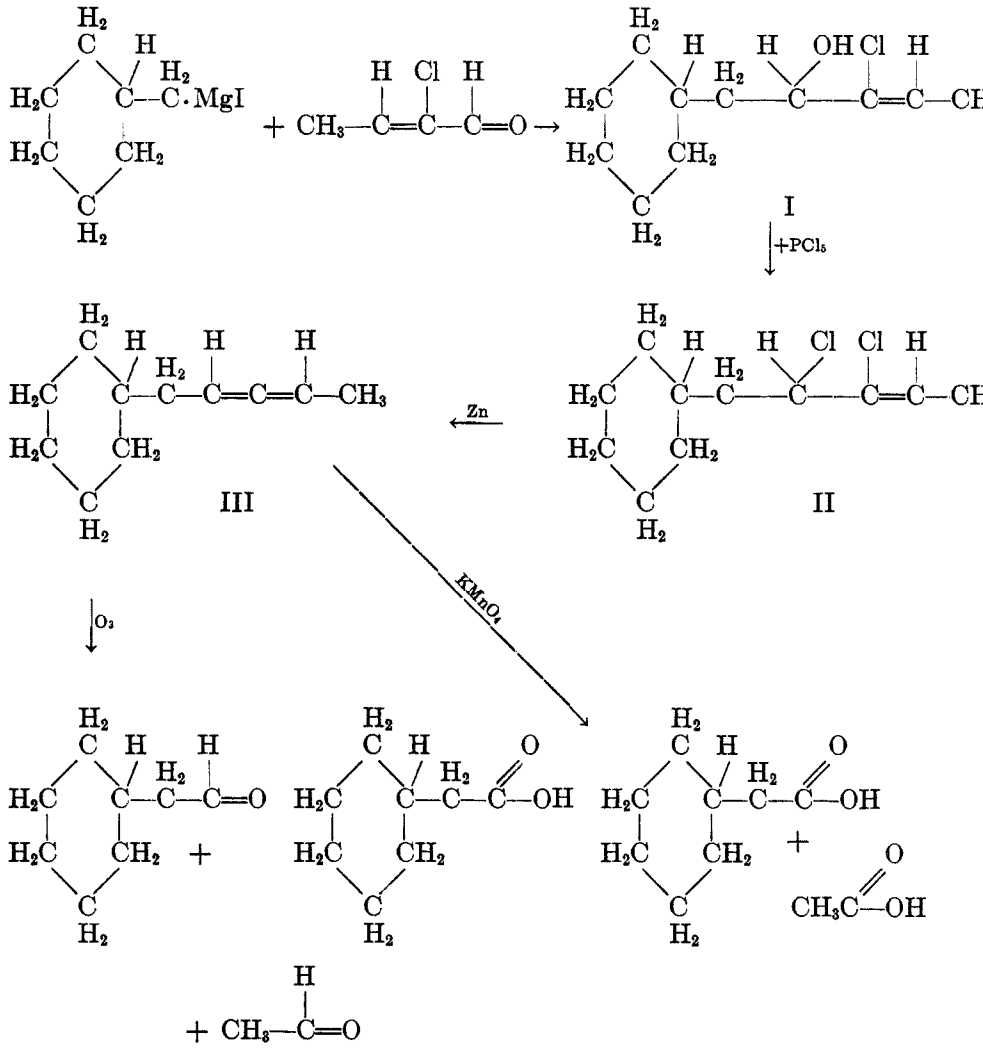
The structure of the five-membered side-chain of pyrethrolone, the cyclopentenolone component of the pyrethrins, still remains the only feature of the molecule which has not been definitely established. Staudinger and Ruzicka[1], who first isolated and studied pyrethrolone, concluded that a side-chain containing a cumulated system of double bonds corresponded best to its chemical behavior. LaForge and Haller[2] have reported results of experiments directed to the solution of this problem, but without reaching a definite conclusion. Their experimental results, especially in regard to the behavior of pyrethrolone and its reduction product, pyrethrone, toward bromine, were difficult to explain with the assumption of the presence of the cumulated system, and they were still more contrary to the known behavior of conjugated systems.

The purpose in preparing substituted allenes was to perform on these compounds the reactions that had been applied to pyrethrolone and pyrethrone and to compare their respective behaviors.

In the first article of this series[3] the preparation of 1-phenyl-1,2-butadiene, $C_6H_5CH{=}C{=}CHCH_3$, was reported. Since this hydrocarbon contains but four members in the side-chain, its analogy with pyrethrolone was not considered sufficiently close. Moreover, it is now contemplated to extend the investigation into the field of ultraviolet absorption study, and for this purpose 1-phenyl-1,2-butadiene is unsuitable as a reference compound because of the presence of the phenyl group. A compound offering a closer analogy with pyrethrone, on the assumption that it contains the cumulated system, and at the same time one that would satisfy the requirements of ultraviolet absorption spectrum study, would be 1-cyclohexyl-2,3-pentadiene, the preparation of which is the subject of this article. It was obtained by the following series of reactions: α-chlorocrotonic aldehyde furnished 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene, $C_6H_{11}CH_2CHOHCCl{=}CHCH_3$ (I), by the Grignard reaction with

[1] STAUDINGER AND RUZICKA, *Helv. Chim. Acta*, **7**, 212 (1924).
[2] LAFORGE AND HALLER, J. ORG. CHEM., **2**, 546 (1938).
[3] ACREE AND LAFORGE, *Ibid.*, **4**, 40 (1939).

hexahydrobenzyl iodide. Substitution of chlorine for the hydroxyl group gave 1-cyclohexyl-2,3-dichloro-3-pentene, $C_6H_{11}CH_2CHClCCl{=}CHCH_3$ (II)*. Dehalogenation of the dichloro compound furnished 1-cyclohexyl-2,3-pentadiene, $C_6H_{11}CH_2CH{=}C{=}CHCH_3$ (III).



* Regarding the possibility of the allylic rearrangement having occurred in the process of chlorination with the formation of 1-cyclohexyl-3,4-dichloro-2-pentene, see the previous article[3].

The structure of III was proved both by ozonization and by oxidation with permanganate. Acetaldehyde was isolated as its dimethone derivative from the water-soluble reaction products after decomposition of the ozonide, while from the product soluble in the organic solvent both cyclohexylacetaldehyde and cyclohexylacetic acid were isolated, the former as its semicarbazone, and the latter as its amide. Oxidation of III with permanganate furnished acetic acid, which was characterized as acetyl-*p*-toluidide, and cyclohexylacetic acid which was isolated as its amide.

An attempt to apply the general series of reactions used previously for 1-phenyl-1,2-butadiene[3] to the preparation of 1-cyclohexyl-2,3-pentadiene failed because hexahydrobenzylmagnesium iodide reduced 2,2,3-trichlorobutanal to the alcohol instead of giving the expected addition reaction.

EXPERIMENTAL

1-Cyclohexyl-2-hydroxy-3-chloro-3-pentene (*I*).—Thirty-five grams of α-chlorocrotonic aldehyde[4] dissolved in 200 cc. of dry ether was added slowly to the ice-cold Grignard reagent prepared from 84 grams of hexahydrobenzyliodide[5] and 10 grams of magnesium in 300 cc. of ether.

The reaction was allowed to continue in the cold for 16 hours. The Grignard reaction product was added slowly to a stirred solution of 25 grams of ammonium chloride in 150 cc. of water to which ice was added in quantity sufficient to maintain a temperature of 0°. Fifteen cubic centimeters of glacial acetic acid was added to break the emulsion that formed, and the reaction products were extracted with ether. The ethereal solution was washed successively with a cold saturated solution of sodium bisulfite, cold 5 per cent. sodium carbonate solution, and water, and then dried over anhydrous sodium sulfate. The solvent was removed by evaporation, and the residue was distilled, yielding 30 grams of oil boiling at 130–135°, p = 9 mm.; n_D^{25} = 1.4893. The distillate crystallized after standing several hours in the refrigerator. It was recrystallized by dissolving in 1 to 2 volumes of low-boiling petroleum ether, cooling to −18°, and filtering at the same temperature. It melted at 39–40°.

Anal. Calc'd for $C_{11}H_{19}ClO$: Cl, 17.5. Found: Cl, 17.2.

The compound did not form a crystalline phenylurethane.

Hydrogenation of 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene (*I*).—One and one-half grams of the alcohol was reduced in the presence of palladium-calcium carbonate catalyst[6] in ethanolic potassium hydroxide solution, absorbing 310 cc. of hydrogen (calc'd for 2 moles, 332 cc.). The reaction product was isolated and distilled, yielding 1 gram of material boiling at 112–114°, p = 9 mm.; n_D^{26} = 1.4620. From its method of preparation this material hardly could be other than 1-cyclohexyl-2-pentanol, a compound that does not appear to be described in the literature.

Anal. Calc'd for $C_{11}H_{22}O$: C, 77.64; H, 12.94.
Found: C, 77.64; H, 12.73.

It did not form a crystalline phenylurethane.

1-Cyclohexyl-2,3-dichloro-3-pentene (*II*)*.—Six grams (10 per cent. excess) of

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[4] MOUREU, MURAT, AND TAMPIER, *Bull. soc. chim.*, [4], **29**, 32 (1921).

[5] GUTT, *Ber.*, **40**, 2067 (1907). [Hexahydrobenzyl alcohol was prepared according to FAVORSKY AND BORGMANN, *Ber.*, **40**, 4865 (1907)].

[6] HOUBEN, "Die Methoden der organischen Chemie," 3 ed., vol. 2, p. 360.

powdered phosphorus pentachloride was slowly added to 5.2 grams of 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene (I) dissolved in 25 cc. of cold petroleum ether. When the initial vigorous reaction had subsided, the mixture was boiled for a few minutes on the steam bath and then poured into water containing ice. The petroleum ether solution was separated and washed with dilute sodium bicarbonate solution and then with water. After drying over anhydrous sodium sulfate, the solvent was removed by evaporation, and the residue was distilled, yielding 4.2 grams of product which boiled at 131–133°, p = 11 mm.; n_D^{26} = 1.4965.

Anal. Calc'd for $C_{11}H_{18}Cl_2$: Cl, 32.1. Found: Cl, 31.7.

1-Cyclohexyl-2,3-pentadiene (III).—Ten grams of 1-cyclohexyl-2,3-dichloro-3-pentene (II) dissolved in 25 cc. of ethanol was dropped into a stirred suspension of 25 grams of zinc dust in 25 cc. of boiling ethanol. (The zinc dust had been treated previously with a large volume of very dilute hydrochloric acid to remove zinc oxide, and then washed free of acid with water and finally with ethanol.) The reaction flask was provided with a dropping funnel and a reflux condenser. The solution of the dichloride was introduced at the rate necessary to cause uniform boiling without the application of heat. Finally, the reaction solution was boiled for 15 minutes, cooled, filtered from the excess zinc, and diluted with several volumes of water. The separated oil was extracted with ether, and the solution was washed repeatedly with water and finally with dilute sodium carbonate solution, and then dried over sodium sulfate. After removal of the solvent by evaporation, the residue was distilled, yielding 4.6 grams of product boiling at 82–85°, p = 12 mm.; n_D^{26} = 1.4810.

Anal. Calc'd for $C_{11}H_{18}$: C, 88.00; H, 12.00.
Found: C, 88.50; H, 12.06.

In comparison with 1-phenyl-1,2-butadiene the compound is relatively stable. The 1-cyclohexyl-2,3-pentadiene (III) showed no evidence of reaction when treated in the usual manner with freshly prepared maleic anhydride.

Hydrogenation of 1-cyclohexyl-2,3-pentadiene (III).—One-half gram of III in ethanol solution, when reduced with hydrogen in the presence of platinum oxide catalyst, absorbed 165 cc. of hydrogen in a few minutes (calc'd for 2 mols, 149 cc.). The reduction product was isolated and on distillation boiled at 200–205°C., p = atmos.; n_D^{11} = 1.4474; yield, 0.35 gram. The boiling point of *n*-amylcyclohexane is reported[7] as 198°C., p = atmos.; n_D^{11} = 1.4466.

Ozonization of 1-cyclohexyl-2,3-pentadiene (III).—An excess of ozone was passed into an ice-cold solution of 1.2 grams of III dissolved in 5 cc. of carbon tetrachloride. The ozonide was decomposed by shaking with a few cubic centimeters of water containing ice and finally by warming. The aqueous solution was separated and added to a solution of 1.6 grams of dimethone dissolved in 400 cc. of water. The crystalline material that had formed by the end of 16 hours was separated and recrystallized from ethanol. It weighed 0.2 gram, melted at 138–140°, and was identified as ethylidenedimethone by the mixture melting point, 137–138°.

The carbon tetrachloride solution was extracted with 5 per cent. aqueous potassium hydroxide solution, washed with water, and dried over sodium sulfate. The solvent was removed by evaporation, and the residue was distilled, yielding 0.4 gram of product boiling at 70–120°, p = 10 mm. This distillate was dissolved in 2 cc. of ethanol and added to a solution of 0.4 gram of semicarbazide hydrochloride in 1 cc. of water and 1 cc. of pyridine. After standing overnight, the reaction mixture was diluted with a few cubic centimeters of water. The crystalline material that separated was removed by filtration, and recrystallized from ethanol. It weighed 0.1

[7] STRATFORD, *Chem. Zentr.*, **1929, II,** 1286.

gram and melted at 157–159°. Skita[8] records the melting point of cyclohexylacetaldehyde semicarbazone as 153°.

Anal. Calc'd for $C_9H_{17}N_3O$: C, 59.02; H, 9.29.
Found: C, 58.80, 58.70; H, 9.28, 9.28.

The aqueous alkaline extract from the carbon tetrachloride solution was concentrated to a small volume and acidified. The oil that separated was dissolved in petroleum ether, washed with water, and dried over sodium sulfate. The solvent was removed by evaporation, yielding 0.4 gram of residue. By treatment with thionyl chloride this acid reaction product was converted into its acid chloride. The addition of concentrated ammonium hydroxide precipitated a crystalline material, which was isolated and recrystallized from water. It melted at 169°C. Gutt[9] records the melting point of cyclohexylacetic acid amide as 171–172°C.

Anal.† Calc'd for $C_8H_{15}NO$: N, 9.93. Found: N, 10.00.

Oxidation of 1-cyclohexyl-2,3-pentadiene (III).—One gram of III was oxidized with 2 grams of potassium permanganate in 60 cc. of acetone previously treated with permanganate. The acetone solution, after being filtered from the manganese dioxide, yielded 0.5 gram of unchanged starting material.

The aqueous extract from the manganese dioxide was acidified and extracted with petroleum ether. The petroleum ether solution was washed with water, dried over sodium sulfate, and the solvent was removed. The residue was treated with thionyl chloride to convert the acid reaction product into the acid chloride. The addition of concentrated ammonium hydroxide precipitated a crystalline material, which was isolated and recrystallized from water. It weighed 0.1 gram and melted at 169°. It was identified as cyclohexylacetic acid amide by the mixture melting point method.

The aqueous solution that had been extracted with petroleum ether was steam distilled. The distillate was made alkaline and evaporated to dryness, yielding 0.4 gram of residue. Treatment of this residue with *p*-toluidine[10] yielded 0.15 gram of recrystallized material which melted at 148–149°. It was identified as acetyl-*p*-toluidide by the mixture melting point, 147–148°.

Reaction of 2,2,3-trichlorobutanal with hexahydrobenzylmagnesium iodide.—Sixty-five grams of 2,2,3-trichlorobutanal dissolved in 200 cc. of dry ether was added slowly to the cold Grignard reagent prepared from 12 grams of magnesium and 102 grams (20 per cent. excess) of hexahydrobenzyl iodide dissolved in 200 cc. of the same solvent. The reaction was allowed to continue for 4 hours. The reaction mixture was then added slowly to a stirred solution of 25 grams of ammonium chloride dissolved in 150 cc. of water to which sufficient ice was added to maintain the solution cold. Fifteen cubic centimeters of glacial acetic acid was added to break the emulsion, and the reaction products were extracted with ether. The ethereal solution was washed with a cold saturated solution of sodium bisulfite, cold 5 per cent. aqueous sodium carbonate, and water, and then dried over sodium sulfate. The solvent was removed by evaporation and the residue was distilled, yielding 58 grams of oil which boiled at 76–95°, p = 1 mm. After being kept cold for several

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[8] SKITA, *Ber.*, **48**, 1694 (1915).

[9] GUTT, *ibid.*, **40**, 2068 (1907).

† This nitrogen analysis was performed by T. H. Harris, Bureau of Agricultural Chemistry and Engineering, U. S. Department of Agriculture.

[10] MULLIKEN, "Identification of Pure Organic Compounds," 1st ed., John Wiley and Sons, Inc., New York City, **1904**, vol. 1, p. 80.

hours, the distillate crystallized. The crystalline material was separated from the non-crystalline portion by filtration at −18° and washing with cold petroleum ether. It weighed 22 grams, and melted at 53–55°. On redistillation it boiled at 97–98°, p = 18 mm. The material was obtained pure, melting point 58–59°, by one recrystallization from petroleum ether.

Anal. Calc'd for $C_4H_7Cl_3O$: Cl, 60.0. Found: Cl, 59.5, 60.0.

The properties of the compound agree with those reported for 2,2,3-trichloro-1-butanol prepared by Garzarolli-Thurnlackh[11] by the action of ethylzinc on 2,2,3-trichlorobutanal.

SUMMARY

The Grignard reaction of hexahydrobenzylmagnesium iodide with α-chlorocrotonic aldehyde furnished 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene, which was converted into 1-cyclohexyl-2,3-dichloro-3-pentene by the action of phosphorus pentachloride. The 1-cyclohexyl-2,3-dichloro-3-pentene was dehalogenated with zinc to 1-cyclohexyl-2,3-pentadiene, the structure of which was proved by the identification of its products of ozonization and oxidation, namely, cyclohexylacetaldehyde, acetaldehyde, cyclohexylacetic acid, and acetic acid.

The Grignard reaction of hexahydrobenzyl iodide with 2,2,3-trichlorobutanal yielded the abnormal reaction product 2,2,3-trichloro-1-butanol.

[11] GARZAROLLI-THURNLACKH, *Ann.*, **213**, 369 (1882).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

ANALOGS OF EPHEDRINE AND ADRENALINE CONTAINING THE MORPHOLINE NUCLEUS AND SOME OF THEIR ESTERS

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INTRODUCTION

Since the advent of cocaine as a local anesthetic, a large amount of literature has appeared on the synthesis of related compounds. The purpose of most of this work was to obtain active local anesthetics which would be less toxic than cocaine. These aims have been accomplished to some extent and there are now available a large number of compounds, mostly benzoates or *p*-aminobenzoates of N-substituted amino alcohols, which compare favorably with cocaine. In general, however, they lack the vasoconstricting power shown by cocaine and consequently must be used in conjunction with adrenaline. The latter, by decreasing the rate at which the anesthetic is carried away from the point of injection, permits the use of lower concentrations and also acts as a hemostatic agent.

Attempts have been made by several workers to combine structures essential for vasoconstriction and structures essential for anesthetic activity with the hope that the physiological effects might be cumulative. In general, pressor activity has been found in compounds possessing the grouping Ar—C—C—N and local anesthetic activity in compounds containing the grouping Ar—CO—O—C—C—N—R. Most of the compounds prepared up to this time that contain both of the required groupings have not been entirely satisfactory. This work has been reviewed in two excellent papers by Hartung (1) and by Alles and Knoefel (2).

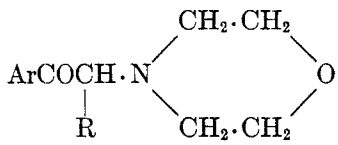
More recently, Coles and Loth (3) prepared some aromatic esters of N-β-hydroxyethyl- and N-γ-hydroxypropyl- *ac*-tetrahydro-β-naphthylamine. Although *ac*-tetrahydro-β-naphthylamine has been shown to have definite pressor action, the new derivatives were lacking in this property.

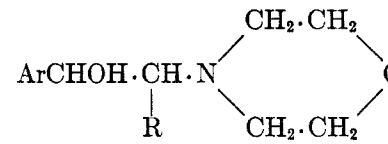
Osborne (4) reported that the synthesis of α-(3,4-dihydroxyphenyl)-β-(*p*-aminobenzoyl-β-diethylaminoethanol)-α-ethanone hydrochloride (epi-

caine) produced a drug which combines both local anesthetic and vasopressor action.

It does not seem possible to draw any definite conclusions from the above work, since the evidence for the various compounds does not agree very well. In some cases both anesthetic and pressor activity were reported and in other cases for closely related compounds pressor activity was lacking. The fact that none of these compounds appears to be in general use might indicate that the problem has by no means been solved.

Since certain morpholino compounds have been shown to possess local anesthetic action (5), it was planned to condense morpholine with structures known to exert vasopressor action, hoping to obtain compounds of medicinal value. Therefore morpholine was condensed with phenacyl bromide, α-bromopropiophenone, *p*-hydroxyphenacyl chloride, 3,4-dihydroxyphenacyl chloride and phenylethyl bromide, to yield amino ketones which in turn were catalytically reduced to the corresponding carbinols. Where R equals H, the side chain





R=H, CH_3 Ar=C_6H_5, *p*-HOC_6H_4, 3,4-$(HO)_2C_6H_3$

is structurally similar to adrenaline and where R equals CH_3, the side chain is similar to that found in ephedrine. The condensation product from phenylethyl bromide, of course contained no alcohol group in the side chain. Since aromatic esters of amino alcohols usually possess anesthetic activity, the benzoates of 1-phenyl-2-morpholinoethanol-1 and 1-phenyl-2-morpholinopropanol-1 were prepared as well as the cinnamate of the ethanol derivative.

Magee and Henze (6) have recently prepared a series of 5-alkylamino hydantoins. Certain hydantoins substituted in the five position have been shown to possess hypnotic activity. Since four new amino ketones were prepared in the course of the present work, it was thought that the corresponding hydantoins might be of some interest. Attempts to prepare these hydantoins by the Bucherer method (7) were successful only in the case of ω-morpholinoacetophenone from which 5-phenyl-5-morpholinomethyl hydantoin was obtained. These compounds are being tested and the pharmacological report will be made later.

EXPERIMENTAL

Analysis.—The semi-micro Kjeldahl method was used for the nitrogen determination. The distillate was absorbed in 15 cc. of 4% boric acid solution and titrated to a methyl-red endpoint according to the method of Meeker and Wagner (8).

Preparation of catalyst.—The catalyst employed in most cases was 10% palladium on charcoal prepared according to the method of Hartung (9). The 20% palladium on charcoal catalyst was prepared similarly. In all cases the catalyst was shaken under an atmosphere of hydrogen until no more gas was absorbed, immediately before the introduction of the sample.

Preparation of phenacyl bromide.—To 30 g. (0.25 mole) of acetophenone dissolved in 35–40 cc. of glacial acetic acid, 40 g. (0.25 mole) of bromine was added all at once. The flask was then immediately attached to a reflux condenser suitably connected for the absorption of hydrogen bromide, shaken in order to make the mixture homogeneous and then allowed to stand. After a few minutes a vigorous reaction took place with the evolution of hydrogen bromide. The straw-colored liquid was poured into a mixture of ice and water and was permitted to stand approximately one hour. At the end of this time the solid was removed by filtration and the oil well pressed out. The solid was then immediately recrystallized from 95% alcohol. Yields of 25–30 g. (50–60%) of pure product melting at 49.5–50° were obtained. This method is similar to that employed by Schmidt (10) for the preparation of α-bromopropiophenone. The method of Rather and Reid (11) gave lower yields of a considerably darker product.

Preparation of α-bromopropiophenone.—This was prepared similarly to the phenacyl bromide according to the method of Schmidt (10). The reaction mixture after being poured into ice water was carefully separated and washed with sodium bicarbonate solution, then with water and finally dried over anhydrous sodium sulfate. This product, obtained in 90% yields, was used without purification in further reactions.

Preparation of p-*hydroxyphenacyl chloride.*—This was prepared according to Tutin, Caton and Hann (14), using ligroin, however, instead of carbon disulfide as the solvent. The use of ligroin greatly reduced the amount of gum formed. Thirty grams (0.277 mole) of anisole and 36 g. (0.318 mole) of chloroacetyl chloride were dissolved in 300 cc. of ligroin. To the rapidly stirred solution, 75 g. (0.56 mole) of anhydrous aluminum chloride was added over a period of three-quarters of an hour, the mixture permitted to stand one hour and then 45 g. (0.34 mole) more of aluminum chloride was added in about half an hour. The resulting mixture was heated for four hours on the water-bath. At the end of this time the solvent was removed by distillation and the complex was decomposed by ice, followed by 30 cc. of concentrated hydrochloric acid. The mixture was taken up in ether and extracted first with 5% ammonium carbonate solution and then with 10% sodium carbonate solution. Acidification of the sodium carbonate extract after treatment with charcoal yielded 17.0 g. of a yellow product. It may be recrystallized from methyl alcohol; m.p. 147.5°.

Preparation of 3,4-dihydroxyphenacyl chloride.—This was prepared essentially according to Mannich and Hahn (15). A mixture of 50 g. (0.454 mole) each of catechol, monochloroacetic acid (0.53 mole) and phosphorus oxychloride (0.325 mole) was placed in a large flask fitted with a reflux condenser and a tube to lead away hydrogen chloride. It was heated on a hot plate until gas was evolved and then immediately removed from the plate. The reaction proceeded spontaneously. By avoiding too long heating at this point a better yield was obtained. At the completion of the reaction, 500 cc. of boiling water was added to dissolve the mass, and the solution allowed to stand in an ice chest for two days. The product was then filtered and dried. Yields averaged from 40–47 g. (52–61%). Recrystallization from hot water, employing charcoal for decolorization, yielded a light colored product melting at 173°.

Preparation of 4-(-β-phenylethyl)-morpholine hydrochloride.—To 18.5 g. (0.1 mole) of phenylethyl bromide dissolved in 30 cc. of alcohol was added 17.4 g. (0.2 mole) of morpholine dissolved in 25 cc. of alcohol. The mixture was refluxed for two hours on a water-bath, and then cooled, whereupon a crystalline precipitate separated. The reaction mixture was diluted with one and one-half times its volume of ether, allowed to stand a short time and was then filtered. The crystalline residue, consisting of morpholine hydrobromide, was washed well with ether and the washings added to the filtrate. Dry hydrogen chloride was passed into the cooled filtrate and yielded 17.75 g. (78%) of crystalline hydrochloride. Recrystallization from hot alcohol gave a colorless product melting at 246° (corr.). This compound has been reported (16) as melting at 238°.

Anal. Calc'd for $C_{12}H_{18}ClNO$: N, 6.15; Cl, 15.57.
Found: N, 5.98; Cl, 15.64.

Preparation of ω-morpholinoacetophenone hydrochloride.—To 9.95 g. (0.05 mole) of phenacyl bromide mixed with 30–40 cc. of alcohol and cooled to 0°, 8.7 g. (0.1 mole) of morpholine was slowly added with stirring, the addition being made at a rate such as to maintain the temperature below 15°. The mixture was then allowed to warm up to room temperature and allowed to stand for two hours, at the end of which time 150 cc. of ether was added. After standing overnight, it was filtered, and the crystalline morpholine hydrochloride was washed with ether, which was added to the filtrate. The amino ketone hydrochloride was precipitated by passage of dry hydrogen chloride over the ether. After collecting on a filter, washing with ether, and drying, 9.5–11 g. (79–91%) of crystalline material was obtained. Recrystallization from hot alcohol yielded a colorless product melting with decomposition at 222–223° (corr.). This compound has just been patented and reported as melting at 213–214° with decomposition (12).

Anal. Calc'd for $C_{12}H_{16}ClNO_2$: N, 5.80; Cl, 14.68.
Found: N, 5.76; Cl, 14.69.

This compound may also be prepared in 70–75% yield by refluxing one equivalent of amine with one equivalent of phenacyl bromide in alcohol solution in the presence of a slight excess of anhydrous potassium carbonate. The free base was obtained only as an impure oil.

Preparation of α-morpholinopropiophenone hydrochloride.—This was prepared similarly to the ω-morpholinoacetophenone hydrochloride in yields averaging 80–85%, employing either two equivalents of morpholine or one equivalent of morpholine with anhydrous potassium carbonate. Recrystallization from hot alcohol yielded a colorless product melting at 224° (corr.) with decomposition. This compound has just been patented and reported as melting with decomposition at 224° (12).

Anal. Calc'd for $C_{13}H_{18}ClNO_2$: N, 5.48; Cl, 13.98.
Found: N, 5.42; Cl, 13.78.

*Preparation of ω-morpholino-*p*-hydroxyacetophenone.*—To 6 g. (0.035 mole) of *p*-hydroxyphenacyl chloride in 10 cc. of alcohol, 6.12 g. (0.07 mole) of morpholine was slowly added, maintaining the temperature below 15°. Ten cubic centimeters of ether was added during the addition in order to keep the mixture from becoming solid. More ether was then added and the mixture allowed to stand overnight. It was then filtered and dried. The dried product was suspended in water to dissolve out the morpholine hydrochloride. The residue was filtered, washed well with water and dried, yielding 7.0 g. (90%) of product. Recrystallization from alcohol, using a small amount of charcoal, yielded colorless needles of melting point 201–201.7° (corr.).

Anal. Calc'd for $C_{12}H_{15}NO_3$: N, 6.33. Found: N, 6.13.

The hydrochloride was prepared by suspending the base in alcohol and passing hydrogen chloride into the solution. It melts with decomposition at 242–243° (corr.).

Anal. Calc'd for $C_{12}H_{16}ClNO_3$: N, 5.44; Cl, 13.76.
Found: N, 5.34; Cl, 13.79.

Preparation of ω-morpholino-3,4-dihydroxyacetophenone.—This was prepared similarly to the *p*-hydroxyacetophenone derivative from morpholine and 3,4-dihydroxyphenacyl chloride. The compound was obtained in 85–90% yields. The base was best recrystallized from 50% alcohol. The colorless product melted at 207° (corr.) with decomposition.

Anal. Calc'd for $C_{12}H_{15}NO_4$: N, 5.86. Found: N, 5.84.

The hydrochloride was obtained by passing hydrogen chloride over an alcoholic suspension of the base. The hydrochloride decomposes at 224–225° (corr.).

Anal. Calc'd for $C_{12}H_{16}ClNO_4$: N, 5.12; Cl, 12.95.
Found: N, 5.05; Cl, 12.97.

Preparation of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—This compound was prepared by the catalytic reduction of the corresponding ketone in 95% alcohol solution, employing 10% palladium on charcoal as the catalyst (9). Ten grams of the amino ketone hydrochloride was added to 200 cc. of alcohol containing 4.5 g. of dry hydrogen chloride and 3.3 g. of catalyst. This was then shaken under an atmosphere of hydrogen in an apparatus similar to that of Schaefer (13) until the calculated volume of hydrogen had been absorbed. At the completion of the reduction the solution was filtered free of catalyst and evaporated to a small volume. After cooling, twice the volume of ether was added, and the mixture was allowed to stand in ice for complete precipitation. After filtration, washing with a small amount of ether and drying, 8.8 g. (87.5%) of product was obtained. Recrystallization from hot alcohol yielded a colorless product melting at 188–188.7° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_2$: N, 5.75; Cl, 14.56.
Found: N, 5.65; Cl, 14.58.

Preparation of 1-phenyl-2-morpholinoethanol-1.—This compound was prepared from the hydrochloride by the addition of dilute ammonia or dilute sodium hydroxide to an aqueous solution of the hydrochloride. It was recrystallized from dilute alcohol; m.p. 80.9–81.3° (corr.).

Anal. Calc'd for $C_{12}H_{17}NO_2$: N, 6.76. Found: N, 6.68.

Preparation of 1-phenyl-2-morpholinopropanol-1 hydrochloride.—This compound was prepared similarly to the ethanol derivative by catalytic reduction, in 80–85% yields. After the reduction, due to the lesser solubility of the propanol derivative, it was necessary to filter the solution hot. Recrystallization from alcohol yielded a colorless product melting at 235° (corr.).

Anal. Calc'd for $C_{13}H_{20}ClNO_2$: N, 5.44; Cl, 13.87.
Found: N, 5.45; Cl, 13.80.

Preparation of 1-phenyl-2-morpholinopropanol-1.—This was prepared from the hydrochloride by the addition of dilute ammonium hydroxide or dilute sodium hydroxide. A pure product, m.p. 73–73.5° (corr.) was obtained by recrystallization from dilute alcohol.

Anal. Calc'd for $C_{13}H_{19}NO_2$: N, 6.33. Found: N, 6.25.

Preparation of 1-(p-hydroxyphenyl)-2-morpholinoethanol-1 hydrochloride.—This was prepared by catalytic reduction of the corresponding ketone hydrochloride in water solution employing 20% palladium on charcoal as the catalyst. After filtering off the catalyst, the aqueous solution was evaporated almost to dryness, cooled, and acetone added. The compound was obtained in 78% yield. Recrystallization of

the compound from alcohol yielded a colorless product melting with decomposition at 178° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_3$: N, 5.39; Cl, 13.65.
Found: N, 5.36; Cl, 13.67.

Preparation of 1-(3,4-dihydroxyphenyl)-2-morpholinoethanol-1 hydrochloride.—This was prepared similarly to the *p*-hydroxy derivative employing 10% palladium on charcoal. After the removal of the catalyst by filtration the solution was evaporated to dryness. Crude yields of 81–98% were obtained. Recrystallization from alcohol and ether and employing charcoal yielded a colorless product decomposing at 250° (corr.).

Anal. Calc'd for $C_{12}H_{18}ClNO_4$: N, 5.08; Cl, 12.86.
Found: N, 4.96; Cl, 12.98.

Preparation of the benzoate of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—Heating the amino alcohol hydrochloride with excess benzoyl chloride on a steam-bath for three hours failed to cause complete esterification. Benzoylation attempted in benzene solution, heating until no more hydrogen chloride was evolved, yielded the apparently unchanged amino alcohol hydrochloride. The ester was best prepared by heating 4.0 g. (0.0164 mole) of the amino alcohol hydrochloride with 15 cc. (0.13 mole) of benzoyl chloride for three hours at 120–130° in an oil-bath. At the end of this time, the solution was cooled, ether was added, and the mixture allowed to stand overnight. The crystalline product was then filtered, washed repeatedly with ether and dried. Recrystallization from hot alcohol and ether yielded 60–65% of a colorless product melting at 173.5–175° (corr.).

Anal. Calc'd for $C_{19}H_{22}ClNO_3$: N, 4.03; Cl, 10.09.
Found: N, 3.97; Cl, 10.20.

Preparation of the cinnamate of 1-phenyl-2-morpholinoethanol-1 hydrochloride.—To 3.35 g. (0.02 mole) of cinnamoyl chloride dissolved in 35 cc. of dry xylene was added 3.11 g. (0.015 mole) of 1-phenyl-2-morpholinoethanol-1 dissolved in 50 cc. of dry xylene. This mixture was heated in an oil-bath maintained at 150° for two hours. At the end of this time, the reaction mixture was cooled, filtered, and the product washed with ether. The yield was 4.96 g. (88%). Recrystallization from alcohol yielded a colorless product melting at 220–221° (corr.).

Anal. Calc'd for $C_{21}H_{24}ClNO_3$: N, 3.75; Cl, 9.49.
Found: N, 3.69; Cl, 9.49.

Preparation of the benzoate of 1-phenyl-2-morpholinopropanol-1 hydrochloride.—The ester was obtained in 85% crude yield by heating the amino alcohol hydrochloride with excess benzoyl chloride for five hours to 120–125°, similar to the ethanol derivative. Recrystallization from hot alcohol and ether yielded a colorless product melting at 210–211° (corr.).

Anal. Calc'd for $C_{20}H_{24}ClNO_3$: N, 3.87; Cl, 9.80. Found: N, 4.04; Cl, 10.23.

Preparation of 5-phenyl-5-morpholinomethyl hydantoin.—This hydantoin was prepared according to the method of Bucherer and Steiner (7). Five grams (0.02 mole) of ω-morpholinoacetophenone hydrochloride was dissolved in 40 cc. of 50% alcohol. To this was added 2 g. (0.03 mole) of potassium cyanide and 8 g. (0.083 mole) of powdered ammonium carbonate. This mixture was shaken well and heated on the water-bath for eight and one-half hours, maintaining the bath between 55–65°. Needles started to separate at the end of two hours. The mixture was allowed to cool, diluted with water, and filtered. The crude yield was 5.3 g. (93%). Recrystallization from hot alcohol yielded colorless needles melting at 204–204.5° (corr.).

Anal. Calc'd for $C_{14}H_{17}N_3O_3$: N, 15.26. Found: N, 15.17.

The hydrochloride of this base was prepared by suspending the base in alcohol and passing in dry hydrogen chloride. Recrystallization from alcohol yielded a product melting at 206° (corr.) with decomposition.

Anal. Calc'd for $C_{14}H_{18}ClN_3O_3$: N, 13.48; Cl, 11.37.
Found: N, 13.40; Cl, 11.26.

Attempts to prepare the hydantoins of α-morpholinopropiophenone, ω-morpholino-*p*-hydroxyacetophenone and ω-morpholino-3,4-dihydroxyacetophenone using the method of Bucherer (7) failed.

SUMMARY

1. The following amino ketones, ω-morpholinoacetophenone, α-morpholinopropiophenone, ω-morpholino-*p*-hydroxyacetophenone and ω-morpholino-3,4-dihydroxyacetophenone, have been prepared.

2. The corresponding carbinols have been prepared by catalytic reduction employing palladium on charcoal as the catalyst.

3. The benzoates of 1-phenyl-2-morpholinoethanol-1 and 1-phenyl-2-morpholinopropanol-1, as well as the cinnamate of the ethanol derivative, have been prepared.

4. The compound 5-phenyl-5-morpholinomethyl hydantoin has been prepared by the method of Bucherer. Attempts to prepare hydantoins of the other amino ketones failed.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF WASHINGTON UNIVERSITY]

THE ACTION OF GRIGNARD REAGENTS ON HEAVY METAL SALTS. III. MIXED GRIGNARD REAGENTS AND SILVER BROMIDE

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Some years ago, Gardner and Borgstrom (1) showed that the reaction between a single Grignard reagent and silver bromide results in the production of the compound formed by the union of two of the organic radicals to form a symmetrical molecule. More recently, Gardner, Joseph and Gollub (2) found that the reaction of a mixture of phenyl- and *p*-anisylmagnesium bromides with silver bromide results in the formation of the three products which would be expected to result from the union of similar and dissimilar radicals. In view of the isolation of a number of silver aryls as the result of the reaction of aromatic Grignard reagents with silver bromide, by Krause and Wendt (3) and by Reich (4), and their demonstration that these compounds decompose to yield metallic silver and biaryls, it has been generally accepted that the coupling reaction proceeds according to the equations:

$$RMgX + AgBr = RAg + MgBrX \qquad (I)$$

$$RAg = R— + Ag \qquad (II)$$

$$2\,R— = R_2 \qquad (III)$$

This view is supported by the isolation by Danehy and Nieuwland (5) of silver *n*-butylacetylide formed as the result of the action of *n*-butylacetylenemagnesium bromide on silver bromide. If this mechanism is correct, it should be possible to predict with a fair degree of accuracy the result of the reaction of a mixture of Grignard reagents with silver bromide on the basis of the stability of the intermediate silver compounds, since silver compounds of equal stability would be expected to give the highest yields of unsymmetrical coupling products. The present work shows that the situation is more complicated than had been previously believed.

At the outset, a study was made of the reaction of a series of mixtures

[1] Based upon a Dissertation submitted by Lionel Joseph in partial fufilment of the requirements for the degree of Doctor of Philosophy, Washington University, June, 1937.

of alkylmagnesium bromides with phenylmagnesium bromides. Since it is known that phenylsilver is sufficiently stable to be isolated and to exist for a short time at room temperature (3, 4), whereas such alkylsilvers as have been worked with are immediately decomposed at $-18°$ (4, 6), it would be expected that, in these cases, there would be little or no coupling of dissimilar radicals. It was found, however, that in every case where the alkyl group was primary or secondary, considerable quantities of the unsymmetrical coupling products were obtained, the amount in the case of the primary alkyl groups usually exceeding that of the symmetrical coupling products.

This study was followed by a similar series of reactions using mixtures of alkylmagnesium bromides with benzylmagnesium chlorides. The results of both series of experiments can be correlated in terms of the electronegativity of the radicals involved, as will be seen later in this paper.

EXPERIMENTAL

Materials.—The bromobenzene used in these experiments was obtained in part by the distillation through an efficient column of material prepared by undergraduate students. The rest was Eastman "Practical" which was found to be of satisfactory purity by distillation tests. Benzyl chloride obtained from the Mallinckrodt Chemical Works was redistilled and the fraction boiling at 176–177° was used. The alkyl bromides were obtained from the Eastman Kodak Company and were used without further purification except that the isobutyl bromide was distilled immediately before use. The magnesium was Mallinckrodt's "Turnings for Grignard's Reactions." Silver bromide was prepared by the method of Gardner and Borgstrom (1).

Preparation of Grignard reagents.—The two Grignard reagents used in each experiment were prepared separately, the alkyl or aryl halide dissolved in ether being added to an excess of magnesium during the course of a half hour, with vigorous mechanical stirring. The mixture was then boiled another half hour. Whenever a halide was used for the first time, an aliquot was taken and decomposed with standard nitric acid and the excess acid titrated with sodium hydroxide. Halogen was determined volumetrically on the same sample. The hydroxyl-halide ratios so obtained indicated yields comparable to those reported by Gilman and his co-workers (7). In the case of *tert.*-butylmagnesium bromide, 2.5 moles of magnesium was used for each mole of *tert.*-butyl bromide. Since it was found that the yield of Grignard reagent in this case was 30–40%, these runs were carried out with the reagents prepared from 0.5 mole of *tert.*-butyl bromide and 0.25 mole of the other halide. In all other cases, the pairs of Grignard reagents were made up from equimolar quantities of the halides.

Reaction with silver bromide.—The two Grignard reagents were mixed in a three-necked flask provided with two reflux condensers and a stirrer of the type described by Joseph (8). The flask was placed in an ice-salt bath. Two equivalents of silver bromide was added slowly, with stirring, through one of the condensers. The flask was allowed to stand in the ice and salt bath for a half hour with continuous stirring. The cooling bath was then removed and the mixture boiled gently for an hour. In some of the earlier experiments, the mixture was then treated with 200 cc. of water acidulated with hydrochloric acid, for each mole of Grignard reagent. The ether layer was separated, dried over calcium chloride, and the products isolated as de-

scribed below. In most of the experiments, the flask was removed from the reflux condensers and connected to a condenser set for distillation. In the other necks there were placed a thermometer and a dropping funnel. The acidulated water was then added at such a rate as to cause the ether to distil quietly. When all of the ether had come over, the flask was arranged for steam distillation and the products were steam distilled. The organic layer was separated from the aqueous layer and dried over calcium chloride. For isolation of the products, the material was distilled through a 70 cm. Vigreux column, taking fractions over fairly large temperature ranges on the first distillation. The biphenyl or bibenzyl which was left in the distilling flask was further purified by steam distillation and drying. The liquid hydrocarbons were washed with concentrated sulfuric acid and redistilled, the final products being collected over a 1–2° range. The results obtained by the two methods of separating the organic material from the reaction mixture agreed well within the limits of experimental error.

RESULTS AND DISCUSSION

The yields of the chief products formed when silver bromide was added to mixtures of phenylmagnesium bromide and various alkylmagnesium bromides are shown in Table I. It will be noted that in all cases except where the alkyl group was *tert.*-butyl, some of the unsymmetrical product was formed. The yields of the unsymmetrical coupling products and of biphenyl are collected in Table II, all calculated to a basis of one mole of each Grignard reagent to facilitate direct comparison. In this table, the alkyl groups are arranged in order of decreasing electronegativity, according to the series of Kharasch and Reinmuth (9), with the exception that *sec.*-butyl has been placed below rather than above isopropyl. The radicals are thus placed also in the order of decreasing yields of alkylbenzene, with the exception of methyl and ethyl, with both of which, experimental difficulties due to the volatility of the halides lead us to doubt whether these data are really quantitatively significant. In all other cases, duplicate runs agreed within a maximum variation of about ten per cent.

The same order of listing the alkyl radicals places them in the order of increasing yields of biphenyl, with the exception of the first and last. The general agreement with the electronegativity of the alkyl radicals seems too pronounced to be without significance.

A similar regularity was noted in the case of benzylmagnesium chloride and the same series of alkylmagnesium bromides. The results of these experiments are given in Table III and the yields of benzylalkanes and of bibenzyl are collected for ease of comparison in Table IV, again calculated to the basis of one mole of each Grignard reagent. In this case, the yields of benzylalkane increase and those of bibenzyl decrease as we descend the series, except in the case of *tert.*-butyl. This is what is to be expected as the benzyl radical is less electronegative than any of the alkyl radicals in the series except the last. Kharasch and Swartz (10) have

TABLE I

THE ACTION OF SILVER BROMIDE ON MIXTURES OF C_6H_5MgBr AND RMgBr

R—	MOLES OF EACH GRIGNARD RGT.	C_6H_5—R		PHYSICAL CONSTANTS	R—R		PHYSICAL CONSTANTS	BIPHENYL M.P. 68°	
		G.	Moles		G.	Moles		G.	Moles
CH_3	0.5	4.0	0.044	b.p. 755 109–11 d^{20} 0.866 n^{20} 1.4962	Ethane not collected			17.0	0.110
C_2H_5	0.5	10.0	0.095	b.p. 755 134–6 d^{19} 0.8670 n^{22} 1.4926	*n*-butane not collected			13.0	0.085
n-C_3H_7	1.0	46.0	0.384	b.p. 751 156–7 d^{25} 0.8699 n^{25} 1.4908	1.0	0.012	b.p. 751 70–1 d^{24} 0.7031 n^{24} 1.4050	27.0	0.180
i-C_3H_7	1.0	13.5	0.110	b.p. 750 149–51 d^{26} 0.8546 n^{26} 1.4879	1.0	0.010	b.p. mic. 162 n^{26} 1.4070	42.0	0.270
n-C_4H_9	1.0	51.0	0.381	b.p. 750 179–81 d^{26} 0.8560 n^{23} 1.4892	7.0	0.062	b.p. 747 125–6 d^{23} 0.7120 n^{23} 1.4050	31.0	0.200
i-C_4H_9	0.5	23.0	0.170	b.p. 755 168–70 d^{25} 0.8534 n^{21} 1.4885	0.7	0.006	b.p. 107–10 d^{18} 0.710 n^{21} 1.3922	16.5	0.107
s-C_4H_9	1.0	9.5	0.070	b.p. 755 169–70 d^{24} 0.8694 n^{26} 1.4872	6.0	0.05	b.p. 755 116–8 d^{24} 0.7223 n^{26} 1.4060	58.5	0.370
t-C_4H_9	0.25	0.0	0.000		2.0	0.018	b.p. 105–6	13.0	0.085

recently shown that the *tert.*-butyl radical is less electronegative than benzyl. Consequently, the relative yields in that case are unpredictable. On the basis of the yield of benzylalkane, the results with ethylmagnesium bromide appear to be out of line, but even in this case the yield of bibenzyl follows the regular course.

There is no regularity in the yields of bialkyls, which is not surprising in view of the fact that the yields of the isomeric octanes in simple coupling experiments carried out under strictly comparable conditions vary markedly with the structure of the butyl radicals involved (11, 12). While these yields are given in this paper, it is felt that they are not to be regarded as significant data for a theoretical interpretation of the general results. Further work on the coupling of aliphatic radicals is in progress at the present time.

TABLE II

PRODUCTS FROM THE REACTION OF $C_6H_5MgBr + RMgBr + AgBr$

R—	C_6H_5R (MOLES)	$C_6H_5C_6H_5$ (MOLES)
CH_3	0.088	0.220
C_2H_5	0.190	0.170
n-C_3H_7	0.384	0.180
n-C_4H_9	0.381	0.200
iso-C_4H_9	0.340	0.214
iso-C_3H_7	0.110	0.270
sec.-C_4H_9	0.070	0.370
tert.-C_4H_9	0.000	0.340

From the results here presented it seems reasonable to conclude that in the reaction of phenylmagnesium bromide or benzylmagnesium chloride with alkylmagnesium bromides, the course of the reaction is determined by the relative electronegativities of the radicals involved, even when these include phenyl and alkyl radicals, in spite of the great difference in the stability of the corresponding silver compounds. The fact that the course of the reaction is very greatly affected by the nature of the halogen of the Grignard reagent, as will be shown in the next paper of this series (11), indicates that the electronegativity of the radicals is by no means the only significant factor. However, it seems reasonable to believe that the effect of the halogen atom is confined to the initial stage of the reaction, that is, the formation of the organosilver compounds, whereas the electronegativity of the radicals very probably determines the relative stability of the organosilver compounds. From the fact that it is possible to obtain quite large yields of the products formed by the coupling of radicals derived from organosilver compounds of such greatly differing

TABLE III

THE ACTION OF SILVER BROMIDE ON MIXTURES OF BENZYL- AND ALKYL- MAGNESIUM BROMIDE

R—	MOLES OF EACH GRIGNARD RGT.	$C_6H_5CH_2$—R		PHYSICAL CONSTANTS	R—R		PHYSICAL CONSTANTS	BIBENZYL M.P. 51	
		G.	Moles		G.	Moles		G.	Moles
CH_3	0.5	1.0	0.010	b.p. 760 130–3 d^{21} 0.8700 n^{21} 1.4929	Ethane not collected			29.0	0.160
C_2H_5	0.5	4.0	0.030	b.p. 747 158–60 d^{20} 0.8675 n^{21} 1.4910	*n*-Butane not collected			29.0	0.160
n-C_3H_7	0.5	1.3	0.010	b.p. 750 175–8 d^{20} 0.8560 n^{20} 1.4900	0.0	0.0		28.0	0.155
i-C_3H_7	0.5	28.0	0.210	b.p. 751 170–1 d^{22} 0.8620 n^{22} 1.4897	0.0	0.0		10.0	0.055
n-C_4H_9	0.5	2.0	0.015	b.p. 750 198–200 d^{18} 0.865 n^{18} 1.4950	4.0	0.035	b.p. 750 124–6 d^{20} 0.712 n^{18} 1.4030	27.0	0.150
i-C_4H_9	0.5	1.5	0.012	b.p. 755 198–9 d^{20} 0.8880 n^{17} 1.4960	trace			21.0	0.115
s-C_4H_9	0.5	32.3	0.216	b.p. 747 193–5 d^{23} 0.8612 n^{18} 1.4895	1.7	0.0		11.0	0.045
t-C_4H_9	0.25	7.0	0.044	b.p. 753 181–3 d^{21} 0.8520 n^{21} 1.4878	2.0	0.018	b.p. 104–6	11.0	0.061

stability as phenylsilver and *n*-butylsilver, it seems reasonable to believe that the decomposition of a relatively stable organosilver compound is promoted by the presence of a less stable compound undergoing decomposition. If this is so, the reaction probably involves an interaction of two molecules of organosilver compound, either the same or different. This is in agreement with the demonstration described in the following paper (11) that free radicals are not involved. As yet it has not been possible to devise any means for the direct measurement of the velocity of these reactions in order to settle these points more definitely.

TABLE IV

YIELDS OF PRODUCTS FROM THE REACTION OF $C_6H_5CH_2MgCl + RMgBr + AgBr$

R—	$C_6H_5CH_2R$ (MOLES)	$(C_6H_5CH_2)_2$ (MOLES)
CH_3	0.020	0.320
C_2H_5	0.060	0.320
n-C_3H_7	0.020	0.310
n-C_4H_9	0.030	0.300
iso-C_4H_9	0.024	0.230
iso-C_3H_7	0.420	0.110
sec.-C_4H_9	0.432	0.090
tert.-C_4H_9	0.176	0.244

SUMMARY

1. The action of silver bromide on a number of pairs of Grignard reagents has been studied.

2. It has been found that there is a definite relation between the course of the reaction and the relative electronegativities of the radicals involved.

3. The significance of these results on the determination of the mechanism of the reaction has been discussed.

ST. LOUIS, MO.

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[CONTRIBUTION FROM THE CHEMISTRY DEPARTMENT OF DUKE UNIVERSITY

ACYLATION OF ALDOXIMES. III. THE CONFIGURATION OF DIPHENYLCARBAMYL AND PICRYL ETHER DERIVATIVES PREPARED FROM *syn* ALDOXIMES[1]

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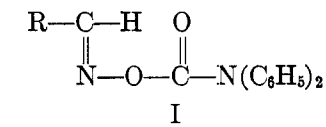
Diphenylcarbamyl aldoximes may be represented in geometrically isomeric forms by (I) and (II), while picryl ether derivatives (which react like acyl derivatives) may be represented by (III) and (IV). Among acyl aldoximes, the more stable α-isomers are assigned the *syn* configuration, while the relatively unstable β-isomers are assigned the *anti* configuration.

syn Derivatives (α) *anti* Derivatives (β)



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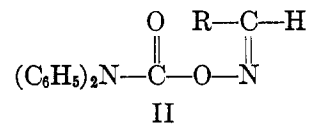

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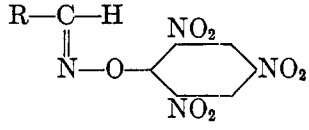
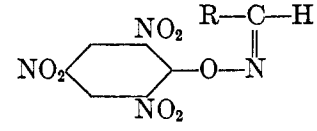


III



IV

Actually, diphenylcarbamyl and picryl ether derivatives have been isolated in but one form. Brady and co-workers (1) have prepared the former by heating a suspension of the sodium salts of *syn* aldoximes in chloroform with diphenylcarbamyl chloride. These workers reported that the same derivatives were obtained from the sodium salts of the corresponding *anti* aldoximes and diphenylcarbamyl chloride. Picryl ether derivatives (2) have been prepared by treating *syn* aldoximes in alcoholic alkali with picryl chloride; *anti* aldoximes under the same conditions give the corresponding nitrile and aldehyde directly.

Although one should expect to obtain the more stable *syn* isomers under these conditions, the earlier workers considered that the diphenylcarbamyl and picryl ether derivatives prepared as described above were the rela-

[1] Paper II of this series, Rainsford and Hauser, *J. Org. Chem.*, **4**, 480 (1939).

tively unstable *anti* isomers, because, when they were heated with alkali, a nitrile or the corresponding acid was obtained. Hence, the preparation of these derivatives from *syn* aldoximes was considered to involve an inversion of configuration. This view seemed reasonable at the time, since in the two cases in which acyl derivatives have been isolated in two geometrically isomeric forms, namely, the acetyl, and carbanilino aldoximes, only the *anti* isomers with alkali give mainly nitrile; the *syn* isomers with this reagent give almost entirely the corresponding *syn* aldoxime. Evidence is presented in this paper, however, that the diphenylcarbamyl, and picryl ether derivatives actually have the *syn* configuration and not the *anti* configuration as was formerly assumed.

We have found that the diphenylcarbamyl derivatives prepared by Brady and co-workers (1) from the sodium salts of *syn* aldoximes and diphenylcarbamyl chloride in chloroform may be prepared equally well by carrying out the reaction in warm alcoholic alkali solution; in certain cases, a little nitrile also was obtained, but this was avoided by carrying out the reaction at lower temperatures. Under the same conditions *anti* aldoximes give nitrile directly.

These results are best explained as follows: The *syn* aldoximes (as sodium salts) react with diphenylcarbamyl chloride to give the corresponding *syn* derivative, which in the presence of warm alkali is slowly decomposed to give nitrile. The *anti* aldoximes (as sodium salts) with diphenylcarbamyl chloride under the same conditions give the corresponding *anti* derivative, which in the presence of the alkali is immediately decomposed to nitrile. It should be expected that the *anti* derivatives would give nitrile more readily than the *syn* isomers. Therefore, on the basis of these results alone, one may conclude that no inversion of configuration occurs in the reaction of the sodium salts of *syn* aldoximes with diphenylcarbamyl chloride. How these diphenylcarbamyl derivatives can have the *syn* configuration and yet give nitrile with hot alkali becomes more understandable on the basis of the following considerations.

It has been pointed out previously (3) that the reactions of a pair of geometrically isomeric acyl aldoximes differ only in degree, not in kind. While the *anti* isomers probably always eliminate HOOCR′ to form nitrile much more readily than the *syn* isomers, certain of the latter also, under certain conditions, may give mainly nitrile. Moreover, both the *syn*, and *anti* isomers may undergo hydrolysis to form the corresponding *syn*, or *anti* aldoxime. The relative yields of nitrile and aldoxime formed in any case depend upon the relative rates of these two competing reactions. Apparently, an elevation of temperature accelerates the elimination reaction more than the hydrolysis, since for example, acetyl *anti* aldoximes give mainly the corresponding *anti* aldoxime with cold alkali (at 0°), but mainly the nitrile with hot alkali (at 30° or above) (3).

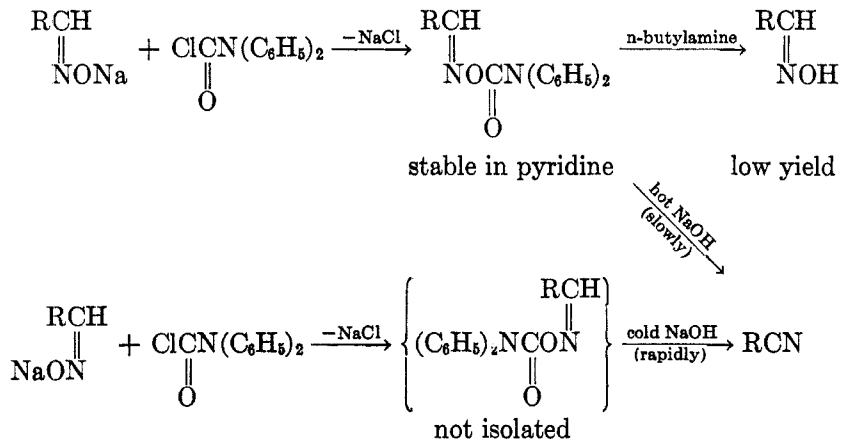
Although acetyl *syn* aldoximes with hot alkali undergo mainly hydrolysis giving *syn* aldoxime, this is not so with certain other acyl *syn* derivatives. Thus, carbethoxy *syn* aldoximes with hot alkali give considerable or even largely nitrile (4). There is little doubt that these carbethoxy derivatives have the *syn* configuration, since (similar to acetyl *syn* aldoximes) they give practically entirely the corresponding *syn* aldoxime (4) with cold alkali. The fact that a carbethoxy *syn* derivative with hot alkali gives a higher yield of nitrile, and a correspondingly lower yield of *syn* aldoxime, than the analogous acetyl *syn* aldoxime is explained on the basis that the former undergoes hydrolysis less readily, and/or the elimination reaction, more readily than the acetyl derivative.

The diphenylcarbamyl derivatives are regarded as examples of acyl *syn* aldoximes which undergo hydrolysis only with great difficulty; consequently, the elimination reaction predominates on heating with alkali. Attempts to hydrolyze these derivatives with hot or cold alkali or with alcoholic ammonia resulted in the formation of only traces of aldoximes.

It should be pointed out that the resemblance of the diphenylcarbamyl derivatives to authentic *anti* derivatives in giving nitrile with hot alkali is not as close as might at first appear. The acetyl *anti* aldoximes are readily decomposed by alkali even at room temperatures, whereas hot alkali is required to decompose the diphenylcarbamyl derivatives at an appreciable rate; in fact, diphenylcarbamyl derivatives may be prepared even in the presence of warm alcoholic alkali with only slight decomposition to nitrile (see experimental). It would probably be very difficult or impossible to prepare acetyl *anti* derivatives in the presence of alkali. On the other hand, the diphenylcarbamyl derivatives resemble acetyl *syn* aldoximes (as well as other acyl *syn* derivatives) in their reactions with certain bases. At room temperature, acetyl *syn* derivatives are stable in pyridine solution, whereas acetyl *anti* derivatives are decomposed readily by this base, giving nitrile (5). Like an acetyl *syn* aldoxime, a diphenylcarbamyl derivative is stable in pyridine solution and may be recovered unchanged even after standing in pyridine solution at room temperatures for several days. When treated with *n*-butylamine, acetyl *syn* aldoximes react without noticeable rise of temperature, giving the corresponding *syn* aldoxime, whereas acetyl *anti* aldoximes react vigorously, generating considerable heat and giving mainly nitrile. Like an acetyl *syn* aldoxime, a diphenylcarbamyl derivative, when treated with *n*-butylamine generates no appreciable amount of heat and on standing with this base (using pyridine as solvent) gives some (10–15% yield) of the corresponding *syn* aldoxime. In order to show that *anti* aldoximes were not first formed in this aminolysis and then converted to the *syn* isomers, *anti* aldoximes were treated with *n*-butylamine (and pyridine) under the same conditions;

the original *anti* aldoximes were recovered practically unchanged from the amine solutions. Although only low yields of *syn* aldoxime were obtained from diphenylcarbamyl derivatives, the result may be taken as evidence supporting the view that the derivatives have the *syn* configuration.

These results show that the diphenylcarbamyl derivatives have the *syn* configuration; therefore, their preparation from *syn* aldoximes involves no inversion of configuration as was formerly assumed. The reactions of *syn*, and *anti* aldoximes with diphenylcarbamyl chloride in alkaline solution and the reactions of the derivatives with certain bases may be represented as follows.



Picryl ether derivatives have been prepared from certain representative *syn* aldoximes, picryl chloride and alcoholic alkali according to the method of Brady and co-workers (2). It seems likely that these derivatives have the *syn* configuration, since under the same conditions, *anti* aldoximes react with picryl chloride to give nitrile and aldehyde. The nitrile is obtained presumably by the decomposition of intermediate picryl ether *anti* derivatives. The formation of the aldehyde apparently involves the hydrolysis of the carbon-nitrogen double bond. Brady and Klein (2) have suggested that the formation of aldehyde in the similar reaction of 2,4-dinitrochlorobenzene with the sodium salt of an *anti* aldoxime involves the intermediate formation of a N-substituted derivative.

Similar to the diphenylcarbamyl derivatives, the picryl ether derivatives appear to be very difficult to hydrolyze. Nevertheless, it has been found that at least the picryl ether derivative of *syn*-3,4-methylenedioxybenzaldoxime undergoes some hydrolysis in the presence of alkali (at room temperature or below) giving the corresponding *syn* aldoxime. It has

been shown that under the same conditions, the isomeric *anti*-3,4-methylenedioxybenzaldoxime may be recovered practically unchanged; consequently, the *anti* aldoxime was not first formed and then isomerized, but the *syn* aldoxime was formed directly. Although the yield of *syn* aldoxime obtained from the picryl ether derivative was low (10–15%), this result supports the view that the derivative has the *syn* configuration. The pyridine-*n*-butylamine test for configuration was not applicable to the picryl ether derivatives.

In connection with this work it has been shown that *anti*-3,4-methylenedioxy-, and *anti*-4-methoxy- benzaldoximes are relatively stable in solutions of pyridine and *n*-butylamine, alcoholic alkali and alcoholic ammonia. After standing for some time, the *anti* aldoximes were recovered practically unchanged from these basic solutions. The results are given in Table I.

TABLE I

MELTING POINTS OF *anti* BENZALDOXIMES RECOVERED FROM BASIC SOLUTIONS

SUBSTITUENT	BASIC SOLN.	DAYS STANDING	M.P. RECOVERED PRODUCT	AUTHENTIC M.P.'S	
				syn	*anti*
3,4-CH_2O_2	Pyridine-*n*-butylamine	8	144–145	110	146
3,4-CH_2O_2	5% alc. NaOH	50	140–143	110	146
3,4-CH_2O_2	4 *N* alc. NH_3	50	142–143	110	146
4-CH_3O	Pyridine-*n*-butylamine	8	129–131	64	133
4-CH_3O	5% alc. NaOH	50	130–132	64	133
4-CH_3O	4 *N* alc. NH_3	50	130–132	64	133

EXPERIMENTAL

Diphenylcarbamyl derivatives were obtained when the sodium salts of *syn*-4-methoxybenzaldoxime and *syn*-3,4-methylenedioxybenzaldoxime were refluxed with chloroform solutions of diphenylcarbamyl chloride according to the method of Brady and Dunn (1a); the melting points of our products agreed with those reported by these earlier workers. Attempts to prepare these derivatives from the corresponding *anti* aldoximes, however, were unsuccessful.

Reactions of syn, *and* anti *aldoximes with diphenylcarbamyl chloride in alkaline solution.*—When *syn*-3,4-methylenedioxy-, *syn*-4-methoxy-, *syn*-3-nitro-, and *syn*-4-dimethylamino- benzaldoximes dissolved in alcoholic alkali (prepared from sodium and 95% alcohol) were treated with warm alcoholic solutions of diphenylcarbamyl chloride, the corresponding carbamyl derivatives were obtained in yields of 65–75%. In the reaction of *syn*-3,4-methylenedioxybenzaldoxime, a small yield of the corresponding nitrile was also obtained. No nitrile could be isolated, however, and a good yield of the diphenylcarbamyl derivative was obtained, when *syn*-3,4-methylene dioxybenzaldoxime was allowed to react with diphenylcarbamyl chloride and

alkali at 0–10°, using acetone and alcohol as solvents. It was shown that the diphenylcarbamyl derivative of *syn*-3,4-methylenedioxybenzaldoxime on standing with warm alcoholic alkali slowly formed the corresponding nitrile.

The reactions of *anti*-3,4-methylenedioxy-, *anti*-4-methoxy-, and *anti*-3-nitrobenzaldoximes with diphenylcarbamyl chloride and alcoholic alkali under similar conditions gave the corresponding nitrile and diphenylamine; no diphenylcarbamyl derivative was obtained.

Treatment of diphenylcarbamyl derivatives with pyridine and n-*butylamine.*—One-gram samples of the diphenylcarbamyl derivatives prepared from *syn*-3,4-methylenedioxy-, *syn*-4-methoxy-, and *syn*-3-nitro- benzaldoximes were shaken with 20 cc. of pyridine and the mixture allowed to stand at room temperature. Most of the solid derivative dissolved in the pyridine. After standing eight days, the mixture was poured on to ice and water. The diphenylcarbamyl derivatives were recovered in almost quantitative yields.

The three diphenylcarbamyl derivatives mentioned above were apparently unaffected when shaken with *n*-butylamine; they appeared to be practically insoluble in this amine. One-gram samples of the derivatives were shaken with a mixture of 10 cc. of *n*-butylamine and 10 cc. of pyridine. After standing for eight days at room temperature, the mixture was poured on 100 cc. of ice and water. The aqueous mixture was filtered and the precipitate washed with 2 *N* sodium hydroxide. From the filtrates and washings were isolated 10–15% yields of the *syn* aldoxime corresponding to the diphenylcarbamyl derivative used. In order to avoid the conversion of any *anti* aldoxime that might possibly have been present, no strong acids were used during the isolation of the aldoximes. The procedure was as follows. The mixture was saturated with carbon dioxide. A rapid stream of carbon dioxide served to remove some of the butylamine. The mixture was extracted with ether and the ether solution extracted with 2 *N* sodium hydroxide. The aldoxime was precipitated from the alkaline layer by means of carbon dioxide in the usual manner.

Stabilities of anti *aldoximes in basic solutions.*—It is well known that *anti* aldoximes readily revert to their *syn* isomers in the presence of acids (especially strong acids); however, *anti* aldoximes are much more stable in basic solutions. In Table I are given the melting points of *anti*-3,4-methylenedioxy-, and *anti*-4-methoxybenzaldoximes recovered from basic solutions after standing at room temperatures for various lengths of time. The alcoholic solutions were evaporated in a current of air at room temperature, the residue dissolved in alkali, and the oxime precipitated with carbon dioxide in the usual manner. The amine solutions were poured onto ice and water and the *anti* aldoximes isolated according to the procedure described in the preceding section. It can be seen that the *anti* aldoximes were recovered practically unchanged from the basic solutions.

Results with picryl ether derivatives.—Picryl ether derivatives were prepared from *syn*-3,4-methylenedioxy-, and *syn*-4-methoxy- benzaldoximes with picryl chloride in alcoholic alkali according to the method of Brady and co-workers (2). Samples of these derivatives were allowed to stand with 5% alcoholic sodium hydroxide at 0° and at room temperature. After 40 days, the alcohol was evaporated and the residue stirred with alkali and the mixture filtered. The filtrate was saturated with carbon dioxide. From the derivative of 3,4-methylenedioxybenzaldoxime, the corresponding *syn* aldoxime was obtained (a yield of 10% at room temperature, and a yield of 15% at 0°), but only a trace of oxime could be isolated from the picryl ether derivative of 4-methoxybenzaldoxime.

SUMMARY

1. Evidence is presented that the diphenylcarbamyl derivatives obtained from the sodium salts of *syn* aldoximes and diphenylcarbamyl chloride have the *syn* configuration, not the *anti* configuration as was formerly assumed.

2. It seems likely that the corresponding picryl ether derivatives prepared from the sodium salts of *syn* aldoximes and picryl chloride likewise have the *syn* configuration.

3. These results are in agreement with the hypothesis held in this laboratory that the acylation of *syn* aldoximes in the presence of a sufficiently strong base involves no change in configuration.

4. A method for preparing diphenylcarbamyl *syn* aldoximes from the sodium salts of *syn* aldoximes and diphenylcarbamyl chloride in alcoholic solution is described.

DURHAM, NORTH CAROLINA.

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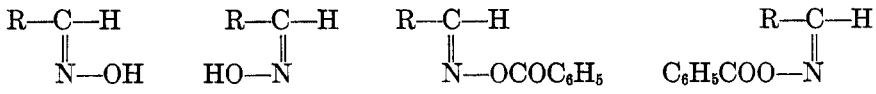
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF DUKE UNIVERSITY]

THE ACYLATION OF ALDOXIMES. IV. THE BENZOYLATION OF *syn*, AND *anti* ALDOXIMES[1]

GERTRUDE VERMILLION, EARL JORDAN AND CHARLES R. HAUSER

The purpose of this investigation has been to study the benzoylation of certain *syn*, and *anti* aldoximes in the presence of bases. Earlier investigators[2] have shown that *anti* aldoximes (II), as well as *syn* aldoximes (I), react with benzoyl chloride in the presence of aqueous alkali to give benzoyl *syn* derivatives (III), instead of the expected *anti* derivatives (IV) or nitriles. They reported[2] also that *anti* aldoximes give *syn* derivatives when the reaction with benzoyl chloride is carried out in pyridine solution, in spite of precautions to avoid isomeric change.



(I) *syn* (α) (II) *anti* (β) (III) *syn* (α) (IV) *anti* (β)

We have confirmed the result of the earlier investigators that *anti* aldoximes with benzoyl chloride in aqueous alkali give *syn* derivatives. Our results in pyridine solution, however, are not entirely in agreement with theirs, in that the product obtained in this solvent is largely or wholly nitrile. We have shown also that, although benzoyl *syn* derivatives are obtained from *anti* aldoximes and benzoyl chloride in the presence of aqueous alkali, nitriles are obtained when the reaction is carried out in a water-dioxane solution (or emulsion) of alkali. Similarly, nitriles are obtained when *anti* aldoximes are benzoylated with benzoic anhydride in an aqueous-dioxane solution (or emulsion) of alkali. The nitriles are formed presumably by the decomposition of intermediate benzoyl *anti* aldoximes (IV), which, although never isolated, would undoubtedly react with alkali or pyridine to give nitriles. It is well known that the corresponding acetyl *anti* aldoximes are decomposed by these bases to give nitriles.

In connection with the change of configuration that occurs during the benzoylation in the presence of aqueous alkali, it should be mentioned that an oil is first formed when the benzoyl chloride is added to the aqueous-alkaline solution of *anti* aldoximes. It seems likely that the change of configuration is in some way connected with the presence of this oil, since

[1] Paper (III), J. Org. Chem., **5**, 68 (1940).

no change of configuration takes place when the benzoylation is carried out in the presence of a suitable solvent (dioxane).

The benzoylation of *anti* aldoximes in pyridine solution requires further comment. Preliminary experiments were carried out with three representative *anti* aldoximes, 3,4-methylenedioxy-, 3-nitro-, and 4-methoxybenzaldoximes, at 0° and at room temperatures, and in all cases high yields (70–90%) of nitriles were obtained; with the first two oximes, small yields (5–10%) of the *syn* derivatives were obtained under certain conditions, but no *syn* derivative was obtained from *anti*-4-methoxybenzaldoxime under the conditions studied. A more thorough study with *anti*-3,4-methylenedioxybenzaldoxime showed that when the benzoylation was carried out (either at 0° or at room temperatures) in the presence of a relatively small amount of pyridine, some (5–10% yield) of the *syn* derivative was formed, but when the benzoylation was carried out in the presence of a relatively large amount of pyridine, only nitrile was obtained. Also, it was found that the benzoylation of this *anti* aldoxime in the presence of a relatively small amount of pyridine together with a small amount of triethylamine gave only nitrile. Thus, at least with *anti*-3,4-methylenedioxybenzaldoxime, no change of configuration takes place when the benzoylation is carried out in a sufficiently basic solution.

Apparently, no one has studied the reaction of *syn* aldoximes with benzoyl chloride in pyridine solution; it was probably considered obvious that the corresponding *syn* derivative would be formed. Contrary to what one might expect, however, we have found that *syn*-3,4-methylenedioxybenzaldoxime with benzoyl chloride in pyridine solution at room temperature gives partly *syn* derivative and partly nitrile, while *syn*-4-methoxybenzaldoxime with benzoyl chloride under similar conditions gives entirely nitrile. Since benzoyl *syn* derivatives are stable in pyridine, the nitrile is formed presumably by the decomposition of benzoyl *anti* derivatives; the formation of the latter from *syn* aldoximes obviously involves an inversion of configuration. Previously, inversion of configuration has been shown to occur in the presence of pyridine (and ether) during the reaction of *syn* aldoximes with phenylisocyanate (1). Since, in the reaction with phenylisocyanate, the presence of a stronger base, for example, triethylamine, prevents inversion, it seemed probably that inversion would likewise be prevented during benzoylation if the reaction were carried out in the presence of triethylamine; this has been found to be the case. The reaction of benzoyl chloride with either *syn*-3,4-methylenedioxybenzaldoxime or *syn*-4-methoxybenzaldoxime in pyridine solution in the presence of triethylamine (two to four equivalents) gives entirely the corresponding *syn* derivative.

The significant results obtained with *syn*- and *anti*-3-4-methylenedioxy

benzaldoximes and benzoyl chloride in the presence of bases are summarized in Table I.

From these results it can be concluded that, although changes of configuration may occur under certain conditions of benzoylation of *syn*-, and *anti* aldoximes, no change of configuration takes place when the benzoylation is carried out in a sufficiently basic solution (conditions listed in 2 and 4 of Table I).

Finally, it should be pointed out that the formation of *syn* derivatives from *anti* aldoximes under certain conditions is not especially surprising, since the more stable configuration of aldoximes and their acyl derivatives is the *syn*. The formation of the relatively unstable *anti* derivatives (or nitriles) from *syn* aldoximes, however, is rather remarkable and may in-

TABLE I

PRODUCTS OF BENZOYLATION OF *syn*-, AND *anti*-3,4-METHYLENEDIOXYBENZALDOXIMES IN THE PRESENCE OF BASES

CONDITIONS	*syn* ALDOXIME	*anti* ALDOXIME
1. With aqueous alkali	*syn* derivative	*syn* derivative
2. With alkali in a water-dioxane solution or emulsion	*syn* derivative	(*anti* deriv.)[a] → nitrile
3. In pyridine solution at room temperature	Partly *syn* derivative, partly nitrile	(*anti* deriv.)[a] → nitrile, plus *syn* derivative,[b] in yields of 0–10%
4. In pyridine and triethylamine solution	*syn* derivative	(*anti* deriv.)[a] → nitrile

[a] *anti* Derivative not isolated.

[b] In the presence of a large excess of pyridine only nitrile is obtained.

volve the formation of salt-like intermediates (1). The factors governing this inversion of configuration during the benzoylation of *syn* aldoximes in pyridine solution is being further studied.

EXPERIMENTAL

Benzoylation of syn *and* anti *aldoximes in the presence of alkali.*—In agreement with Brady and co-workers,[2] the corresponding benzoyl *syn* derivative was obtained when either the *syn*, or the *anti* isomer of 3,4-methylenedioxybenzaldoxime-, or of 4-methoxybenzaldoxime was treated with benzoyl chloride in the presence of aqueous sodium hydroxide; however, the yields of *syn* derivatives obtained from the *anti* aldoximes were lower than those obtained from the *syn* aldoximes.

Although *anti* oximes with benzoyl chloride and aqueous sodium hydroxide give *syn* derivatives, it has been found that only nitriles are obtained when the reaction is

[2] See especially Brady and McHugh, *J. Chem. Soc.*, **127**, 2415 (1925).

carried out in the presence of alkali in an aqueous-dioxane solution or emulsion. Two cubic centimeters of benzoyl chloride dissolved in 25 cc. of dioxane was added, with shaking, to 2 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in 25 cc. of 4 *N* aqueous sodium hydroxide solution at room temperature. The mixture was emulsified by shaking. The temperature rose to 60–70°. After standing for several hours, the mixture was evaporated almost to dryness in a current of air. Water was added to the residue, and, after the mixture was shaken, the solid was filtered off and washed with water. The solid was identified as 3,4-methylenedioxybenzonitrile by the mixture melting point method. The yield of nitrile was 60% of the theoretical amount. Fifteen per cent of the original oxime was recovered by saturating the filtrate with carbon dioxide in the usual manner. Similar results were obtained with *anti*-4-methoxy-, and *anti*-3-nitro- benzaldoximes.

anti Aldoximes with benzoic anhydride in the presence of aqueous-dioxane mixtures of sodium hydroxide likewise give nitrile. To a solution of 2 g. of *anti*-3,4-methylenedioxybenzaldoxime in 50 cc. of 2 *N* sodium hydroxide was added slowly, with constant stirring, a solution of 3.5 g. of benzoic anhydride in 10 cc. of dioxane. After the mixture had stood for several hours, a 60% yield of nitrile was obtained. Some oxime was isolated from the filtrate in the usual manner. Similar results were obtained with *anti*-4-methoxy-, and *anti*-3-nitro- benzaldoximes.

Benzoylation of anti-*aldoximes in pyridine solution.*—Eastman's pyridine was dried over "Drierite" and distilled; the fraction boiling at 114–115° was collected for use. Eastman's benzoyl chloride was distilled under diminished pressure before use.

To 1 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in 5 cc. of pyridine was added slowly 1 cc. of benzoyl chloride dissolved in 3 cc. of pyridine. The reaction was carried out both in an ice-bath and at room temperature. After standing for several hours, the mixture was poured on approximately 75 g. of ice. The precipitate that formed was filtered off and washed with water until free from pyridine. Some nitrile was obtained by working up the filtrate. The solid remaining in the funnel was washed with alcohol. The nitrile dissolved, leaving the relatively insoluble benzoyl *syn* derivative on the funnel; the nitrile was obtained by evaporation of the alcoholic solution. The yield of benzoyl *syn* derivative was 5–10%, while that of the nitrile was 70–75%.

When the reaction described above was carried out either in an ice-bath or at room temperature, using more than twice as much pyridine (20 cc.), only nitrile was obtained. Also, nitrile was the only product that could be isolated when 1 cc. of benzoyl chloride dissolved in 1 cc. of pyridine was added to 1 g. of *anti*-3,4-methylenedioxybenzaldoxime dissolved in a mixture of 2 cc. of pyridine and 2 cc. of triethylamine.

anti-3-Nitro-, and *anti*-4-methoxy- benzaldoximes were benzoylated in pyridine solution but no attempt was made to determine the effect of the relative amount of pyridine used. A 10% yield of the benzoyl *syn* derivative has been obtained from the former oxime, but no derivative has been obtained from the latter oxime. The yields of nitrile were 70–90% of the theoretical amounts.

Benzoylation of syn *aldoximes in pyridine solution.*—*syn*-3,4-Methylenedioxy-, and *syn*-4-methoxy- benzaldoximes were benzoylated in pyridine solution at room temperature, using purified reagents. The former oxime gave partly benzoyl *syn* derivative and partly nitrile, while the latter oxime gave apparently only nitrile. When the benzoylation of either *syn* aldoxime was carried out in the presence of two to four equivalents of triethylamine, however, the corresponding benzoyl *syn* derivative was obtained in yields of 60–80%; no nitrile could be isolated.

SUMMARY

1. A study has been made of the benzoylation of certain *syn*, and *anti* aldoximes in the presence of bases.

2. *anti* Aldoximes with benzoyl chloride, in the presence of aqueous alkali, give benzoyl *syn* derivatives, but, in the presence of a water-dioxane solution (or emulsion) of alkali, give nitriles. *anti* Aldoximes with benzoyl chloride in pyridine solution give largely or entirely nitriles; in the presence of triethylamine, nitrile is obtained.

3. *syn* Aldoximes with benzoyl chloride in pyridine solution give partly or entirely nitriles, but, in the presence of triethylamine, give entirely benzoyl *syn* derivatives.

4. From these results it is concluded that, although changes of configuration may occur under certain conditions, no change of configuration takes place when either *syn*, or *anti* aldoximes are benzoylated in a sufficiently basic solution.

DURHAM, N. C.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY, PRINCETON UNIVERSITY]

PROPERTIES OF THE THIOMETHYLENE RADICAL. II. THE BEHAVIOR WITH CHLORINE AND WATER

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There are a number of references in the literature to the use of chlorine in the presence of water as an oxidizing agent for organic sulfur compounds. For example, alkyl sulfides have been oxidized to sulfoxides and sulfones (1); aryl mercaptans have been converted to sulfonyl chlorides (2); sulfonyl chlorides have also been obtained from S-alkyl isothioureas (3), mercaptans, disulfides, thiol esters, and other types of sulfur compounds (4). Kostsova (5) reported that chloromethane sulfonyl chloride is formed in 50% yield when chlorine is passed into a water suspension of trithiane (5).

This paper is mainly concerned with the action of chlorine on normal alkyl and benzyl mercaptals, and trithiane when the compounds are dissolved or suspended in a mixture of acetic acid and water. It was found that the formaldehyde mercaptals of ethyl, *n*-butyl, *n*-amyl, and benzyl mercaptans reacted to form the alkane sulfonyl chlorides in good yields. Formaldehyde was liberated in each case, and it was assumed that the reactions proceeded approximately as follows:

$$\text{(I)}\quad R{-}S{-}CH_2{-}S{-}R + 5H_2O + 6Cl_2 \rightarrow 2RSO_2Cl + 10HCl + HCHO.$$

Acetone diethyl mercaptol behaved similarly, yielding ethane sulfonyl chloride and a mixture of the chlorination products of acetone. It was also found that the reagent, as used, acted upon both di-*n*-butyl and dibenzyl sulfides to give the corresponding sulfonyl chlorides.

The question arose, at what stage in the above reactions scission of the sulfur-methylene bond occurred. In order to determine whether the oxidation proceeded first to the sulfone stage, sulfonal and di-*n*-butyl sulfone were treated in the manner mentioned above. Both compounds were obtained from this and even more drastic treatment unchanged. On the other hand, butane sulfonyl chloride was formed from dibutyl sulfoxide. Spring and Winssinger (6) obtained similar results with diethyl sulfoxide. Thus it may be said that the breaking of the sulfur-carbon

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bond occurs before the sulfone stage of oxidation is reached, but may take place after the formation of the sulfoxide. More positive information was obtained with the mercaptals by carrying out the reaction with an amount of chlorine insufficient to complete the process as indicated in equation (I). In particular, with formaldehyde dibenzyl mercaptal, dibenzyl disulfide, and dibenzyl "disulfoxide" were isolated in rather large amounts. Evidently the initial step is substantially as follows:

(II) $$C_6H_5—CH_2—S—CH_2—S—CH_2—C_6H_5 + Cl_2 + H_2O \rightarrow$$
$$C_6H_5—CH_2—S—S—CH_2—C_6H_5 + HCHO + 2HCl.$$

This is followed by:

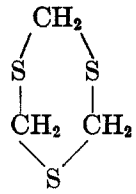
(III) $$C_6H_5—CH_2—S—S—CH_2—C_6H_5 + 2Cl_2 + 2H_2O \rightarrow$$
$$C_6H_5—CH_2—S(=O)—S(=O)—CH_2—C_6H_5 + 4HCl.$$[2]

The oxidation continues at least to the "disulfoxide" stage before scission of the sulfur-sulfur bond occurs. No other intermediate oxidation products could be isolated, so that it cannot be said definitely at what stage of oxidation the actual breaking of the sulfur-sulfur bond takes place.

From equations (II) and (I), it is evident that the action of chlorine on alkyl disulfides dissolved in acetic acid and water should produce alkane sulfonyl chlorides in yields as high as those obtained from the mercaptals (70–95%). This is the fact with diethyl, di-*n*-amyl, and dibenzyl disulfides. As a method of preparation for normal or aryl substituted alkane sulfonyl chlorides, this process is probably superior to the more common procedures.

It was thought that Kostsova's (5) reaction involving trithiane might be similar to that which the mercaptals undergo. That is, trithiane may be considered to be a cyclic mercaptal, which would pass through the steps outlined for those compounds, *i.e.*, (a) loss of a methylene group as formaldehyde, and (b) conversion of the resulting cyclic disulfide to two molecules of chloromethane sulfonyl chloride. Also, according to this mechanism, one atom of sulfur would be liberated, either as free sulfur, or as an oxide or a chloride of sulfur. The overall reaction would be represented by the approximate equation:

[2] There is some question about the structure of "disulfoxides" of this kind. The other possible structure is $C_6H_5—CH_2—SO—SO—CH_2—C_6H_5$.

(IV)  $+ 7Cl_2 + 5H_2O \rightarrow 2ClCH_2SO_2Cl + HCHO + S + 10HCl.$

This equation accounts for all the products obtained when Kostsova's work was repeated. His low yields may be explained by his assumption that each molecule of trithiane is capable of forming three molecules of chloromethane sulfonyl chloride.

EXPERIMENTAL

The general procedure in the experiments reported was to dissolve the sulfur compound in acetic acid (two to five volumes) containing enough water to furnish the required amount of oxygen, and to pass chlorine gas into the solution at a slow rate until a permanent excess was present. The reactions were as a rule complete in a few minutes, and continued addition of the chlorine for several hours did not noticeably alter the yield of the desired products. The reaction-flask was cooled externally, and maintained at about room temperature. The acetic acid-water solution of the compound was sometimes saturated with gaseous hydrogen chloride previous to the addition of the chlorine; this gave a slightly higher yield of the alkane sulfonyl chlorides. At the end of the reaction, when liquid product was expected, two to three volumes of cold water was added to the reaction-mixture, whereupon the water-insoluble, dense alkane sulfonyl chloride formed a bottom layer. This layer was separated and washed once with cold water. The product was purified by distillation, at atmospheric or reduced pressure, and identified by boiling point, density, and refractive index determinations. In the compounds containing the benzylthio-radical, this separation and purification was not needed, for toluene-*alpha*-sulfonyl chloride, m.p. 92–93°, crystallized from the reaction-mixture. In some experiments, as previously noted, the starting materials were not changed under the conditions of the reactions.

The Action of Chlorine in Aqueous Acetic Acid (I) on Certain Sulfides and Disulfides

Di-n-*butyl and dibenzyl sulfides.* Eight grams of di-*n*-butyl sulfide gave 6.5 g. of *n*-butane sulfonyl chloride (about 80% of the theory), of boiling point 100–103°/27–8 mm., of d_4^{23} 1.215, and n_D^{20} 1.4548. These constants compare favorably with those reported by Douglass and Johnson (4).

Five grams of dibenzyl sulfide yielded 3 g. of toluene-*alpha*-sulfonyl chloride crystals, m.p. 92–93°. This was converted to the corresponding sulfonamide, m.p. 105–106°. Two grams of benzyl chloride was extracted from the filtrate with petroleum ether.

Diethyl, di-n-*amyl, and dibenzyl disulfides.* Twelve and two-tenths grams of diethyl disulfide yielded 22 g. of ethane sulfonyl chloride (b.p. 172–175°, d_4^{24} 1.351, and n_D^{20} 1.4518, all in accord with accepted values). This represented a yield of 90%.

Ten grams of di-*n*-amyl disulfide was converted to 7 g. of *n*-pentane sulfonyl chloride, b.p. 83–5°/5–6 mm., d_4^{24} 1.171, and n_D^{20} 1.4565. (*Cf.* values of Douglass and Johnson (4)).

Dibenzyl disulfide (5 g.) gave 7.4 g. of toluene-*alpha*-sulfonyl chloride, m.p. 92–93°. In experiments in which the amount of chlorine added was in slight excess of that required in equation III, benzyl toluene-*alpha*-thiosulfonate (dibenzyl "disulfoxide") was isolated in good yields. (This parallels the experiment of Douglass and Johnson (4).) This "disulfoxide" was best crystallized from absolute alcohol, and melted at 108°. Calc'd for $C_{14}H_{14}O_2S_2$: S, 23.0; Found: S, 22.9. This compound was quantitatively converted into toluene-*alpha*-sulfonyl chloride by treatment with a slight excess of chlorine. The reaction required only a few minutes for completion.

The Action of (I) on Certain Formaldehyde Mercaptals and on Acetone Mercaptol

*Diethyl, di-*n*-amyl, and dibenzyl mercaptals of formaldehyde.* Twenty-five grams of formaldehyde diethyl mercaptal (free from formaldehyde) gave 28 g. of ethane sulfonyl chloride, or 72% of the theory. The acetic acid–water layer from this reaction was about two-thirds neutralized with sodium hydroxide solution, and tested for formaldehyde with dimethyldihydroresorcinol. A copious precipitate was obtained, which melted at 189° after one crystallization from alcohol. A mixed melting point with the known product from formaldehyde and dimethyldihydroresorcinol showed no depression.

Seventeen and six-tenths grams of normal primary amyl mercaptan was converted into its formaldehyde mercaptal, by saturating the acetic acid solution of the mercaptan and formalin with hydrogen chloride gas. The mercaptal was not isolated, but was chlorinated directly. It yielded 26 g. of *n*-pentane sulfonyl chloride. This represents a yield of about 95%.

Formaldehyde dibenzyl mercaptal gave toluene-*alpha*-sulfonyl chloride in yields of 80–85%. The product was of high purity. In experiments in which the chlorine was added in small, measured amounts, it was possible to isolate appreciable quantities of dibenzyl disulfide, m.p. 69–70°. A mixed melting point with authentic disulfide likewise melted at 69–70°.

Acetone diethyl mercaptol. Sixteen and four-tenths grams of acetone diethyl mercaptol was converted into chlorination products of acetone, and 18 g. of ethane sulfonyl chloride. The properties of the sulfonyl chlorides obtained from the mercaptals and the mercaptol were the same as those noted in the preceding experiments.

The Action of (I) on Trithiane

Trithiane. Fourteen grams of formaldehyde-free trithiane gave 22.5 g. of chloromethane sulfonyl chloride, about 75% yield on the basis of equation IV. The compound had the following properties: B.p. 70–72° at 23 mm., d^{23} 1.600, n_i^{15} 1.4788, n_i^{20} 1.4771.

The acetic acid–water layer from this reaction contained at least one-third of the formaldehyde to be expected from the equation. The formaldehyde was estimated as in the above experiment. In some experiments, this layer gave a positive test for the sulfate ion; in others, the third sulfur atom appeared as a chloride of sulfur.

*The Action of (I) on Di-*n*-butyl Sulfoxide*

*Di-*n*-butyl sulfoxide.* Five grams of di-*n*-butyl sulfoxide gave 2 g. of *n*-butane sulfonyl chloride. No attempt was made to isolate the butyl chloride formed.

SUMMARY

1. The reactions of several types of organic sulfur compounds with chlorine and water, in acetic acid as a medium, have been studied.

2. Normal and aryl substituted alkyl sulfides are oxidized and converted by the reagent to alkane sulfonyl chlorides and alkyl chlorides. The splitting of the molecule may occur after oxidation to the sulfoxide stage; it must occur before oxidation to the sulfone stage is reached.

3. Several formaldehyde mercaptals and acetone mercaptol have been converted to alkane sulfonyl chlorides and their parent carbonyl compounds. This reaction probably proceeds stepwise from the mercaptal to the disulfide, the "disulfoxide," and finally by oxidation and splitting to the alkane sulfonyl chloride.

4. If one starts with the alkyl disulfide, this reaction offers an excellent method of preparing the corresponding alkane sulfonyl chloride.

5. This reaction of trithiane has been found to be similar to that of the structurally related mercaptals.

PRINCETON, N. J.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA]

CALCULATION OF THE NUMBER OF STEREOISOMERS IN CARBON CHAIN COMPOUNDS

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INTRODUCTION

A simple method can be devised for obtaining the number of stereoisomers of any carbon chain compound, whether simple or branched, which can readily be applied to chains containing units of geometric isomerism alone or in combination with asymmetric atoms.

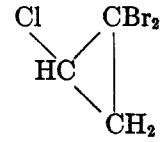
This general method consists in working from the periphery of the molecule inward, by treating each region successively in a manner determined by the arrangement of the groups, until finally the complete solution is made about an initially determined part of the molecule.

A structural formula only shows which atoms are bonded together, and a single formula may represent two or more compounds. In the same way, parts of a structural formula may be identical as far as the structural formula goes, and yet represent different things. When two structural formulas or two parts of a structural formula are the same, we shall say that the things represented are structurally identical, but when the things represented are the same, we shall use "identical" without any qualifying adverb. We shall follow the same convention with respect to "different". The things represented by a region of a structural formula we shall call the possibilities of the region, and their number will be expressed by the symbol p. The number of stereoisomers may be obtained from the p-values of all the regions, and the number of possibilities of a compound region from the p-values of the component regions. To do this it is necessary to have certain formulas to express the number of possibilities of a compound region in terms of the p-values of the component regions. These formulas will depend on the procedure adopted for dividing the structural formula into regions and the order of combining the regions, as well as upon the stereochemistry of the elements in the compound. It appears that if we follow certain rules for selecting and combining regions, quite simple formulas are adequate for noncyclic carbon compounds that contain no elements having stereochemical properties other than those characteristic of carbon.

OPTICAL ISOMERISM

In the present section we shall restrict ourselves to saturated compounds. For these the fundamental assumption is that a region containing one atom with four different groups attached to it has two possibilities. If the groups are structurally different such an atom may be recognized from the structural formula, and we shall call such an atom asymmetric. This does not quite conform to common usage. For instance text books refer to compounds of the type $a_3CC_{ab}C_{ab} \cdots C_{ab} \cdot C_{a_3}$ having either an odd or an even number of asymmetric atoms, while in our use of asymmetric atom such a compound cannot have an odd number of such atoms.

In using the test of four structurally different groups, a group includes everything that can be reached by passing along bonds, and has an order starting with the bond. Thus



has an asymmetric atom as the groups $—CBr_2CH_2$ and $—CH_2CBr_2$ are not structurally identical.

In a saturated noncyclic compound no atom can have four different groups attached to it unless the molecule contains atoms with four structurally different groups.

When structurally different regions are combined, the number of possibilities is given by the formula $N = p_a \cdot p_b \cdot p_c \cdots$, where N is the number of stereoisomers or the number of possibilities in the compound region according as $a + b + c \cdots$ is the whole structural formula or part of it.

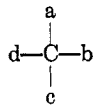
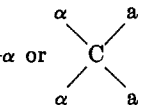
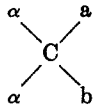
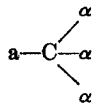
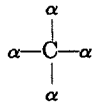
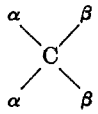
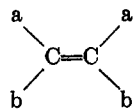
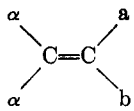
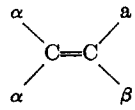
If in a formula, or part of one, there are no structurally identical regions for which $p > 1$, there are no atoms except asymmetric ones that can have four different groups, and $N = 2^n$ where n is the number of asymmetric atoms. N may refer to the whole molecule or to a region connected by bonds. When we speak of structurally identical regions, the identity must exist not only in the contents of the region but also in any groups to which they are bonded. Thus in $H_3C—CHCl—CH_2—CH_3$ the two methyl groups are not identical regions, but the three hydrogen atoms attached to one carbon atom are.

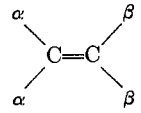
When a formula contains structurally identical regions for which $p > 1$, we use the following procedure for selecting and combining regions. Working inwards from the periphery we select the first region that includes an asymmetric atom. From this we proceed along the bonds until another region is found containing an asymmetric atom, and these regions are

TABLE

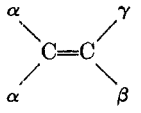
NUMBER OF INACTIVE FORMS FOR THE VARIOUS TYPES OF STRUCTURE

Greek letters represent simple or complex groups of asymmetric or geometric units

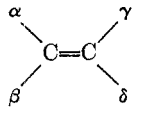
Structural type	Equation
	$N_i = 0$
α—β	$N_i = p_{\alpha i}\, p_{\beta i}$
α—α or 	$N_i = I_2^{p_i} + \frac{p_a}{2}$
	$N_i = p_i + p_a$
	$N_i = I_3^{p_i} - p_i C_3 + p_a p_i$
	$N_i = I^{p_i} - p_i C_4 + \frac{p_a}{2}(I^{p_i} + p_i C_2) + \frac{p_a}{2}$
	$N_i = I^{p_{\alpha i}} \times I_2^{p_{\beta i}} - p_{\alpha i} C_2 \times p_{\beta i} C_2 + \frac{p_{\alpha a}}{2}(I_2^{p_{\beta i}} + p_{\beta i} C_2) + \frac{p_{\beta a}}{2}(I_2^{p_{\alpha i}} + p_{\alpha i} C_2)$
	$N_i = 2$
	$N_i = I^{p_i} + p_i C_2$
	$N_i = p_{\beta i}(I_2^{p_{\alpha i}} + p_{\alpha i} C_2)$



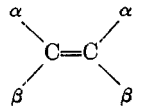
$$N_i = I_2^{p_{\alpha i}} \times I_2^{p_{\beta i}} + p_{\alpha i} C_2 \times p_{\beta i} C_2 + \frac{p_{\alpha a} p_{\beta i}}{2} + \frac{p_{\alpha i} p_{\beta a}}{2} + \frac{p_{\alpha a} p_{\beta a}}{2}$$



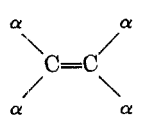
$$N_i = p_{\beta i} p_{\gamma i} (I_2^{p_{\alpha i}} + p_{\alpha i} C_2)$$



$$N_i = 2 p_{\alpha i} p_{\beta i} p_{\gamma i} p_{\delta i}$$



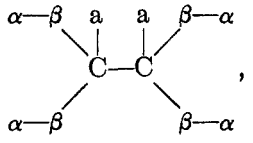
$$N_i = 2 I_2^{p_{\alpha i} p_{\beta i}} + p_{\alpha a} p_{\beta a}$$



$$N_i = I_2^{p_{Ai}} + I_2^{S_i} + \frac{p_a p_i}{2} + 2 \times I_2^{p_{a/2}} + 4 \times \frac{p_a}{2} C_2 \text{ in which } p_{Ai} = I_2^{p_i} \text{ and } S_i = \frac{p_i(p_i - 1)}{2}$$

combined, this process being carried on until a region is obtained which is bonded directly to a region structurally identical with it, or bonded to the same atom as one or more regions identical with it. These regions are then combined. When structurally identical regions are attached to the same atom, this atom and the structurally identical regions are combined to give R_1. One then starts at another part of the periphery and proceeds as before until a region, R_2, attached to R_1, or to the same atom as R_1 is obtained. R_1 and R_2 are then combined. Constant repetition of this procedure eventually leads to the inclusion of the whole formula.

We shall show the procedure by applying it to



in which Greek letters indicate regions with asymmetric atoms. Working from the periphery we find the first simple region α. This is then combined with the next such region to give the compound region α—β. This is structurally identical with another α—β region attached to the same carbon atom. We combine the two α—β regions and the atom to which they are attached to form $(\alpha\text{—}\beta)_2C_a^-$. This region is structurally identical

with and bonded to the other $(\alpha—\beta)_2C_a^-$, and these are combined, the whole formula being then included. Had the group "a" contained asymmetric atoms it would have been necessary to start at the periphery and calculate p for a and combine a and $(\alpha—\beta)_2C$ before the final combination of $(\alpha—\beta)C_a$ with $(\alpha—\beta)_2C_a$.

In the above example the p value of $\alpha—\beta$ is $p_\alpha \cdot p_\beta$ or 2^n. But multiplication cannot be used to obtain the p values for other compound regions, as all the combinations of the possibilities of $\alpha—\beta$ and $\alpha—\beta$ or of $—\overset{a}{C}(\alpha\beta)_2$ and $—\overset{a}{C}(\alpha\beta)_2$ do not represent different things. Also the atom represented by C can have four different groups according to the possibilities chosen for the two $\alpha\beta$-groups even though C is not an asymmetric atom by our definition. Although this atom does not have four structurally different groups it has no structurally identical groups that do not contain asymmetric atoms. We shall call this type of atom quasiasymmetric. When we include unsaturated compounds it will be necessary to modify slightly the above definition. The central atoms in C_{α_4}, $C_{\alpha_3 a}$, $C_{\alpha_2 ab}$, $C_{\alpha_2\beta_2}$ are quasiasymmetric. In the first two of these, if α has only two possibilities, the quasiasymmetry will not contribute to the stereoisomerism.

In combining identical regions about a central atom, we divide the groups of this atom into two parts, A and B. One of these, A, contains all structurally identical groups, the other, what is left. The central atom will produce an extra possibility when all four groups are different. This number is $S_A \cdot S_B$, in which S_A is the number of ways in which the groups comprising A may be chosen from their possibilities so that none are identical. S_B has the same meaning for B. If B is composed of one group or of structurally different groups, it cannot introduce any identity in the groups attached to the central carbon atom, and the number of possibilities of the region A plus the central atom can be taken as $p_A + S_A$, and we may proceed to the next region. When B is composed of structurally identical groups, the value of S_B is zero, if the groups have only one possibility, but S_B has a finite value if the groups have more than one possibility. In this case the whole formula is ACB or $\alpha_2C\beta_2$. The number of possibilities for β must be calculated by starting at the peripheral point. The total number of isomers is then $N = p_A \cdot p_B + S_A \cdot S_B$.

The essence of the method of selecting and combining regions is that we never combine structurally identical regions that are neither attached to the same atom nor form two identical halves of the molecule. In this way we combine structurally identical regions having the same equivalence as that between identical groups attached to a carbon atom. This we shall call complete equivalence. It is defined by the condition that if the structurally identical regions, a_1, a_2 $\cdots$ are replaced by a set of non-

identical regions, m, n $\cdots$, the structural formula obtained is independent of the order of the changes. That is, if in the formula $A_{a_1a_2a_3}$, a_1, a_2, and a_3 are completely equivalent, then A_{mno}, A_{mon}, A_{nmo}, A_{nom}, A_{omn}, and A_{onm} are all the same formula, even though more than one substance may be represented by this formula. We shall call the number of completely equivalent regions the degree of equivalence and represent it by the symbol q. The number of possibilities obtainable from the combination of q completely equivalent regions is a function of q and p for one of the component regions, and we shall represent this function by the symbol $\left|{}^{p}_{q}\right.$. When the regions are attached to a quasiasymmetric atom, S, extra forms are introduced when the quasiasymmetric atom is included. That is $N = \left|{}^{p}_{q}\right. + S$.

It is obvious that $\left|{}^{p}_{q}\right.$ is the number of combinations of p dissimilar things taken q at a time, when repetitions of the p elements are allowed. This is equal to the number of combinations of $p + q - 1$ dissimilar things taken q at a time. S is the number of combinations of p dissimilar things taken q at a time.

$$\left|{}^{p}_{q}\right. = \frac{(q+1)(q+2)\cdots(q+p-1)}{(p-1)!} = \frac{(q+p-1)(q+p-2)\cdots(p+1)p}{q!}$$

$$= \frac{(q+p-1)!}{(p-1)!q!} = (p+q-1)C_q.$$

$$S = \frac{p(p-1)(p-2)\cdots(p-q+1)}{q!} = \frac{p!}{(p-q)!q!} = pC_q.$$

The fundamental formulas are:

$N = p_a \cdot p_b \cdot p_c \cdots = 2^n$, when structurally different regions are combined:

$N = \left|{}^{p}_{q}\right. = (p + q - 1)C_q$, when completely equivalent regions are combined.

$N = \left|{}^{p}_{q}\right. + S = (p + q - 1)C_q + pC_q$, when completely equivalent regions and a quasiasymmetric atom are combined:

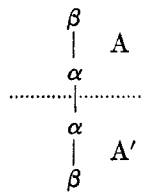
$N = p_A \cdot p_B + S_A S_B = \left|{}^{p_\alpha}_{2}\right. \cdot \left|{}^{p_\beta}_{2}\right. + S_A \cdot S_B = (p_\alpha + 1)C_2 \cdot (p_\beta + 1)C_2 + p_\alpha C_2 \cdot p_\beta C_2$, when two pairs of completely equivalent regions and a quasiasymmetric atom are combined, that is, when the compound belongs to the type $C_{\alpha_2\beta_2}$. Often it is convenient in compounds of the type $C_{\alpha_2\beta\gamma}$ to use the formula $N = p_A \cdot p_B + S_A \cdot S_B$ in which B is the region $\beta\gamma$. S_B is then equal to p_B, and $N = \left|{}^{p_\alpha}_{2}\right. \cdot p_B + p_\alpha C_2 \cdot p_B = \left|{}^{p_\alpha}_{2}\right. \cdot p_\beta \cdot p_\gamma + p_\alpha C_2 \cdot p_\beta \cdot p_\gamma$.

When $q = 2$ and there is only one center of equivalence the formulas $N = \left|{}^{p}_{q}\right.$ and $N = \left|{}^{p}_{q}\right. + S$ reduce to the common expressions, $N = 2^{n-1} + 2^{n/2-1}$ and $N = 2^{n-1}$, used for the number of stereoisomers of a compound

of the type α_3CCabCab $\cdots$ CabCα_3, according as n is even and odd respectively. With our definition of an asymmetric atom, the latter case is one with an even number of asymmetric atoms plus a quasiasymmetric atom. It becomes $N = 2^n$, when n is the number of carbon atoms having four structurally different groups. This formula, $N = 2^n$, holds whenever completely equivalent regions having $p > 1$ occur only in pairs attached to the same atom, as in examples V and VI. The formula $N = 2^{n-1} + 2^{n/2-1}$ holds whenever completely equivalent regions having $p > 1$ occur only in pairs, but finally reduce to one of the types, α–α, α_2Ca$_2$ or α_2Cβ_2. Examples I and II and IV are cases of this. For the above formulas to hold for complex cases, it is necessary that n is the number of asymmetric atoms by our definition.

It should, perhaps, be pointed out that although the method outlined is general and can be applied to any type of non-cyclic stereoisomerism of tetrahedral atoms by the use of a few simple formulas, it is only in certain cases involving equivalence that Senior's (1) formulas are not also applicable.

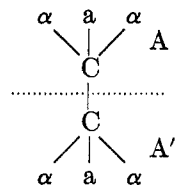
Examples.—The application of the above method can best be shown by considering a variety of examples. In the following examples the Greek letters, α, β, etc. represent asymmetric units, the letters a, b, etc. represent symmetrical groups, capital letters A, B, etc. stand for regions of the molecule, N_A, N_B, etc. are the number of possibilities in regions A, B, etc. respectively, and N is the total number of stereoisomers.



Example I

$N_A = N_{A'} = 2^2 = 4.$

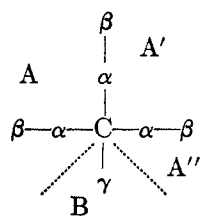
Then $N = I_2^4 = \frac{3 \cdot 4 \cdot 5}{3 \cdot 2} = 10.$



Example II

$N_A = N_{A'} = I_2^2 + S = \frac{3}{1} + \frac{2 \cdot 1}{2 \cdot 1} = 4.$

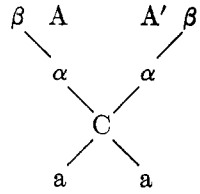
For the whole molecule, $N = I_2^4 = 10.$



Example III

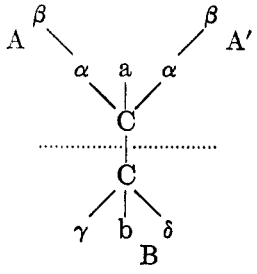
$N_A = N_{A'}N_{A''} = 2^2 = 4, N_B = 2.$

Then $N = pp' + SS' = I_3^4 \cdot p' + Sp' = \frac{4 \cdot 5 \cdot 6}{3 \cdot 2 \cdot 1} \cdot 2 + \frac{4 \cdot 3 \cdot 2}{3 \cdot 2 \cdot 1} \cdot 2, N = 48.$



Example IV

$N_A = N_{A'} = 2^2 = 4$. $N = I_2^4 = 10$.
The SS′ term is dropped since the two symmetrical groups are identical.

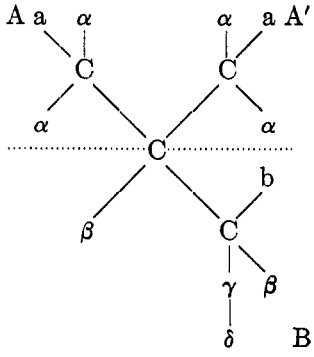


Example V

$N_A = N_{A'} = 2^2 = 4$, $N_B = 2^3 = 8$.

$N_{AA'} = I_2^4 + S = 10 + \frac{4 \cdot 3}{2 \cdot 1} = 16.$

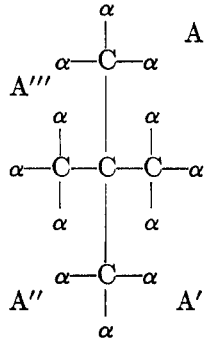
Finally, $N = pp' = 8 \cdot 16 = 128$.



Example VI

$N_A = N_{A'} = I_2^2 + S = 3 + \frac{2 \cdot 1}{2 \cdot 1} = 4.$

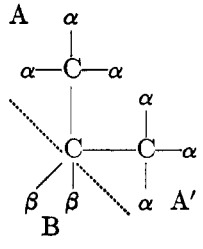
$N_{AA'} = I_2^4 = 10$. $N_B = 2^5 = 32$.
Then $N = pp' + SS' = pp' + Sp' = 10 \cdot 32 + \frac{4 \cdot 3}{2 \cdot 1} \cdot 32$, and $N = 512$.



Example VII

$N_A = I_3^2 + S = 4 + \frac{2 \cdot 1 \cdot 0}{3 \cdot 2 \cdot 1} = 4.$

$N = I_4^4 + S = \frac{5 \cdot 6 \cdot 7}{3 \cdot 2 \cdot 1} + \frac{4 \cdot 3 \cdot 2 \cdot 1}{4 \cdot 3 \cdot 2 \cdot 1} = 36.$



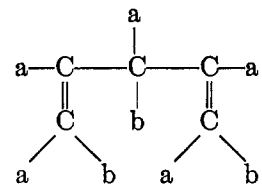
Example VIII

$N_A = N_{A'} = I_3^2 + S = 4 + \frac{2 \cdot 1 \cdot 0}{3 \cdot 2 \cdot 1} = 4.$

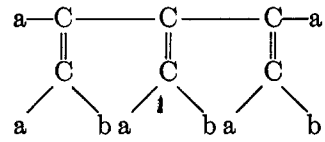
$N_{AA'} = I_2^4 = 10$, $N_B = I_2^2 = 3$, $N = pp' + SS' = 10 \cdot 3 + \frac{4 \cdot 3}{2 \cdot 1} \cdot \frac{2 \cdot 1}{2 \cdot 1} = 36.$

GEOMETRIC ISOMERISM

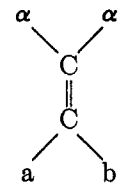
A pair of doubly bonded carbon atoms having different groups attached to each carbon atom allows two possibilities for a region including the pair of carbon atoms. If both the differences are structural they can be recognized from the structural formula, and the double bonded system may be called a geometric unit. But the isomerism exists whether the differences are structural or not. Hence it is possible to have a quasi-geometric unit analogous to the quasiasymmetric atom. Further, since two structurally identical geometric units can exist in different forms, it is possible to have four different groups attached to an atom that is not asymmetric without having an asymmetric atom in the molecule. It is therefore advisable to modify the definition of quasiasymmetry. A quasiasymmetric atom is one whose four groups are not all structurally different, but has no structurally identical groups that contain neither an asymmetric atom nor a geometric unit. Similarly, a quasigeometric unit is a pair of doubly bonded carbon atoms that has two structurally identical groups attached to at least one of the atoms, but in which neither carbon atom has structurally identical groups that contain neither an asymmetric atom nor a geometric unit. Thus the central carbon atom in



is quasiasymmetric, and the central pair of doubly bonded carbon atoms in



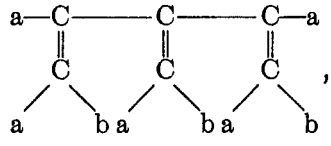
and the pair of doubly bonded carbon atoms in



are quasigeometric units. When both the carbon atoms of a quasigeometric unit are different an extra possibility or stereoisomer can exist.

When a structural formula or part of one shows no structurally identical regions for which p exceeds unity no quasiasymmetric atom nor quasigeometric unit is present. For such a formula or part of one, $N = p_a \cdot p_b \cdot p_c \cdots$ and $N = 2^n$, where n is the sum of asymmetric atoms and geometric units.

When structurally identical regions having $p > 1$ are present, quasiasymmetric atoms and quasigeometric units may exist, and all combinations of the possibilities of component regions are not different. Hence N need no longer be equal to the product of the numbers of possibilities of component regions. Structurally identical geometric units attached to the same carbon atom or to themselves, or two structurally identical regions attached to a doubly bonded carbon atom, have the same complete equivalence that exists in structurally identical regions in a saturated chain compound. Hence, except when the double bond introduces a new kind of equivalence, the method of selecting and combining regions described in the previous section and the formulas used will enable us to calculate the number of stereoisomers for a given structural formula whether it contains asymmetric atoms, geometric units, or both. In most cases doubly bonded carbon atoms introduce no new equivalences or methods of combination. Thus for



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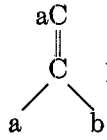
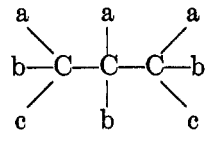
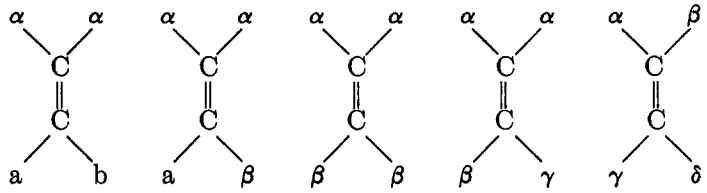


has two possibilities and there are two of these groups joined by a quasigeometric unit, so $N = |\,^2_2 + S = 3C_2 + 2C_2 = 4$, just as for

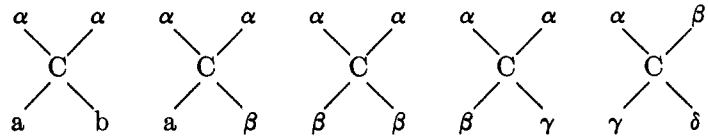


$N = |\,^2_2 + S = 3C_2 + 2C_2 = 4$. The following examples show fundamental cases of complex quasigeometric units, and geometric units and the corresponding analogous cases of quasiasymmetric and asymmetric atoms. For each member of an analogous pair, the number of stereoisomers is the same and is also given. In the formulas Greek letters have been used to represent regions resulting from any combination of asymmetry, quasiasymmetry and geometric and quasigeometric isomerism.

IX X XI XII XIII



IX′ X′ XI′ XII′ XIII′



Examples IX and IX′, $N = \left|\frac{p_\alpha}{2}\right. + S$ where $S = \frac{p_\alpha(p_\alpha - 1)}{2}$

Examples X and X′, $N = \left[\left|\frac{p_\alpha}{2}\right. + \frac{p_\alpha(p_\alpha - 1)}{2}\right] p_\beta$

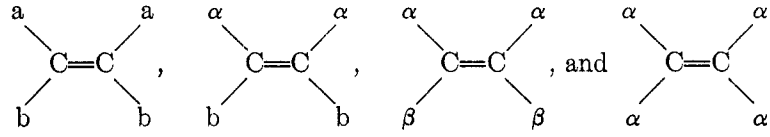
Examples XI and XI′, $N = p_A \cdot p_B + S_A \cdot S_B$ where $p_A = \left|\frac{p_\alpha}{2}\right.$, $p_B = \left|\frac{p_\beta}{2}\right.$,

$$S_A = \frac{p_\alpha(p_\alpha - 1)}{2} \text{ and } S_B = \frac{p_\beta(p_\beta - 1)}{2}.$$

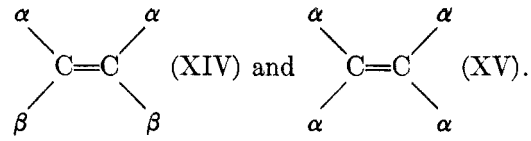
Examples XII and XII′ $N = \left[\left|\frac{p_\alpha}{2}\right. + \frac{p_\alpha(p_\alpha - 1)}{2}\right] p_\beta \cdot p_\gamma$

Examples XIII and XIII′, $N = 2p_\alpha \cdot p_\beta \cdot p_\gamma \cdot p_\delta$.

However, geometric isomerism does include a type of equivalence not found in saturated compounds. This is the possibility of the structural identity of the two carbons of the geometric unit. The analogous case is not possible in optical isomerism as the fundamental unit, the asymmetric atom, consists of one atom. Examples are



In the first of these the equivalence is immaterial. The next two are essentially the same, so we shall give the solution for the more complex of the two. Hence we have the two special cases

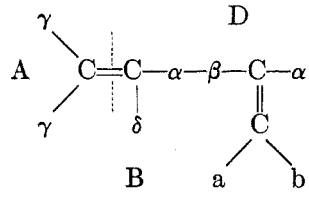


The solutions are:

Example XIV. $N = 2\left|\begin{matrix} p_A \\ 2 \end{matrix}\right.$, where $p_A = p_\alpha \cdot p_\beta$.

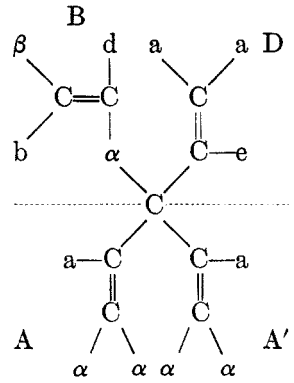
Example XV. $N = \left|\begin{matrix} p_A \\ 2 \end{matrix}\right. + \left|\begin{matrix} S_A \\ 2 \end{matrix}\right.$, where $p_A = \left|\begin{matrix} p_\alpha \\ 2 \end{matrix}\right.$ and $S_A = \dfrac{p_\alpha(p_\alpha - 1)}{2}$

The following are more specific examples (here α, β etc. are again single, asymmetric units):



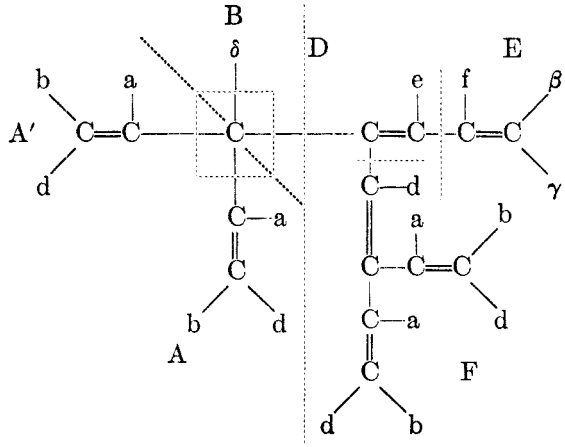
Example XVI

$N_D = 2^4 = 16$, $N_B = 2$, $N_{BD} = 16 \cdot 2 = 32$, and $N_A = I_2^2 = 3$.
Then $N = pp' + SS' = pp' + Sp' = 3 \cdot 32 + \dfrac{2 \cdot 1}{2 \cdot 1} \cdot 32 = 128$.



Example XVII

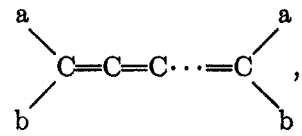
$N_B = 2^3 = 8$, $N_D = 1$, $N_A = N_{A'} = I_2^2 + S = 3 + 1 = 4$, and $N_{BD} = 8 \cdot 1 = 8$.
$N = pp' + SS' = pp' + Sp' = I_2^4 \cdot 8 + \dfrac{4 \cdot 3}{2} \cdot 8 = 10 \cdot 8 + 6 \cdot 8 = 128$.



Example XVIII

$N_E = 2^3 = 8$, $N_F = I_2^2 + S = 3 + \dfrac{2 \cdot 1}{2 \cdot 1} = 4$, and $N_D = 2N_E N_F = 2 \cdot 8 \cdot 4 = 64$.
$N_B = 2$, $N_A = N_{A'} = 2$, whence $N_{AA'} = I_2^2 = 3$.
Then $N_{BD} = 2 \cdot 64 = 128$.
Finally, $N = pp' + SS' = pp' + Sp' = 3 \cdot 128 + \dfrac{2 \cdot 1}{2 \cdot 1} \cdot 128$, $N = 512$.

Groups of the spirane type,



are analogous to geometric units and may be included in this method as geometric units, as long as no distinction between optically active and inactive forms is made. When the number of unsaturated atoms is odd, these units produce optical, and when even, geometric isomers.

Isomerism resulting from steric hindrance has not been included in our method. The assumption is made that rotation about a single bond is sufficiently easy to prevent isomerism, and that about a double bond is sufficiently hindered to produce isomerism.

OPTICALLY INACTIVE FORMS

The method of working from the periphery to a chosen final group can be used to obtain the number of meso forms. It is necessary to keep account of both active and inactive possibilities. The number of inactive possibilities in a region, p_i, or of inactive isomers in the molecule N_i can be calculated for different types of structures by the equations given below. The number of active possibilities or active isomers, p_a or N_a, can be obtained by difference.

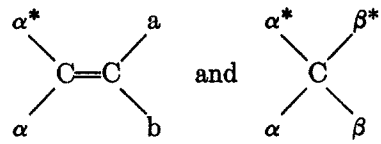
The fundamental rules used to obtain these formulas are as follows:

(a) A geometric unit produces inactive isomers;

(b) an asymmetric atom produces active isomers;

(c) an asymmetric atom assures optical activity unless its mirror image is also present;

(d) even then, compounds of the type



are active;

(e) Compounds of the type $abC{=}C_a - C_{ab} - C_a = C_{ab}$ have two inactive and two active forms.

We are indebted to Dr. James K. Senior for some valuable criticism.

SUMMARY

A method for calculating the number of stereoisomers of straight or branched carbon chain compounds is described.

It is pointed out that the method is applicable to compounds containing asymmetric carbon atoms, units of geometric isomerism, or both.

The method can be used to calculate the number of optically inactive forms, but it is then necessary to introduce a number of additional equations. These additional equations are given, with the type of structures to which they are applicable.

BERKELEY, CALIF.

REFERENCE

(1) SENIOR, *Ber.*, **60B**, 73 (1927).

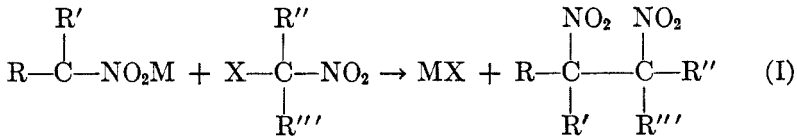
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND PURDUE RESEARCH FOUNDATION, PURDUE UNIVERSITY]

A NEW SYNTHESIS OF DINITROPARAFFINS

L. W. SEIGLE AND H. B. HASS

Received July 5, 1939

The interesting work of Professor Shriner and co-workers (1), (2) on the reactions of the salts of nitro compounds with organic halides suggested the present investigation. This paper deals with the preparation of dinitro compounds by the reaction of salts of nitroparaffins with halonitroparaffins. The halonitro compounds have the halogen atom and nitro group on the same carbon atom. The reaction (I) involves the formation of a new carbon-to-carbon linkage.



(I)

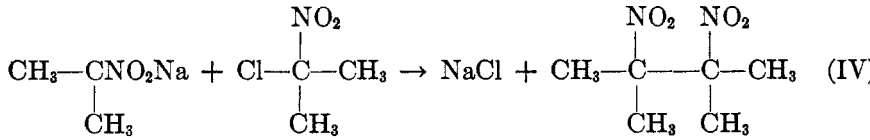
Nenitzescu (3) has shown that 1,2-dinitro-1,2-dibiphenylene ethane was formed by treatment of the potassium salt of 9-nitrofluorene with iodine. Nenitzescu and Isacescu (4) obtained an almost quantitative yield of 1,2-dibiphenylene ethane by heating a solution of 9-iodo-9-nitrofluorene. These reactions indicate that the new carbon-to-carbon linkages might be formed according to the equations (II) and (III).

$$X_2 + R_2CNO_2M \longrightarrow MX + R_2C(NO_2)X \qquad \text{(II)}$$

$$R_2C(NO_2)X + R_2C(NO_2)X \rightarrow X_2 + R_2C(NO_2)—(NO_2)CR_2 \qquad \text{(III)}$$

These equations may account for the formation of symmetrical dinitro compounds, but they do not account for the formation of unsymmetrical dinitro compounds.

A study was made of the reaction (IV).



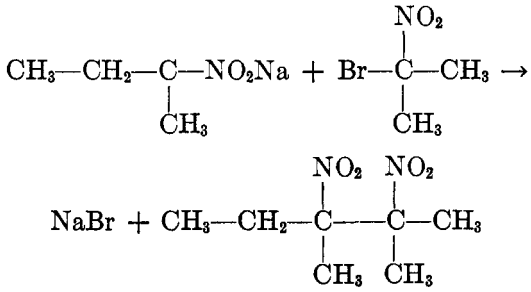
(IV)

A solid compound of melting point 208.4–209° was isolated from the reaction-mixture. This compound was identified as 2,3-dimethyl-2,3-dinitrobutane. The percentage conversion to the dinitro compound was

dependent upon the halogen compound used. With the chloride the conversion was approximately 9%, with the bromide 29%, and with the crude iodide 43%. No other product was isolated from the reaction-mixture. A 14% conversion to the dinitro compound was obtained by allowing the calcium salt to react with 2-bromo-2-nitropropane. Refluxing a mixture of sodium bicarbonate, 2-bromo-2-nitropropane, and 2-nitropropane gave a 14% conversion to the dinitro compound.

The sodium salt of 2-nitrobutane was allowed to react with 2-bromo-2-nitrobutane. A white solid having a camphoraceous odor and melting at 78° was isolated from the reaction-product. This solid was found to be 3,4-dimethyl-3,4-dinitrohexane. The conversion was 16%. Substituting crude 2-iodo-2-nitrobutane for the bromo compound in the reaction gave a 34% conversion to the dinitro compound. No other product was isolated from the reaction-mixture.

The reaction between the sodium salt of 2-nitrobutane and 2-bromo-2-nitropropane produced 2,3-dimethyl-2,3-dinitropentane of melting point 88–88.6°. The conversion to the dinitro compound was 8%. The equation for this reaction is shown in (V).



(V)

A small quantity of 2,3-dimethyl-2,3-dinitrobutane was isolated from the reaction-mixture.

A solid of melting point 140–141° was obtained when the sodium salt of nitrocyclohexane was allowed to react with 2-bromo-2-nitropropane. The analysis of this compound indicated that it was 1-nitro-1-(2-nitroisopropyl)-cyclohexane. The conversion to the dinitro compound was approximately 19%. The reaction-mixture in these experiments contained a small amount of insoluble unreacted halonitro compound. The remainder of the solution, which was not analyzed, was water-soluble.

No product was obtained when the sodium salt of nitroethane was allowed to react with 1-bromo-1-nitroethane or with 2-bromo-2-nitropropane, or when the sodium salt of 1-nitropropane was allowed to react with 1-bromo-1-nitropropane, or when the sodium salt of 2-nitropropane and 1-bromo-1-nitroethane was used. These results seem to indicate

that carbon-to-carbon linkages are not produced when primary nitro compounds are involved. Nenitzescu and Isacescu (4) obtained 1,2-diphenyl-1,2-dinitroethane by allowing phenyliodonitromethane to react with the sodium salt of phenylnitromethane. The reaction tending to form the dinitro compounds is competing with other reactions and the yield of the dinitro compounds depends upon the reaction rates. It appears that the formation of the dinitro compounds is determined by the nature of the group or groups attached to the carbon atom holding the nitro group.

EXPERIMENTAL

2-Chloro-2-nitropropane. This compound was prepared by stirring 2-nitropropane with an aqueous solution of sodium hydroxide until all of the nitro compound dissolved. The alkaline solution was cooled and chlorine was bubbled into the vigorously stirred solution (5). The chloronitro compound separated as an oil. The oil was washed with sodium hydroxide solution, with water, dried over anhydrous calcium chloride, and rectified in a modified Podbielniak column. The boiling point of the material was 57° at 50 mm. The boiling point corrected to 760 mm. was 131° (6).

2-Bromo-2-nitropropane. This compound was prepared in a manner similar to that of the chloro compound. The calculated amount of bromine was added to the alkaline solution from a dropping-funnel. The liquid boiled at 73–75° at 50 mm. The boiling point corrected to 760 mm. was 150–152° (7).

2-Iodo-2-nitropropane. This compound was prepared by adding a water solution of iodine and potassium iodide to the vigorously stirred solution of the sodium salt of 2-nitropropane. It was washed with water and dried. The crude, dry iodo compound was used in the synthesis, since efforts to purify it by rectification resulted in its decomposition.

2-Bromo-2-nitrobutane. This compound was prepared in the same manner as 2-bromo-2-nitropropane. The boiling point was 78° at 30 mm. The boiling point corrected to 760 mm. was 171° (8).

2-Iodo-2-nitrobutane. The method used to prepare 2-iodo-2-nitropropane was used. The crude material was used in the synthesis.

1-Bromo-1-nitroethane. The method described for 2-bromo-2-nitropropane was used. The fraction boiling between 69 and 76° at 50 mm. was collected. The boiling point corrected to 760 mm. was 146–152° (9).

1-Bromo-1-nitropropane. This compound was prepared by the method described previously. The material boiled at 82–85° at 50 mm. The boiling point corrected to 760 mm. was 159–164° (10).

2,3-Dimethyl-2,3-dinitrobutane. A. From sodium salt of 2-nitropropane and 2-chloro-2-nitropropane. The sodium salt of 2-nitropropane was prepared by adding sodium to absolute alcohol, followed by the addition of 2-nitropropane in absolute ether. The solid salt which precipitated was filtered and dried.

One-tenth mole of the sodium salt was refluxed with one-tenth mole of 2-chloro-2-nitropropane and 100 ml. of absolute alcohol for seven hours. The reaction-mixture was cooled, and a white crystalline solid formed. The solid was filtered and recrystallized from absolute alcohol. The conversion was approximately 9%. The solid had the melting point 208.4-209°.

Anal.[1] Calc'd for $C_6H_{12}N_2O_4$: C, 40.88. Found: C, 41.34.

The previous experiment was repeated. Sodium iodide was added to the mixture. A 2% conversion to the dinitro compound was obtained.

The use of 2-methoxyethanol, methanol, 80% ethanol, or 1,4-dioxane as a solvent did not increase the percentage conversion. The most convenient procedure was to dissolve the nitro compound in a solution of sodium hydroxide in 80% ethanol. The chloronitro compound was added and the solution was refluxed for three hours. A 6% conversion was obtained by this method. Substitution of calcium oxide for sodium hydroxide did not increase the percentage of conversion.

B. From the sodium salt of 2-nitropropane and 2-bromo-2-nitropropane. 2-Nitropropane (0.2 mole) was added to a solution of sodium hydroxide in 80 ml. of 50% alcohol. This alkaline solution was added dropwise to a refluxing solution of 2-bromo-2-nitropropane (0.2 mole) in alcohol over a period of 3.5 hours. The reaction-mixture was cooled and diluted with a small amount of water. The dinitro compound separated. After recrystallization from alcohol the material melted at 208–209°. The conversion to the dinitro compound was 29%.

C. From the sodium salt of 2-nitropropane and crude 2-iodo-2-nitropropane. One-tenth mole of 2-nitropropane was dissolved in 100 ml. of 80% alcohol containing one-tenth mole of sodium hydroxide. One-tenth mole of crude 2-iodo-2-nitropropane was added to the solution. The solution was refluxed for one hour. Upon cooling, 6.5 g. of the solid of melting point 208–209° separated. This corresponds to a 37% conversion. By adding the iodonitro compound dropwise to the refluxing solution of the sodium salt in alcohol, the conversion was increased to 43%.

D. From 2-nitropropane, 2-bromo-2-nitropropane and sodium bicarbonate. One-tenth mole of 2-nitropropane and one-tenth mole of 2-bromo-2-nitropropane in 50 ml. of 80% alcohol was refluxed for sixteen hours with a 20% excess of sodium bicarbonate. The dinitro compound was separated in the usual manner. A 14% conversion to the dinitro compound was obtained.

3,4-Dimethyl-3,4-dinitrohexane. A. From the sodium salt of 2-nitrobutane and 2-bromo-2-nitrobutane. The nitro compound was dissolved in 80% alcohol containing sodium hydroxide, 2-bromo-2-nitrobutane was added, and the solution was refluxed for seven hours. The product separated as white flakes. A 16% conversion was obtained. After recrystallization the solid was identified as 3,4-dimethyl-3,4-dinitrohexane by its melting point of 78° (11).

B. From the sodium salt of 2-nitrobutane and crude 2-iodo-2-nitrobutane. 2-Nitrobutane (0.2 mole) was dissolved in 100 ml. of 80% alcohol containing 0.2 mole of sodium hydroxide. Two-tenths mole of crude 2-iodo-2-nitrobutane was added slowly to the refluxing alkaline solution over a two-hour period. Fourteen grams of the dinitro compound was obtained. This corresponds to a 34% conversion.

2,3-Dimethyl-2,3-dinitropentane. 2-Nitrobutane (0.2 mole) was dissolved in 100 ml. of 80% alcohol containing 0.2 mole of sodium hydroxide. Two-tenths mole of 2-bromo-2-nitropropane was added to the alkaline solution, which was refluxed for three hours. Three grams of a white solid was obtained. This corresponds to approximately an 8% conversion, assuming that all of the solid was the expected product. The melting point of the material was 104–109°. Recrystallization from alcohol separated the material into two fractions, the smaller of which melted at 204–205° and was found to be impure 2,3-dimethyl-2,3-dinitrobutane. The larger

[1] Analyses in which only carbon was determined were carried out by the wet method.

fraction had the melting point 88–88.6°. A portion of the second fraction was sublimed. The melting point of the sublimed material was 88–88.4°.

Anal. Calc'd for $C_7H_{14}N_2O_4$: C, 44.17; H, 7.42.
Found: C, 43.28, 44.41; H, 7.50, 7.41.

1-Nitro-1-(2-nitroisopropyl)-cyclohexane. Nitrocyclohexane was obtained by the vapor-phase nitration of cyclohexane. One-tenth mole of nitrocyclohexane was dissolved in 75 ml. of 80% alcohol containing one-tenth mole of sodium hydroxide and refluxed with one-tenth mole of 2-bromo-2-nitropropane for three hours. Four grams of a white solid was obtained. This corresponds to a 19% conversion. The solid was dissolved in acetone and the solution was filtered. The solid was precipitated by the addition of water, filtered and recrystallized several times from alcohol. The melting point was 140–141°.

Anal. Calc'd for $C_9H_{16}N_2O_4$: C, 49.97. Found: C, 50.50, 50.60.

Attempted Syntheses. A. From the sodium salt of nitroethane and 1-bromo-1-nitroethane. This reaction was carried out in a manner similar to that used for preparing 2,3-dimethyl-2,3-dinitropentane. The only product isolated was a small amount of 2,3-dimethyl-2,3-dinitrobutane. It is believed that this compound is derived from the small amounts of 2-nitropropane present. It is very difficult to separate nitroethane completely from 2-nitropropane and the bromo derivatives also offer the same difficulty.

B. From the sodium salt of 2-nitropropane and 1-bromonitroethane. No product, other than a small amount of 2,3-dimethyl-2,3-dinitrobutane, was isolated.

C. From the sodium salt of nitroethane and 2-bromo-2-nitropropane. No product, other than a small amount of 2,3-dimethyl-2,3-dinitrobutane, was isolated.

D. From the sodium salt of 1-nitropropane and 1-bromo-1-nitropropane. No product was isolated from the reaction-mixture.

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The synthesis described in this paper is covered by U. S. Patent 2,181,531 of November 28, 1939, assigned to the Purdue Research Foundation.

SUMMARY

A method has been described for preparing tertiary dinitroparaffins by condensing a halogen derivative of a secondary nitroparaffin with the sodium salt of a secondary nitroparaffin.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

ORGANOALUMINUM COMPOUNDS

I. METHODS OF PREPARATION[1]

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INTRODUCTION

In view of the possible rôle played by organoaluminum compounds[2] in various hydrocarbon reactions catalyzed by aluminum halides,[3] the synthesis of a number of these compounds was undertaken. This paper is limited to the methods used for these syntheses. The physical properties[3a] and reactions[3a] of the compounds will be discussed in subsequent papers.

The number of theoretically possible aluminum compounds represented by the simple types AlA_3, AlA_2B and AlABC, and derivable from n substituents is $\frac{n(n+1)(n+2)}{6}$. This mounts rapidly from 220 with 10 substituents to 1540 with 20.[3b] The radicals from which our compounds are derived are as follows:

Alkyl[4]	Aryl	Alkoxy	Halide
Methyl	Phenyl	Methoxy	Chloride
Ethyl	*p*-Tolyl	Ethoxy	Bromide
n-Propyl			Iodide

[1] Presented in part at the 97th Meeting of the American Chemical Society at Baltimore, Md., in April 1939.

[2] This idea finds recent support in the work of Hall and Nash (*J. Inst. Petroleum Tech.*, **23**, 679 (1937); **24**, 471-95 (1938)) who report the formation of large quantities of ethylaluminum chlorides during the polymerization of ethylene with aluminum chloride in the presence of aluminum metal.

[3] See especially Ipatieff and Grosse, articles in *J. Am. Chem. Soc.* and *J. Org. Chem.* since 1935.

[3a] *Cf.*, Grosse and Mavity, Abstracts of Papers presented before the Organic Division at the 95th Meeting of the American Chemical Society at Dallas, Texas, in April 1938, p. M-14; Library Bulletin of Abstracts, Universal Oil Products Co., **13**, 69 (May 4, 1938).

[3b] These figures include in addition to the organoaluminum compounds, any combinations which can be made from inorganic substituents.

[4] In the text, "Die Chemie der metall-organischen Verbindungen" by E. Krause and one of the authors, the term "alphyl" is used to denote the aliphatic radicals, and "alkyl" in a broader sense to include *both* aliphatic and aromatic groups. Conforming to common usage in this country, the term alkyl as used in the present paper refers *only* to aliphatic radicals.

In addition to these simple types of aluminum compounds, there is the possibility of forming a large number of *alumoniides*, those saltlike compounds which may be considered as being derived from the combination of compounds of these simple types with alkyls and alkoxides of the more electropositive metals. Since the Werner coördination number of aluminum is four or more rarely six the formulas of the compounds are

$$M^{I}\,[AlR_4] \qquad \text{or} \qquad M^{I}_{3}\,[AlR_6]$$

M^{I} being a monovalent metal, and R an alkyl group. By substituting the organyl groups in the above formulas step by step with halogens or other acidic groups, a gradual transition into the purely inorganic tetra- or hexa-acido aluminates takes place. The compounds

$$Na\,[AlCl_4] \qquad \text{and} \qquad Na\,[AlF_6]$$

may serve as examples of the limiting cases. Alumoniides, such as $Li\,[Al(C_2H_5)_4]$ or $Na\,[Al(C_2H_5)_3OC_2H_5]$, will be discussed in a subsequent paper.[5]

HISTORICAL

The best approach in the preparation of organoaluminum compounds is through the old but practically unused reaction of alkyl and (to a more limited extent) aryl halides with metallic aluminum. The reaction results in the formation of an equimolecular mixture of two compounds as follows:

$$3RX + 2Al \rightarrow R_2AlX + RAlX_2 \qquad (I)$$

(For the sake of convenience these mixtures will be hereafter referred to as alkyl- or arylaluminum "*sesquihalides.*")

This reaction was recognized as early as 1859 by Hallwachs and Schafarik (1) who describe the *distillation* of a liquid of the general composition $(C_2H_5)_3Al_2I_3$ obtained by reacting ethyl iodide with aluminum. Cahours (2) at about the same time investigated this product as well as that formed from aluminum and methyl iodide. Several decades later Fürstenhoff (3) studied the reaction of ethyl bromide with aluminum. Spencer and Wallace (4) also reacted aluminum with a number of alkyl and aryl halides. Leone (5) and his co-workers in a series of publications have described the preparation and reactions of a number of solutions of alkyl and aryl aluminum sesquihalides. None of these workers ever isolated or identified their compounds. V. Grignard and R. Jenkins (6), in 1924, first separated

[5] *Cf.*, Grosse and Mavity, Abstracts of Papers presented before the Organic Division at the 96th Meeting of the American Chemical Society at Milwaukee, Wisconsin, in September 1938, p. M-11; Library Bulletin of Abstracts, Universal Oil Products Co., **13**, 164 (October 12, 1938).

such a mixture into its two constituents. They were able to do this in the case of ethylaluminum sesquiiodide by fractional vacuum distillation. The two iodides isolated by them, namely $(C_2H_5)_2AlI$ and $C_2H_5AlI_2$ were the only known organoaluminum halides when our work was begun. Subsequently Hall and Nash (7) described the isolation of diethylaluminum chloride; and Hnizda and Kraus (8) reported the separation of the two methylaluminum chlorides prepared from the reaction of methyl chloride with aluminum. The latter reaction was also investigated by Walker and Wilson (9). Just recently Gilman and Apperson (10) have described the reaction of ethyl chloride with aluminum and have presented evidence for the formation of phenylaluminum chlorides in reactions of organolead compounds with aluminum chloride.

DISCUSSION OF METHODS

1. Reaction of alkyl or aryl halides with aluminum

The successful application of this reaction (see equation I) to *methyl* and *ethyl chlorides, bromides* and *iodides*, n-*propyl iodide* and to the aromatic *iodides, phenyl* and p-*tolyl* is described in the experimental part of this paper.

Preliminary experiments have as yet been unsuccessful[6] with the other propyl halides, and with several butyl and amyl halides which were tried, due to a vigorous decomposition reaction involving the formation of saturated hydrocarbon containing the same number of carbon atoms as the alkyl halide, some aluminum halide and some gummy material. This decomposition reaction also occurred several times during attempted preparations of ethylaluminum chlorides; and likewise during the preparation of *n*-propylaluminum iodides. In the last reaction, the decomposition could be prevented by proper cooling and by keeping the metallic aluminum completely covered with liquid. Although the factors (of which some may be catalytic) influencing this side-reaction are still not entirely clear, the fact that it has been controlled in the reactions of ethyl chloride and *n*-propyl iodide shows that it is not always a structural property of the alkyl halide, and points to the possibility of eventually obtaining higher alkylaluminum halides by these methods.

Of the aryl halides (with the halogen in the nucleus), only the iodides have thus far been made to react.

The formation of the sesquihalides is a practically quantitative reaction. In the aliphatic series, these mixtures were mobile liquids, with the exception of the methyl chloride derivative, which was obtained as a mixture of liquid and crystals. Although all of the aliphatic mixtures were readily distillable at reduced pressures, satisfactory separation by a single vacuum

[6] Leone (loc. cit.) has described the reaction of isoamyl iodide with aluminum to form a colorless crystalline compound, and the reaction of octyl bromide with aluminum to give a viscous mass.

Podbielniak fractionation was effected only with the methyl derivatives. Disproportionation according to the reaction

$$2RAlX_2 \rightarrow R_2AlX + AlX_3 \qquad (II)$$

was pronounced during the distillation of the methylaluminum bromides, and was so complete with the methylaluminum iodides that the distillate was almost wholly dimethylaluminum iodide.[7] The alkylaluminum dihalides were further purified by crystallization from *n*-pentane, using a three bulb apparatus described by E. Krause and Polack (11). These are white crystalline solids.

2. Reactions of two or more aluminum compounds to produce another

Equation III is typical of a rather obvious general method of preparing dihalides. It was particularly useful with mixtures of sesquihalides which were difficult to separate.

$$R_2AlX + AlX_3 \rightarrow 2RAlX_2 \qquad (III)$$

Aluminum alkyls, employed in an analogous manner, converted sesquihalides to monohalides.

Similarly, combinations of aluminum alkyls or aryls[8] with aluminum halides produced either mono- or di-halides. The reaction to form the latter was used to advantage in the aryl series where the sesquichlorides and sesquibromides were not available (equation IV).

$$Al(C_6H_5)_3 + 2AlX_3 \rightarrow 3C_6H_5AlX_2 \qquad (IV)$$

Mono- and di-alkylaluminum alkoxides, new types of organoaluminum compounds, resulted from the reaction of aluminum alkyls with aluminum alkoxides.[9]

Extension of these methods to include the production of aluminum compounds with three different substituents although not yet tried, should be possible. A convenient application would consist in adding to an alkylaluminum sesquihalide some aluminum compound with the third substituent (equation V).

$$((CH_3)_2AlCl + CH_3AlCl_2) + Al(C_6H_5)_3 \rightarrow 3(CH_3)(C_6H_5)AlCl \qquad (V)$$

[7] Disproportionation went still further, in fact, during the removal of the first dimethylaluminum iodide fractions, giving a distillate containing 2 to 3% of aluminum trimethyl.

[8] Aluminum triphenyl was prepared in the conventional manner from mercury diphenyl and aluminum. *Cf.*, Hilpert and Gruttner, Ber. **45**, 2828 (1912).

[9] Prepared in the customary way by reacting activated aluminum with the alcohol.

3. Use of other metals in the preparation of organoaluminum compounds

A. Dialkylaluminum halides. The *direct* preparation of dialkylaluminum halides was accomplished by the reaction of alkyl halides with an *aluminum-magnesium alloy* (equation VI).

$$(2Al + Mg) + 4RX \rightarrow 2R_2AlX + MgX_2 \qquad (VI)$$

The alloy called for by this equation has the composition 69% Al, 31% Mg, and is closely approximated by the commercial alloy, magnalium (Dow Chemical Co., 70% Al, 30% Mg). The monohalides prepared from the commercial alloy were 90 to 95% pure by analysis, containing a small percentage of the dihalide, due to the slight excess of aluminum in the alloy.

The compounds were isolated either by *direct* distillation from the reaction mixture, or by preliminary filtration of the colorless aluminum compound from the white precipitate of magnesium halide, using an inert wash solvent.

Another method of preparing dialkylaluminum halides consists in treating the sesquihalide with an *alkali metal.* Metallic aluminum is precipitated and the monoalkylaluminum compound in the mixture is converted to the dialkyl according to the equation:

$$2RAlX_2 + 3Na \rightarrow R_2AlX + Al + 3NaX \qquad (VII)$$

Since the alkali metal will react further with the reaction product as shown below, the quantity used must be carefully controlled.

B. Aluminum trialkyls. By using larger amounts of alkali metal than those required for the conversion of the sesquihalides to the dialkylaluminum halides, the sesquihalides were converted to the aluminum trialkyls (see equations VIII and IX). The reaction can, of course, also be applied to the dialkylaluminum halides.

$$(R_2AlX + RAlX_2) + 3Na \rightarrow AlR_3 + 3NaX + Al \qquad (VIII)$$

$$3R_2AlX + 3Na \rightarrow 2AlR_3 + 3NaX + Al \qquad (IX)$$

These reactions make the simple aluminum alkyls readily obtainable from the corresponding alkyl halides. The classical method for preparing these compounds involved refluxing the rare and toxic mercury alkyls with aluminum, and the yields were none too good.

From crude methylaluminum sesquichloride, by refluxing, first over sodium ribbon, and finally over liquid sodium-potassium alloy, a 63% yield of aluminum trimethyl was obtained. The liquid alloy was found

useful since sodium *alone* became coated with a hard crust of aluminum, retarding the reaction.

Aluminum triethyl was prepared in yields of 40 to 50% from ethylaluminum sesquibromide and sodium, or 60% from diethylaluminum bromide and sodium. With the ethyl derivatives, an excess of the alkali metal is to be avoided[10] since it will react with the aluminum triethyl to form non-volatile tetraethylalumoniides:

$$3Na + 4(C_2H_5)_3Al \rightarrow 3NaAl(C_2H_5)_4 + Al \qquad (X)$$

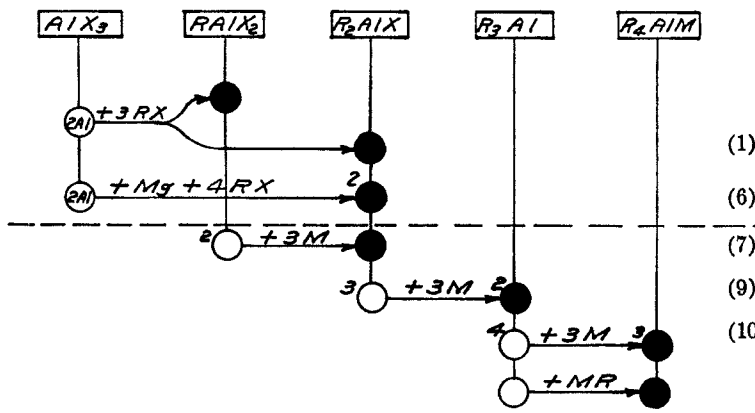

FIGURE I

R = Alkyl or Aryl
X = Inorganic Group (Halogen)
M = Alkali Metal

In one instance where this occurred, aluminum triethyl was obtained by adding more ethylaluminum sesquibromide to the non-volatile residue. A reaction such as the following evidently takes place:

$$(C_2H_5)_2AlBr + Na[Al(C_2H_5)_4] \rightarrow 2Al(C_2H_5)_3 + NaBr \qquad (XI)$$

This reaction is not reversible; aluminum triethyl can be recovered quantitatively from sodium bromide by distillation.

Resumé of methods

The methods used in alkylating the aluminum to successively higher degrees, up to the tetraalkyl stage, are illustrated in Figure I.

The different reactions between two alkylaluminum compounds, leading to an intermediate stage of alkylation, are summarized in Figure II.

[10] This precaution is apparently unnecessary with the methyl derivatives, since no appreciable reaction occurs between aluminum trimethyl and the alkali metals.

Each of the five vertical columns represents a different alkylation state (from 0 to 4 alkyl groups (R) per aluminum atom). Methods for producing a given type are indicated, the white circles representing the compounds entering into the reaction, the dark circles the reaction product;[11] where more than one molecule of a starting material enters into the reaction this number is indicated next to the circle. Examples illustrating the particular reactions are indicated in the last column by numbers corresponding to the equations of the text. Those reactions which have not yet been accomplished are indicated by a question mark.

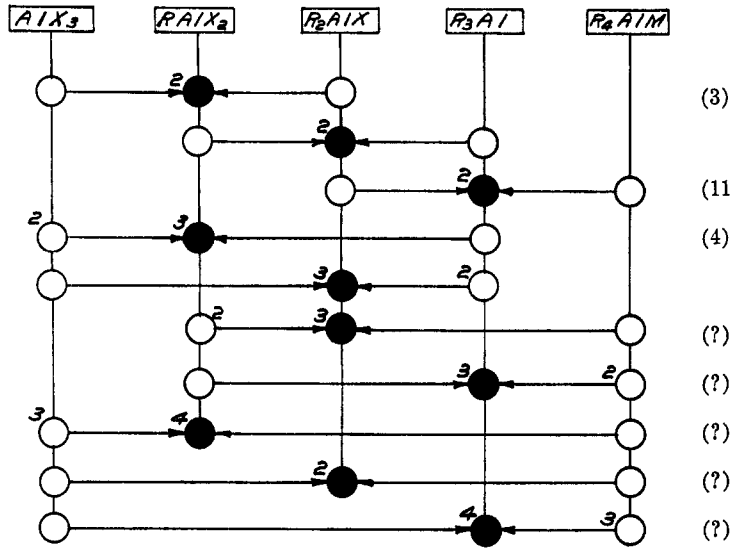

FIGURE II

R = Alkyl or Aryl
X = Inorganic Group (Halogen or Alkoxy)
M = Alkali Metal

EXPERIMENTAL

Since organoaluminum compounds are all decomposed by moisture and since the majority of them react with oxygen, many to the extent of spontaneous inflammability, it was necessary to carry out their preparation in an atmosphere of dry, inert gas, according to the general procedure developed by A. Stock and W. Schlenk.[12] For this purpose nitrogen, stored under pressure over alkaline sodium hydrosulfite ($Na_2S_2O_4$) was used.[12] It was dried with phosphorus pentoxide immediately before using.

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[11] In some cases the reaction product may not correspond to the simple formula given at the head of the table, but exists as an alumoniide (e.g., instead of $(C_2H_5)_2AlBr$ as $(C_2H_5)_2AlBr \cdot KBr$ or $K[Al(C_2H_5)_2Br_2]$.

[12] See E. Krause and A. V. Grosse, "Die Chemie der metall-organischen Verbindungen," Gebrüder Borntraeger, W 35 Koester Ufer 17, Berlin, 1937, pp. 802–811.

Analyses.—The aliphatic compounds were analyzed by measuring the volume of gas evolved by hydrolysis of a weighed sample. This is a quantitative reaction; and can also be used for binary mixtures (e.g. $R_2AlX + RAlX_2$; $R_3Al + R_2AlX$; or $RAlX_2 + AlX_3$) to determine the percentage of each constituent present.[13] The gas was investigated in several experiments and found to consist only of the pure paraffin hydrocarbon having the same number of carbon atoms as the original alkyl group. The aromatic and several aliphatic compounds were analyzed gravimetrically for aluminum and halogen. The sample was dissolved in ether, and the ether solution decomposed with water containing sufficient nitric acid to prevent precipitation of the aluminum. Aluminum was determined as the 8-hydroxyquinolate.

I. Reaction of alkyl or aryl halides with aluminum

This reaction is conveniently carried out in glass apparatus by adding the alkyl or aryl halide dropwise or in small portions to aluminum, preferably in the form of turnings. The mixture is mechanically stirred. It is important that the reaction be properly catalyzed at the start, either with iodine, an aluminum halide, a previous preparation of an organoaluminum halide or, for the aryl iodides, with a small amount of ether.[14] Since the reactions of the aliphatic halides are decidedly exothermic, cooling is advisable. The halides which are gases at ordinary temperatures (methyl chloride, methyl bromide and ethyl chloride) are best reacted in autoclaves, either of the rotating or stirrer type.

1. Ethyl chloride and aluminum.—A mixture of 38 g. of aluminum turnings and 38 g. of granular aluminum was placed in a stirrer-autoclave of 1 liter capacity. The autoclave was closed, evacuated and 1.4 g. of ethylaluminum bromide was added as catalyst. The autoclave was cooled in ice water and ethyl chloride pressed in from a charging cylinder, in several portions, until 149 g. had been added. After each addition the temperature of the mixture rose sharply, necessitating cooling, and then dropped as the ethyl chloride all reacted. After the reaction was complete, a small amount of gas was released from the autoclave. This amounted to 1.2 liters and contained 93% ethane, probably due to traces of water in the apparatus and reagents.

The liquid product decanted from the bomb amounted to 181 g., unreacted aluminum, 33 g. The molar ratio of ethyl chloride to aluminum reacting amounted to about 1.45, in line with equation I.

The liquid was distilled in a vacuum through a Podbielniak column. The composition[15] of three of the fractions as determined by gas evolution (reaction with water) is included in Table I. It will be noted that ethylaluminum dichloride concentrates in the lower boiling fractions.

2. Methyl chloride and aluminum.—This reaction was usually carried out in an 800 cc. Ipatieff rotating autoclave (12) equipped with a simple glass liner. The induction period was usually longer than with the other halides, sometimes amounting to several days.

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[13] In all such calculations, the true molecular volumes of the hydrocarbon gases were used. These volumes were calculated from the selected values of Blanchard and Pickering (Bureau of Standards Scientific Papers, No. *529*, p. 175 (1926)) and are as follows at N.T.P.: CH_4, 22.38 l.; C_2H_6, 22.17 l. and C_3H_8, 21.83 l.

[14] In general, the use of ether was avoided in order to preclude the possibility of forming etherates.

[15] Each fraction is considered as a binary mixture of mono- and di-ethylaluminum chloride.

Satisfactory separation of the mono- and di-methylaluminum chlorides was effected by fractionation in a Podbielniak column.

a) Dimethylaluminum chloride.—A fraction distilling chiefly at 70–76° (100 mm.) was redistilled. The main fraction was a water-white liquid boiling at 83–84° (200 mm.). *Anal.* Sample, 0.1662 g. Gas @ N.T.P.: Found, 77.8 cc.; Calc'd for $(CH_3)_2AlCl$, 80.4 cc.

b) Methylaluminum dichloride.—The fraction distilling at 97–101° (100 mm.) was a white crystalline solid melting at 72.7°.

Anal. Calc'd for CH_3AlCl_2: Al, 23.88; Cl, 62.80.
Found: Al, 23.81; Cl, 62.27.

Gas evolution: Sample, 0.6359 g. Gas @ N.T.P.: Found 127 cc. Calc'd for CH_3AlCl_2, 126 cc.

This compound is quite soluble in *n*-pentane and can be purified by crystallization from this solvent.

3. Methyl bromide and aluminum.—This reaction proceeded vigorously in a stirrer-autoclave. Fractionation in a Podbielniak column resulted in fair separation.

TABLE I

Charge 176.5 g.

FRACTION	BOILING RANGE AT 50 MM.	GRAMS	WT. % [a] $C_2H_5AlCl_2$	REMARKS
In dry ice trap		2.9		Water-white liquid
1	80–120°	7.4		Some crystals at room temp.
2	120°	30.2	65.7	Water-white liquid
3	120–122°	100.5	62.4	Water-white liquid
4	122°	18.4		Water-white liquid
5	122°	4.6	44.8	Water-white liquid
Residue		12.4		Dark, viscous liquid
Losses		0.1		

[a] An equimolecular mixture of $C_2H_5AlCl_2$ and $(C_2H_5)_2AlCl$ contains 51.3% by weight of the former.

That some disproportionation occurred during distillation was evident from the fact that the residue contained an excess of aluminum bromide.

a) Dimethylaluminum bromide.—This compound was obtained as a water-white liquid distilling at 74–77° (50 mm.). It crystallized to beautiful white needles at dry ice temperature. *Anal.* Sample, 0.9408 g. Gas @ N.T.P. 300 cc. Calc'd for $(CH_3)_2AlBr$, 307 cc.

A portion of this material further purified by distillation in a high vacuum apparatus had the following analysis: Calc'd for $(CH_3)_2AlBr$: Al, 19.69; Br, 58.36. Found: Al, 19.46; Br, 58.68.

b) Methylaluminum dibromide.—The fraction which distilled at 124–139° (50 mm.) was practically pure methylaluminum dibromide. The purest sample was obtained by crystallization from pentane, in the form of large transparent plates melting at 79°.

Anal. Calc'd for CH_3AlBr_2: Al, 13.36; Br, 79.19.
Found: Al, 13.34; Br, 79.33.

Gas evolution: Sample, 1.4220 g. Gas, @ N.T.P. Found, 158 cc. Calc'd for CH_3AlBr_2, 158 cc.

4. n-*Propyl iodide and aluminum.*—Aluminum turnings (25.4 g.) were placed in a Pyrex flask and covered with a weighed quantity of *n*-propyl iodide. Reaction was started by heating a small portion of the mixture in a test tube with iodine and adding this to the flask. The mixture was mechanically stirred and kept at 40 to 50° by cooling. *n*-Propyl iodide was added until a total of 229 g. was introduced. After 3 hours the temperature dropped. The mixture was finally stirred at 100° for 1 hour.

The reaction products consisted of gas, 1.4 g., which proved to be propane; decanted liquid 237 g. and unreacted aluminum 3.3 g.

Fractionation of the decanted liquid in a Podbielniak column under reduced pressure gave partial separation of the two constituents (see Table II). The last fraction contained some aluminum iodide due to disproportionation.

a) n-*Propylaluminum diiodide.*—A sample (32.2 g.) of fraction 5 (Table II), which was shown by analysis to be about 97.5% pure, was sealed in a three bulb apparatus (11) with *n*-pentane (66 cc.) and crystallized several times at −78°. Pure

TABLE II

PODBIELNIAK DISTILLATION OF *n*-PROPYL ALUMINUM IODIDES

Charge 237.1 g.

FRACTION	BOILING RANGE, °C.	PRESSURE, MM.	GRAMS	COMPOSITION % BY WT.[a]
In dry ice traps			7.3	Hydrocarbons + propyl iodide
1	80–128	1.0–0.8	16.9	Pr_2AlI, 77.4; $PrAlI_2$, 22.6
2	128	0.8–0.7	37.5	" 62.9; " 37.1
3	128–127	0.7–0.5	56.6	
4	127–142	0.5–0.7	36.5	
5[b]	142–143	0.7–0.5	59.3	Pr_2AlI, 2.5; $PrAlI_2$, 97.5
6	143–139	0.5–0.4	5.1	$PrAlI_2$, 73.7; AlI_3, 26.3
Residue			5.3	
Losses			12.5	

[a] Calculated from gas evolution data.

[b] Sample, 2.3410 g.; Gas @ N.T.P., Found, 164.5 cc.

white crystalline masses of *n*-propylaluminum diiodide were deposited. The purest fraction (25.8 g.) melted at 3–4°.

5. Methyl iodide and aluminum.—This reaction proceeded smoothly at the reflux temperature of methyl iodide. Distillation at 50 mm. resulted in disproportionation of the product, producing a distillate which was chiefly dimethylaluminum iodide, a residue of aluminum iodide and a relatively small intermediate fraction.

a) Dimethylaluminum iodide.—The fraction distilling at 109–110.5° (50 mm.) was essentially dimethylaluminum iodide. Gas evolution in excess of the theoretical indicates further disproportionation to aluminum trimethyl to the extent of 2 or 3%. *Anal.* (1) Sample, 1.0128 g. Gas @ N.T.P.: Calc'd for $(CH_3)_2AlI$, 247 cc. Found, 269 cc. (2) Sample, 0.5449 g. Gas @ N.T.P.: Calc'd 132 cc. Found, 141.5 cc.

6. Other halides and aluminum.—*Ethyl bromide* and *ethyl iodide* reacted readily with aluminum. Separation of the mono- from the dialkyl compounds by a single Podbielniak distillation was not satisfactory; these constituents were more readily obtained in pure form by other methods (see below).

The reactions of *phenyl iodide* and p-*tolyl iodide* with aluminum are described

below in connection with the preparation of the corresponding arylaluminum diiodides.

II. Interaction of two aluminum compounds to produce a third

1. Ethylaluminum dichloride.—To an ethylaluminum sesquichloride distillate (57.60 g.), which was equivalent by analysis to 21.17 g. of diethylaluminum chloride and 36.43 g. of ethylaluminum dichloride, was added 22.8 g. of anhydrous aluminum chloride[16, 17] (97.5% of the theoretical). The materials were heated to a temperature of 180–190° and became a clear colorless liquid. On cooling to room temperature this liquid crystallized, forming beautiful, large, thick transparent plates (4 and 6 sided). The product was distilled from an ordinary flask into the following fractions:

Fraction No.	B.p. at 50 mm. °C.	Grams
1	113 -114.5	7.41
2	114.5–115.5	57.16
3	115.5–118	12.99
Residue		3.21

Fraction 2 was analyzed by measuring the gas evolved on decomposing a weighed sample with water. Sample, 1.381 g. Gas @ N.T.P.: Found, 243 cc.; Calc'd for $C_2H_5AlCl_2$, 241.1 cc.

This fraction was further purified by crystallizing a sample (9.6 g.) from dry *n*-pentane (25 cc.) in a three bulb apparatus. The white crystals thus obtained melted at 32°. Calc'd for $C_2H_5AlCl_2$: Al, 21.25; Cl, 55.86. Found Al, 20.88; Cl, 55.81.

2. Diethylaluminum chloride.—To an ethylaluminum sesquichloride which was equivalent by analysis to 17.3 g. of diethylaluminum chloride and 26.0 g. of ethylaluminum dichloride, was added 23.09 g. of aluminum triethyl. Appreciable warming occurred. The product was fractionated in a Podbielniak column. Over 51 g. (77%) distilled at 125–126° (50 mm.). *Anal.* Sample, 0.5482 g. Gas @ N.T.P.: Calc'd for $(C_2H_5)_2AlCl$, 201.6 cc. Found, 200 cc.

3. Ethylaluminum dibromide.—This preparation from ethylaluminum sesquibromide and aluminum bromide[17] was entirely analogous to that of ethylaluminum dichloride. The fraction distilling at 120–122.5° (10 mm.) crystallized from *n*-pentane in clear, colorless, interlocking plates melting at 23.5–24.4°. *Anal.* Sample 1.2509 g. Gas @ N.T.P.: Calc'd for $C_2H_5AlBr_2$, 128.5. Found, 124 cc.

4. Methylaluminum diiodide.—Dimethylaluminum iodide (18.4 g.) and aluminum iodide (38.5 g.) were melted together by heating to a temperature of 170°. The product was cooled and distilled from an ordinary flask at 0.2 mm. (vapor temperature 85 to 100°). Disproportionation was bad even under these conditions and 15 g. of residue, essentially aluminum iodide was obtained. The middle cuts (27.3 g.), crystallized three times from *n*-pentane (60 cc.), gave pure white, diamond-shaped crystals of methylaluminum diiodide (11.9 g.). The compound melted chiefly in the range 68–71° softening at 63°. The lack of a sharp melting point is probably due to disproportionation at this temperature. *Anal.* Sample 1.7377 g. Gas @ N.T.P.: Calc'd for CH_3AlI_2, 131 cc. Found, 129 cc.

5. Diethylaluminum iodide.—This compound was prepared by vacuum distillation of a mixture of aluminum triethyl (10.0 g.) and aluminum iodide (17.5 g.). *Anal.* Sample, 1.8638 g. Gas @ N.T.P.: Calc'd for $(C_2H_5)_2AlI$, 389.8. Found, 385 cc.

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[16] Purified by melting under pressure with aluminum metal.

[17] An excess of the aluminum trihalide is to be avoided since it tends to crystallize from pentane along with the dialkylaluminum halide.

6. Ethylaluminum diiodide.—During the vacuum fractionation of ethylaluminum sesquiiodide some disproportionation occurred and the higher fractions contained as much as 10% aluminum iodide. By recombining them with selected intermediate fractions a mixture containing by analysis some 97 to 98% ethylaluminum diiodide and 2 to 3% diethylaluminum iodide was obtained. Fifty-one grams of this mixture was crystallized several times from *n*-pentane. The purest fraction (30.5 g.) was obtained in the form of beautiful large diamond-shaped plates melting at 39.0 to 40.0°. *Anal.* Sample, 1.2902 g. Gas @ N.T.P.: Calc'd for $C_2H_5AlI_2$, 92.3. Found, 91.5 cc.

7. Phenylaluminum dichloride.—A mixture of aluminum triphenyl (6.63 g., 25.7 millimoles) and anhydrous aluminum chloride (6.92 g., 51.8 millimoles) was heated in a distilling flask at 200° for 20 minutes. The completely molten mixture was then cooled and distilled at reduced pressure into a series of bulbs, sealed directly to the side arm of the distilling flask (see Table III).

Fraction 2 distilled as a water-white liquid which crystallized slowly on standing. Crystallized from dry benzene (15 cc.) in a three bulb apparatus (11), it yielded 4.3 g. of white thick needles or prisms melting at 93–95.5°.

TABLE III

DISTILLATION OF PHENYL ALUMINUM DICHLORIDE

FRACTION	B.P. °C.	PRESS, MM.	GRAMS	REMARKS
In dry ice trap			0.24	Benzene, $AlCl_3$
1	103–177	7–15	2.79	White, crystalline[a]
2	177–208	15– 0.5	7.87	Crystallized slowly
Residue			2.53	Some white crystals

[a] Analytical data indicate that this fraction is chiefly aluminum chloride in all probability mixed with some phenylaluminum dichloride. *Anal.* Al, 18.75, 18.70; Cl, 68.27, 68.14. Atomic Ratio: Cl:Al 2.77.

Anal. Calc'd for $C_6H_5AlCl_2$: Al, 15.41; Cl, 40.53.
Found: Al, 14.49; Cl, 39.68.
Atomic Ratio: Cl: Al, 2.08.

A sample sublimed at a pressure of 2×10^{-3} mm. gave pure white needles melting at 94–95°.

8. Phenylaluminum dibromide.—This preparation was carried out in the manner already described for phenylaluminum dichloride, from aluminum triphenyl (4.12 g., 16.0 millimoles) and aluminum bromide (13.96 g., 52.5 millimoles). The distillate, after crystallization from benzene, still contained aluminum bromide, as shown by analysis.

Crystal fraction 1 melted from 73.5 to 78°, fraction 2 from 73.5 to 87° (mostly liquid at 80°). *Anal.* Calc'd for $C_6H_5AlBr_2$: Al, 10.22; Br, 60.56. Found: Fraction 1: Al, 10.15, 10.11; Br, 69.89, 70.05; Atomic Ratio: Br: Al, 2.33, 2.34. Fraction 2: Al, 10.07; Br, 66.99; Atomic Ratio: Br: Al, 2.25.

9. Phenylaluminum diiodide.—Phenylaluminum sesquiiodide was prepared from a mixture of 16.8 g. of aluminum turnings and 172.0 g. of phenyl iodide (5). After starting the reaction by heating a small portion of the materials in a test tube and adding these to the reaction flask, the bulk of the reactants was introduced in several portions. The mixture was kept at a temperature of 100° and was mechanically stirred during 44 hours. Separation of the reaction product from unreacted aluminum was accomplished by diluting with dry benzene (40 cc.) and filtering while hot

through a coarse sintered-glass filter. Benzene and unreacted phenyl iodide were separated by heating to 100°[18] and reducing the pressure to 2 mm. The products recovered consisted of unreacted aluminum, 1.8 g.; unreacted phenyl iodide, 6.7 g.; and phenylaluminum sesquiiodide 178.6 g. (90–100 cc.). The phenylaluminum sesquiiodide was a viscous liquid which slowly crystallized at room temperature, becoming completely solid. It was sparingly soluble in hot heptane, crystallizing from this solvent in white needles.

Phenylaluminum diiodide was prepared by melting together phenylaluminum sesquiiodide (49.9 g., 75 millimoles) and aluminum iodide (30.5 g., 75 millimoles). Heated at 100° for ½ hour, the mixture became completely liquid. It was dissolved in benzene (75 cc.) and the solution filtered through an alundum cup to separate suspended material. The clear, pale brown filtrate was concentrated; on standing over night it deposited lustrous, hard, white prisms. The mother liquor was decanted and the prisms were again crystallized from benzene in a three bulb apparatus. Two fractions were obtained consisting of 32.5 g., melting at 106–101° (fraction 1); and 3.2 g., melting at 100–110° (fraction 2).

Anal. (fraction 1). Calc'd for $C_6H_5AlI_2$: Al, 7.54; I, 70.92. Found: Al, 7.34; I, 71.37.

This compound crystallized very slowly and could often be kept at room temperature for 24 hours or longer as a very viscous, colorless liquid. It is quite soluble in benzene and carbon disulfide, sparingly so in pentane and heptane. Attempted distillation always resulted in decomposition even at low pressures.

10. p-*Tolylaluminum diiodide.*—p-*Tolylaluminum sesquiiodide* was prepared from aluminum and *p*-tolyl iodide. It reacted with aluminum iodide to give p-*tolylaluminum diiodide.* The procedure was similar to that described for the preparation of phenylaluminum diiodide, toluene being substituted for benzene as the solvent for crystallization.

The crystallized product melted chiefly from 140 to 145° but traces of liquid began to appear as low as 111°.

Anal. Calc'd for $C_7H_7AlI_2$: Al, 7.25; I, 68.25.
Found: Al, 6.79; I, 69.35.

11. Dimethylaluminum methoxide.—Aluminum methoxide[19] (5.80 g., 48 millimoles) was placed in a distilling flask and aluminum trimethyl (6.95 g., 96 millimoles) added portionwise. Considerable heat was evolved during the addition. The mixture was heated for 20 minutes at 100° and finally the temperature was raised to 135°. The mixture became completely liquid and remained liquid at room temperature. It distilled chiefly at 119–122° at 50 mm., leaving a residue of 1.0 g. The distillate was fractionated further in a 20 inch wire spiral column to give the following fractions:

Charge 11.5 g.

Fraction	Boiling Range	Pressure	Grams	Remarks
1	73–87	10	1.8	Liq. at room temp.
2	87–88	10	7.3	M.p. 30–33°
3		3	0.8	M.p. 30–33°
Residue			0.9	Turbid liq. at room temp.

[18] Temperatures above 100° were avoided since phenylaluminum iodides decompose at elevated temperatures.

[19] Prepared by reacting activated aluminum with methanol and distilling off the excess methanol. *Cf.*, Adkins, *J. Am. Chem. Soc.*, **44**, 2178 (1922).

Fractions 2 and 3 crystallized at room temperature to a beautiful translucent mass.

Anal. (fraction 2) 0.4749 g. gave 254 cc. of gas at N.T.P. Calc'd for $(CH_3)_2AlOCH_3$, 242 cc.

12. Methylaluminum dimethoxide.—Aluminum trimethyl (6.51 g., 90 millimoles) was added gradually to aluminum trimethoxide[19] (21.7 g., 180 millimoles). Considerable heat was evolved during the addition. In an attempt to distil, the product was heated as high as 280° at a pressure of 2 mm. but only 1 cc. of distillate was obtained. The residue was a bulky white solid, resembling aluminum trimethoxide in non-volatility and infusibility. In contrast to the more volatile organoaluminum compounds, decomposition with water was vigorous but not violent.

Anal. 1.38 g. gave 288 cc. of gas at N.T.P. Calc'd for $CH_3Al(OCH_3)_2$, 297 cc.

13. Diethylaluminum ethoxide.—A mixture of aluminum ethoxide[20] (3.34 g., 20.6 millimoles) and aluminum triethyl (4.51 g., 39.5 millimoles) was heated to 170° to form a clear liquid. Fractionated in a 20-inch column (wire spiral type), 80% distilled at 108–109° (10 mm.). The main fraction (4.2 g.) crystallized when chilled in ice, to a translucent mass, distinguishable only by careful observation from a slightly turbid liquid. It melted at 2.5 to 4.5°. *Anal.* Sample, 0.5221 g. Gas @ N.T.P. Calc'd for $(C_2H_5)_2AlOC_2H_5$: 177.9 cc. Found: 181 cc. After further fractionation in a high vacuum apparatus: Calc'd for $(C_2H_5)_2AlOC_2H_5$: Al, 20.72. Found: Al, 20.12.

14. Ethylaluminum diethoxide.—Ethylaluminum diethoxide prepared in a similar manner from aluminum ethoxide[20] (15.24 g., 94 millimoles) and aluminum triethyl (5.62 g., 49 millimoles) distilled from an ordinary distilling flask at a practically constant temperature of 137° (0.1 mm.). The fractions, originally clear, colorless liquids, slowly became turbid (after several hours). On standing for several days they became more and more viscous, finally changing to a jelly-like solid. This material had no definite melting point but changed to a perfectly clear liquid on warming. *Anal.* Sample 0.8944 g. Gas @ N.T.P.: Calc'd for $C_2H_5Al(OC_2H_5)_2$, 135.7 cc.: Found: 134 cc.

III. Use of other metals in the preparation of organoaluminum compounds

1. Aluminum triethyl.—Diethylaluminum bromide was prepared in a one liter 3-necked flask equipped with a reflux condenser, a dropping funnel, an efficient mechanical stirrer, and an inlet for dry nitrogen. Magnalium turnings (107 g.; 30% Mg, 70% Al) were placed in the flask and a small quantity of ethyl bromide was added. The reaction was catalyzed by iodine, and started after about 20 minutes. The flask was surrounded by an oil bath to dissipate the heat and ethyl bromide was added over a period of 2½ hours until a total of 496 g. had been added. The temperature was kept at 120 to 140° for 1 hour to insure complete reaction. The reaction product was then distilled from the precipitated magnesium bromide *in vacuo*. The water-white distillate boiled chiefly at 75° at 2 mm. The yield was 376 g. (91%).

Anal. 0.7091 g. gave 188 cc. of gas @ N.T.P. Calculated composition: $(C_2H_5)_2AlBr$, 97.8%; $C_2H_5AlBr_2$, 2.2%.

Sodium ribbon (50.3 g.)[21] was pressed into a three-necked round-bottom flask in

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[20] Prepared by Mr. R. C. Wackher from activated aluminum and ethanol. *Cf.*, Adkins, loc. cit.

[21] This represents an excess of 5%.

a nitrogen atmosphere, and diethylaluminum bromide (150 g.) was added. The temperature was raised to 105° and after 15 minutes a powerful reaction started, causing the mixture to reflux and necessitating cooling. After the first reaction subsided, additional diethylaluminum bromide (186 g.) was added. The mixture was heated for 1 hour at 110° and finally for 16 hours at 200–210.[22] On cooling, most of the liquid was soaked up by the gray and white porous mass. The volatile product was distilled off *in vacuo*. Most of the material distilled before the bath temperature reached 220° at a pressure of 2 mm. The yield of distillate was 107.4 g., residue 368.2 g.

Anal. Gas from 0.2619 g. of sample, 143.5 cc. @ N.T.P. (94% of theor. for $Al(C_2H_5)_3$). Calculated composition, $Al(C_2H_5)_3$, 89.0%; $(C_2H_5)_2AlBr$, 11.0%. A qualitative test confirmed the presence of halogen.

To purify the product, 106.7 g. was again heated with sodium (2.1 g.), this time under efficient mechanical stirring, for 1 hour at 110–120° and finally for ½ hour at 155–160°. The product was distilled *in vacuo*. Yield, 93.71 g. Residue 14.60 g.

Anal. Gas from 0.2702 g., 155 cc. @ N.T.P. (98.5% of theor. for $Al(C_2H_5)_3$).

Final purification consisted in vacuum Podbielniak distillation. The aluminum triethyl distilled at 128–130° at 50 mm. and gave 99% of the theoretical quantity of gas on hydrolysis.

2. Diethylaluminum bromide.—In an early attempt to prepare aluminum triethyl by the reaction of sodium with ethylaluminum sesquibromide incomplete reaction occurred in the first treatment, and the distillate proved to be pure diethylaluminum bromide. This was obtained as a colorless liquid boiling at 147–148° (50 mm.). *Anal.* Sample 1.2501 g. Gas @ N.T.P.: Calc'd for $(C_2H_5)_2AlBr$, 335.9. Found, 340 cc.

3. Aluminum trimethyl.—Methylaluminum sesquichloride (216 g., crude product) was treated several times with an excess of sodium ribbon (146 g. in all). Each treatment consisted in refluxing, followed by removal of the liquid from the solid mass by vacuum distillation. Formation of a crust on the sodium apparently prevented the reaction from going to completion. This difficulty was overcome by two final treatments with liquid sodium-potassium alloy[23] (35 g.; 23% potassium) including efficient agitation. The yield of aluminum trimethyl was 48 g. or 63% of the theoretical. It distilled at 125–126° (755 mm.) and crystallized readily when chilled in ice water.

*4. Di-*n*-propylaluminum iodide.*—*n*-Propyl iodide (213 g.) was added portionwise during 3 hours to magnalium turnings (24.1 g.; 30% Mg, 70% Al) with mechanical stirring. The reaction was catalyzed by heating a small portion of the reactants in a test tube and adding this to the main mixture. After heating for 1½ hours at 100°, the colorless supernatant liquid was decanted from the precipitate of white magnesium iodide and the latter washed with pentane. The liquid was fractionated in a Podbielniak column at reduced pressure. Yield 99 g. or 66% of the theoretical.

The main fraction distilled at 153–156°, (4.2–4.7 mm.). *Anal.* Samples 0.8608 g.; 1.049 g. Gas @ N.T.P. Calc'd for $(C_3H_7)_2AlI$: 156.6 cc.; 190.8 cc. Found: 153 cc.; 181 cc.

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[22] Heating for such a long period at this temperature is probably unnecessary, and if so, should be avoided since it causes slow decomposition.

[23] If the material treated in this step still contains considerable halogen, the accumulation of a large excess of unreacted alloy at any time is to be avoided, since the reaction may become quite vigorous.

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The authors wish to express their appreciation to Mr. J. J. Ottens who assisted in the preparation of these compounds.

SUMMARY

1. Organoaluminum compounds have been prepared by the reaction of aluminum metal with a series of alkyl halides. These halides are methyl and ethyl chlorides, bromides and iodides, and *n*-propyl iodide.

2. By diverse methods each of the dialkylaluminum halides and alkylaluminum dihalides corresponding to the above alkyl halides has been obtained in pure form.

3. The preparation of phenylaluminum dichloride, dibromide, diiodide and *p*-tolylaluminum diiodide is described.

4. Alkylaluminum alkoxides have been prepared by the reaction of aluminum alkyls with aluminum alkoxides.

5. Dialkylaluminum halides have been prepared directly by the reaction of alkyl halides with an aluminum-magnesium alloy.

6. A new method for preparing aluminum alkyls involving the reaction of alkylaluminum halides with alkali metals is described.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORIES OF THE UNIVERSITY OF MARYLAND AND NORTHWESTERN UNIVERSITY]

AN IMPROVED APPARATUS FOR THE LABORATORY PREPARATION OF KETENE AND BUTADIENE

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Ketene is now commonly prepared by the pyrolysis of acetone. This is accomplished by passing acetone vapors either through a hot tube (1) or over an electrically heated metal filament (2). An apparatus of the latter type which gives very satisfactory results is the improved lamp described in this paper. It serves efficiently also in the preparation of 1,3-butadiene from cyclohexene (3, 2c).

The lamp contains a shorter heating element than is used in the devices previously described. It uses an inexpensive Chromel A filament, which is more efficient than platinum or tungsten. Less carbonization occurs when Chromel A is used. Use of the smaller filament results in a shorter contact time, and a higher percentage yield may be obtained (in the case of ketene).

DESCRIPTION OF APPARATUS

The apparatus consists essentially of a Chromel filament (O in fig. II), suspended from the top portion of ground glass joint H so that the filament may be removed from chamber E whenever desired.

Filament O is prepared from 175 cm. B. and S. gauge 24 Chromel A wire, an alloy of 80% nickel and 20% chromium, by wrapping the wire tightly in a spiral around a rod 3 mm. in diameter, and stretching the coil thus formed to a length of 70 cm. The filament is supported on platinum hooks, N, 15 mm. in length and sealed into the Pyrex glass rod which supports them. The three hooks at the bottom of the rod are spaced 120° apart. Two platinum hooks support the filament at a distance of 11 cm. above the end. The ends of the filament O are connected to tungsten leads by means of the nickel sleeves P, which are 10 mm. in length, 3.5 mm. internal diameter and are equipped with two set screws. The tungsten leads are of B. and S. gauge 24 wire and are sealed into the glass at the points Q, and above these junctions are soldered to B. and S. gauge 24 copper wire (S) at the points R. The copper leads S are insulated by pieces of 6 mm. glass tubing T, which are held by the cork stopper W.

The copper wire leads are connected to a source of 110 volt A.C., preferably through a variable resistance, such as a Variac transformer. A satisfactory fixed

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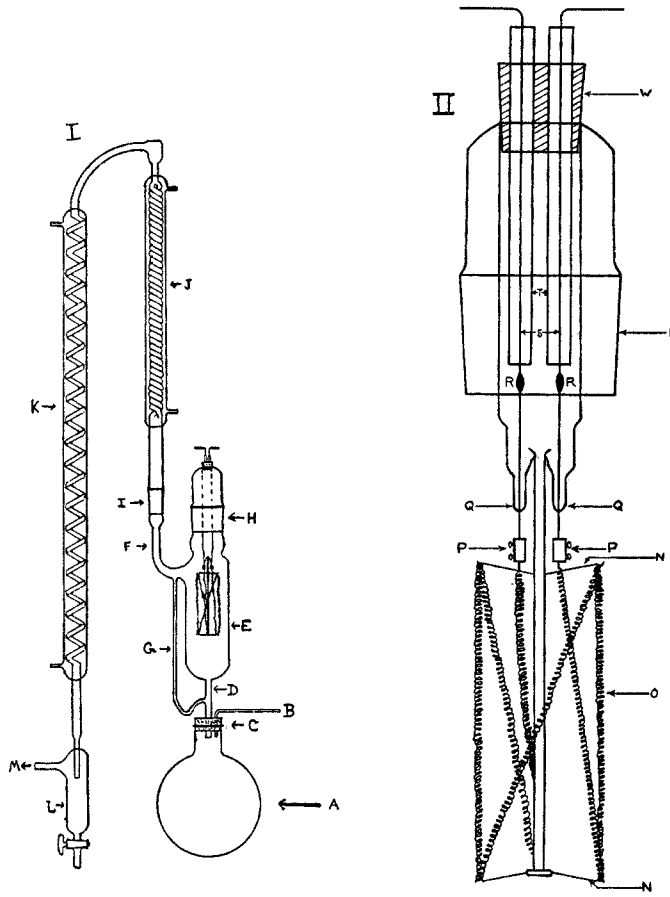
resistance may be made of Chromel wire wound around a porcelain form. The proper length of resistance wire necessary to keep the filament heated at a dull red must be determined by experiment.

All the glass used in the apparatus is Pyrex. The ground glass joint H is a 55/50 standard taper. Chamber E is constructed from a 25 cm. length of glass tubing of 70 mm. internal diameter. Connecting tube D is 12 mm. tubing, side arm F is 15 mm. tubing and reflux return tube G is 6 mm. tubing. Joint I is a 19/38 standard taper.



Condensers J and K may be of any efficient type. In the apparatus illustrated J is a double spiral condenser 50 cm. long, and K is a single spiral 90 cm. in length. The two are connected at the tops by a glass seal. The liquid trap L sealed to the lower end of condenser K is constructed of 35 mm. tubing and is 125 mm. long, with a stopcock for removal of liquid from the trap. The ketene or butadiene is conducted away through the tube M, of 8 mm. diameter.

OPERATION

The reagent (acetone or cyclohexene) is placed in A, a 2-liter, round-bottomed flask which is attached to the lamp by means of a rubber stopper C. Through this stopper extends a piece of 6 mm. glass tubing B which may be used to introduce more reagent when needed. It must be closed when the apparatus is being operated. The introduction into A of sufficient glass wool to extend a few cm. above the surface of the liquid serves to prevent bumping.

After M is connected to the proper apparatus, the stopcock on L is closed and the liquid in A is heated until it refluxes gently from condenser J. Five minutes refluxing should be allowed to drive the air from chamber E. The current may then be passed through filament O, which should be heated to a dull red glow (temperature 700–750°).

After the starting operations the apparatus needs little attention. Occasionally condensed liquid must be removed from trap L, the amount collecting there being dependent upon the temperature of the water in condensers J and K. If J and K allow too much acetone or cyclohexene to pass, a trap surrounded by ice water may be placed between M and the reaction flask.

At the end of a run the following operations must be carried out rapidly in this order: (1) the source of heat is removed from flask A, (2) the filament current is turned off, and (3) the stopcock on L is opened.

CALIBRATION

The amount of ketene produced per hour may be determined either by weighing the acetanilide produced on passing the effluent gas stream through excess aniline for a measured period of time, or by passing the gas stream through standard alkali with subsequent titration of the unused alkali. By the second method the apparatus described was found to deliver 0.45 mole of ketene per hour. In a continuous run of ten hours 4.53 moles of ketene was produced with a net consumption of but 350 ml. of liquid from flask A. If the residual liquid and condensate were pure acetone, this would represent a 95% yield, but the figure is too high, for although the liquid is chiefly acetone, it also contains small amounts of acetic anhydride, acetic acid and acetylketene. The lamp should be operated for fifteen minutes to expel air from the system before starting to calibrate the apparatus.

To determine the yield of butadiene, the gas from M may be absorbed in a solution of bromine in carbon tetrachloride and the resulting butadiene tetrabromide weighed, or it may be liquefied at −80° and distilled (at about −5°) by means of a Davis column (4). By the first method the present apparatus was found to produce 0.28 mole of butadiene per hour. The unrecovered cyclohexene was 0.45 mole, which represents a 62% yield.

By increasing the filament temperature to 800–850°, a flow of 0.55 mole of butadiene per hour may be obtained. The yield under these conditions, however, is only 32%. Hershberg and Ruhoff (2c) report that Chromel C, a nickel-iron-chromium alloy, is superior to Chromel A for butadiene production. They obtained a 65–75% yield under conditions giving 0.46–0.55 mole per hour.

In a similar apparatus constructed with an uncoiled filament made of 150 cm. B. and S. gauge 22 platinum wire, the flow of ketene (5) per hour was 0.1 mole, and the flow of butadiene (6) was 0.11 mole.

The authors are indebted to Dr. R. H. Munch for his suggestion that a ground

glass joint be used in the top of the lamp, and to Professor N. L. Drake for his suggestion that coiled Chromel A wire be tried as a filament.

SUMMARY

A lamp is described which is capable of delivering 0.45 mole of ketene per hour from acetone, or 0.28 mole of 1,3-butadiene per hour from cyclohexene. The lamp contains a coiled, electrically-heated Chromel filament.

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THE ACTION OF GRIGNARD REAGENTS ON HEAVY METAL SALTS. IV. THE MECHANISM OF THE REACTION WITH SILVER BROMIDE

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In the first paper of this series (1), it was shown that the reaction of silver bromide with certain Grignard reagents results in the coupling of the organic radicals of the Grignard reagents. In succeeding papers (2, 3), it has been shown that, with a mixture of two Grignard reagents, silver bromide reacts with the production of all possible coupling products. In this case, it was found that there is a systematic variation in the yields of the several products with the electronegativity of the radicals involved, the more nearly equal the relative electronegativities, the higher being the yield of the unsymmetrical coupling product. It was further noted that relatively stable organosilver compounds such as phenylsilver decompose more rapidly in the presence of a decomposing unstable organosilver compound than they do alone (3). This suggests that the reaction in its final stages is bimolecular, two molecules of organosilver compound reacting with the production of the coupling product and silver. The present investigation is a study of the mechanism of this reaction from a number of viewpoints.

In order to determine whether the solvent plays an essential part, *p*-tolylsilver and *p*-anisylsilver were prepared free of unchanged Grignard reagent, magnesium salts, and solvent, and were then mixed and decomposed by heating. From the products of this reaction, after demethylation, bi-*p*-tolyl, 4,4′-dihydroxybiphenyl and *p*-tolylphenol were isolated, showing that all possible coupling products were formed in the absence of a solvent, and that the solvent, when present, probably plays no part in the reaction.

In the earlier papers of this series, it was postulated that the coupling of organic radicals through organosilver compounds involved the initial formation of silver and free radicals followed by the union of the radicals to form the coupling products (1, 2). In the last paper (3), reasons for

[1] Based upon a dissertation submitted by E. Allen Bickley in partial fulfilment of the requirements for the degree of Doctor of Philosophy, Washington University, June, 1939.

discarding this view were presented. In the present investigation, an attempt was made to obtain a more definite answer to this question.

In a large number of reactions in which it seems certain that free phenyl radicals are produced in solution, it has been found that the radicals always react with the solvent and never with each other (4). Thus, with carbon tetrachloride, chlorobenzene is formed, with aliphatic hydrocarbons, benzene, and with aromatic liquids, derivatives of biphenyl. Biphenyl is formed only in the presence of benzene. In an effort to detect any sign of free phenyl radicals in the decomposition of phenylsilver, samples of this compound were allowed to decompose under a number of solvents. In no case was there any evidence of reaction with the solvent, biphenyl always being obtained in good yield and high purity. While the criticism may be advanced that, since phenylsilver is extremely insoluble in all solvents used, the reaction may not be carried out under conditions such as to produce phenyl radicals in solution, it seems most probable that, since the phenylsilver was in intimate contact with the solvent in every case, some reaction with the solvent should have been detected had any free radicals been formed. This indicates that the reaction occurs through a binary reaction between two molecules of phenylsilver rather than through an initial dissociation of a single molecule into silver and a free radical.

The entire reaction from Grignard reagent to coupling products can be divided into two distinct parts, the formation of the organosilver compounds, and their decomposition. Because of the instability of the silver compounds, the separate study of these two parts is virtually impossible in the majority of cases, but an observation by Joseph (5) that the results are sometimes affected by the nature of the halogen of the Grignard reagent suggests a means by which some information as to the first part of the reaction chain may be obtained. As an initial series of experiments, silver bromide was made to react in the usual way with *n*-butylmagnesium chloride, bromide and iodide separately. It was found that the yield of *n*-octane obtained from the bromide was about 70% higher than that from either of the others. Similarly, phenylmagnesium bromide gave nearly twice as great a yield of biphenyl as did the iodide. Similarly, using mixtures of phenyl- and *n*-butyl- magnesium halides or mixtures of benzylmagnesium chloride and *sec.*-butylmagnesium halides, very considerable variations in the yields of the various coupling products were noted. Since all of these results involve the halogen atom, they must be due to occurrences during the first part of the reaction chain, and may be connected with differences in reaction velocity.

A number of attempts were made to estimate roughly the relative velocities of the reactions between various Grignard reagents and silver

bromide by the disappearance of the Michler's ketone test (6). Nearly always, the reaction proceeded too rapidly to be measured in this way, so indirect methods had to be found. Such a method was provided by the reaction between pairs of Grignard reagents and one-half of the amount of silver bromide theoretically required to react with them. After completion of the reaction, the unchanged Grignard reagents were decomposed with dilute acid and the amount of each radical coupled was determined by isolating the reaction products. It is obvious that in this procedure, when two Grignard reagents react with silver bromide at equal rates, the amounts of the radicals coupled will be equal. Further, when the reaction rates are unequal, the radical of the reagent reacting most rapidly will be coupled to the greatest extent. By carrying out this experiment with suitably selected pairs of Grignard reagents, it is possible to set up a series in terms of reaction velocity. This was done for phenylmagnesium bromide with *n*-butylmagnesium chloride, bromide and iodide and for phenylmagnesium iodide with *n*-butylmagnesium bromide. In this way, it was found that these reagents react with silver bromide in the order of increasing velocity:

$$C_6H_5MgI < C_6H_5MgBr < C_4H_9MgBr < C_4H_9MgCl < C_4H_9MgI$$

The detailed results upon which this series is based are given in the Experimental Part.

With this series in mind, the results obtained in coupling experiments in which silver bromide was present in excess become understandable. Using phenyl- and *n*-butyl-magnesium halides, the largest yield of *n*-butylbenzene was obtained when both were bromides, that is, in the case in which the relative reaction velocities with silver bromide were most nearly equal. The yields with *n*-butylmagnesium chloride and iodide decreased in that order. When phenylmagnesium iodide was used, the yield of *n*-butylbenzene was always less than with the bromide, and again the yields decreased in the order *n*-butylmagnesium bromide > chloride > iodide. It is probable that a similar correlation between reaction velocity and yield of the unsymmetrical coupling product could be shown in the series of reactions between benzylmagnesium chloride and the three *n*-butylmagnesium halides, but time did not permit determination of the relative rates in this case.

An interesting and perhaps important side-reaction was noted in the course of this work. It was found that, whenever iodides were used, the octane fraction always contained considerable quantities of the corresponding butyl iodide. In order to determine the source of this material, *n*-butylmagnesium bromide was mixed with an ethereal solution of magnesium iodide, with and without the addition of silver bromide. It

was found that when silver bromide was present, *n*-butyl iodide was formed in large yield, but none was detected in the absence of silver bromide. This may be accounted for on the basis of the equation:

$$n\text{-}C_4H_9Ag + MgI_2 = n\text{-}C_4H_9I + Ag + MgI$$

Similarly, phenylsilver reacted with magnesium iodide to give iodobenzene and a phenylmagnesium halide. No evidence of similar reactions was noted with the other halides. These reactions are to be further investigated.

TABLE I

n-BUTYLMAGNESIUM HALIDES AND SILVER BROMIDE

GRIGNARD REAGENT	YIELD OF *n*-OCTANE	
	g.	Per Cent
$n\text{-}C_4H_9MgCl$	10.8	37.8
$n\text{-}C_4H_9MgBr$	18.4	64.4
$n\text{-}C_4H_9MgI$	10.4	36.4

TABLE II

PHENYLMAGNESIUM HALIDES AND SILVER BROMIDE

GRIGNARD REAGENT	YIELD OF BIPHENYL	
	g.	Per Cent
C_6H_5MgBr	25.0	64.8
C_6H_5MgI	10.5	27.2

EXPERIMENTAL

Thermal decomposition of a mixture of p-*tolylsilver and* p-*anisylsilver.*—The silver compounds were prepared separately by the action of the Grignard reagents on silver bromide, washed with dry ether until Michler's ketone test was no longer given, centrifuged from the ether and mixed. The mixture was heated for one-half hour at 100°. The products were extracted from the silver residue and demethylated with constant boiling hydriodic acid in an equal volume of glacial acetic acid. The precipitate formed on dilution with water was extracted with 2% sodium hydroxide. The residue was di-*p*-tolyl, m.p. 119–120°, from alcohol. Ullmann and Meyer give the m.p. 121–122° (7). Acidification of the extract gave a precipitate which was crystallized from benzene. The fraction more soluble in benzene was 4-methyl-4′-hydroxybiphenyl, m.p. 152–153°, benzoate, m.p. 185–186°. Kliegel and Huber give the respective melting points 154–155° and 188° (8). The fraction less soluble in benzene was 4,4′-dihydroxybiphenyl, m.p. 266–268° from acetic acid, diacetate, m.p. 157–159°. Schmidt and Schultz give the respective melting points 272° and 159–160° (9).

Attempts to capture free radicals in the decomposition of phenylsilver.—Phenylsilver was prepared by the reaction of phenylmagnesium bromide and silver bromide and washed with dry ether until no test was given for a Grignard reagent. Portions were

then decomposed successively under carbon tetrachloride, chlorobenzene and nitrobenzene. In all experiments the only product isolated was biphenyl; no evidence of reaction with the solvent was found.

Reaction between n-*butylmagnesium halides and silver bromide.*—These experiments were carried out according to the procedure of Gardner and Borgstrom (1), using one-half mole of alkyl halide in each. The *n*-octane from *n*-butylmagnesium iodide was contaminated with *n*-butyl iodide, and the actual yield was estimated from a composition-refractive index curve for *n*-octane and *n*-butyl iodide. The results are given in Table I.

Reaction between phenylmagnesium halides and silver bromide.—These experiments were conducted according to the procedure of Gardner and Borgstrom (1), using one-half mole of the halide in each case. The results are given in Table II.

Reaction of mixtures of phenyl- and n-*butyl- magnesium halides with silver bromide.*—Grignard reagents were prepared separately from one-half mole of each halide,

TABLE III

COUPLING PRODUCTS FROM PHENYL- AND *n*-BUTYL-MAGNESIUM HALIDES

REAGENTS	YIELDS, G.		
	n-Octane, B.p. 125-6°	*n*-Butyl-benzene, B.p. 177-8°	Biphenyl, M.p. 65-7°
C_6H_5MgBr with			
n-C_4H_9MgBr	6.0	25.0	12.0
n-C_4H_9MgCl	4.8	18.0	13.3
n-C_4H_9MgI	10.7	1.5	27.0
C_6H_5MgI with			
n-C_4H_9MgBr	11.2	4.0	23.0
n-C_4H_9MgCl	8.5	2.0	23.5
n-C_4H_9MgI	8.8	1.0	23.5

mixed, and caused to react with one mole of silver bromide according to the procedure of Joseph and Gardner (3). Whenever an iodide was used, the *n*-octane was contaminated with *n*-butyl iodide and the yield was estimated from a composition-refractive index curve. The results are given in Table III.

Reaction of mixtures of benzylmagnesium chloride and sec.-*butylmagnesium halides with silver bromide.*—These experiments were carried out according to the procedure of Joseph and Gardner (3), using one-half mole of each halide and one mole of silver bromide in each. The 3,4-dimethylhexane from the runs in which *sec.*-butyl iodide was used was contaminated with *sec.*-butyl iodide. The yield in this case was estimated from a refractive index-composition curve. The results are given in Table IV.

Relative rates of reaction of phenyl- and n-*butyl- magnesium halides with silver bromide.*—These experiments were carried out as before except that only one-half mole of silver bromide was used for a mixture of Grignard reagents prepared from one-half mole of each of two halides. The results are expressed in terms of moles of phenyl hydrolysed, detected as benzene in the final product, moles of phenyl coupled (biphenyl + *n*-butylbenzene), and moles of *n*-butyl coupled (*n*-butyl-

benzene + *n*-octane). Since the unreacted *n*-butylmagnesium halide was finally converted into *n*-butane, the amount of unreacted *n*-butyl Grignard reagent was not determined. The results are given in Table V. The radical which is coupled to the greater extent corresponds to the Grignard reagent in the pair which reacts the more rapidly with silver bromide.

Reaction of n-*butylmagnesium bromide with magnesium iodide in the presence of silver bromide.*—Slightly more than the equivalent amount of silver bromide was added to an ethereal solution of 0.25 mole of *n*-butylmagnesium bromide and 0.25 mole of magnesium iodide. The mixture was stirred at 0° for a half hour and then for an hour at the boiling point. The reaction mixture was treated with very dilute

TABLE IV

COUPLING PRODUCTS FROM BENZYLMAGNESIUM CHLORIDE AND *sec.*-BUTYLMAGNESIUM HALIDES

REAGENTS	YIELDS, G.		
	3,4-Dimethylhexane, B.p. 110-3°	2-Benzylbutane, B.p. 190-3°	Bibenzyl, M.p. 51-3°
$C_6H_5CH_2MgCl$ with			
sec.-C_4H_9MgCl		34.0	11.0
sec.-C_4H_9MgBr	1.5	32.2	11.0
sec.-C_4H_9MgI	13.7	13.0	21.0

TABLE V

DATA FOR RELATIVE RATES

REAGENTS	PHENYL HYDROLYSED MOLES	PHENYL COUPLED MOLES	*n*-BUTYL COUPLED MOLES
C_6H_5MgBr with			
n-C_4H_9MgBr	0.207	0.223	0.293
n-C_4H_9MgCl	0.264	0.198	0.250
n-C_4H_9MgI	0.292	0.165	0.379
C_6H_5MgI with			
n-C_4H_9MgBr	0.350	0.089	0.387

hydrochloric acid and the products were steam-distilled, dried over calcium chloride and distilled. There was obtained in this way 15 g. of a mixture of *n*-octane and *n*-butyl iodide, b.p. 122-129°, d_4^{21} 1.200, n_D^{21} 1.4480. The refractive index corresponds to that of a mixture containing 32% *n*-octane and 68% *n*-butyl iodide. A blank experiment in which the silver bromide was omitted yielded neither *n*-octane nor *n*-butyl iodide.

Reaction of phenylsilver and magnesium iodide.—Phenylsilver prepared from 0.20 mole of phenylmagnesium bromide was washed free of the Grignard reagent with dry ether and was then stirred with an excess of magnesium iodide in dry ether solution for two hours at 0°. The ether solution then gave a strong Michler's ketone test for Grignard reagent. After stirring an additional two hours at the boiling

point, the suspended solids became brown. After hydrolysis with very dilute hydrochloric acid, there were isolated from the organic layer 3.0 g. of benzene, b.p. 78–80°, n_D^{22} 1.4980, 1.0 g. of iodobenzene, b.p. 180–190°, n_D^{22} 1.5962 and 2.0 g. of biphenyl m.p. 64–65°. When phenylsilver was stirred in the cold for two hours with dry ether, the liquid gave a negative Michler's ketone test.

SUMMARY

1. Organosilver compounds have been shown to decompose by a bimolecular reaction not involving free radicals.

2. It has been shown that the course of the reaction between Grignard reagents and silver bromide is determined by reaction velocities.

3. Various side-reactions have been studied.

St. Louis, Mo.

REFERENCE

(1) Gardner and Borgstrom, *J. Am. Chem. Soc.*, **51**, 3375 (1929).
(2) Gardner, Joseph and Gollub, *J. Am. Chem. Soc.*, **59**, 2583 (1937).
(3) Joseph and Gardner, *J. Org. Chem.*, **5**, 61 (1940).
(4) Hey and Waters, *Chem. Rev.*, **21**, 193 (1937).
(5) Joseph, Dissertation, Washington University (1937).
(6) Gilman and Schulze, *J. Am. Chem. Soc.*, **47**, 2002 (1925).
(7) Ullmann and Meyer, *Ann.*, **332**, 44 (1904).
(8) Kliegel and Huber, *Ber.*, **53**, 1652 (1920).
(9) Schmidt and Schultz, *Ann.*, **207**, 337 (1881).

[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

SOME REACTIONS OF AMIDINES AS AMMONO-CARBOXYLIC ACIDS OR ESTERS[1]

E. C. WAGNER

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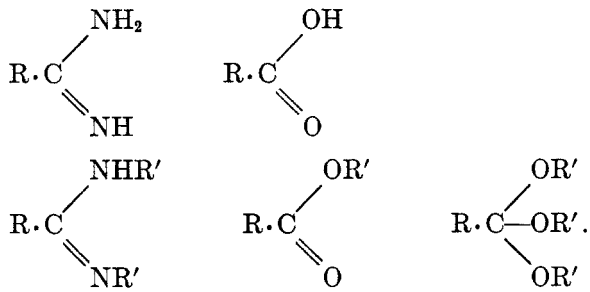
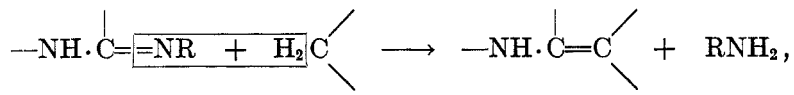
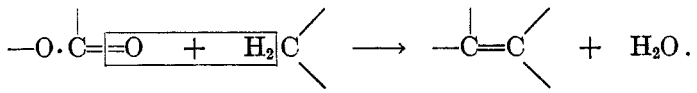
Amidines may be regarded as ammonia-system analogs of carboxylic acids or esters:



There is some evidence that this structural analogy is validated by a functional analogy. Examples include the condensation of isatin-α-anil and indoxyl, and the condensations of formamidines with reactive methylene compounds (1). Others are discussed by Franklin (2). Both the above examples involve the essential reaction



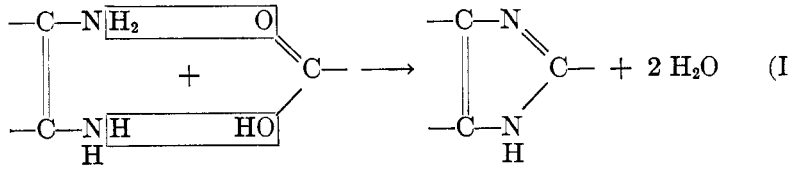
which is the ammonia-system counterpart of the reaction



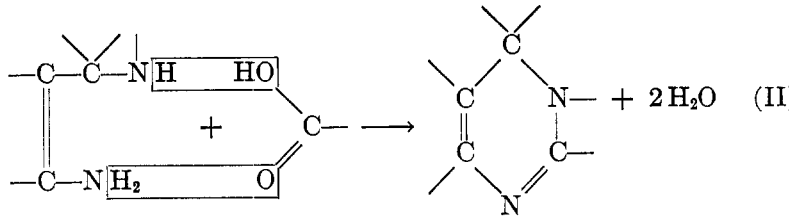
In these reactions only part of the amidine structure is involved, so that the functional analogy suggested above is only partially revealed. A reaction whose extension permits a more searching test of the analogy is the closure of 1,3-diazole (imidazole) or 1,3-diazine (pyrimidine) rings by action of formic acid or ester, or of their homologs, upon compounds with

[1] Presented in part at the 97th meeting of the American Chemical Society, Baltimore, Md., April 3 to 7, 1939.

two nitrogen atoms in $-NH_2$ or $-NH-$ groups separated by two or three carbon atoms:

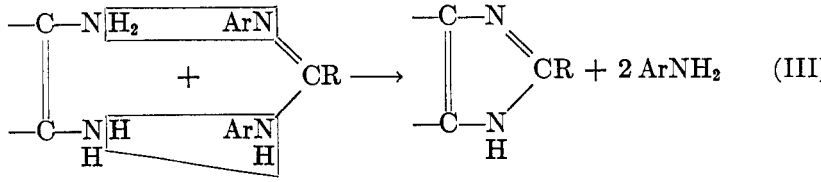


(I)

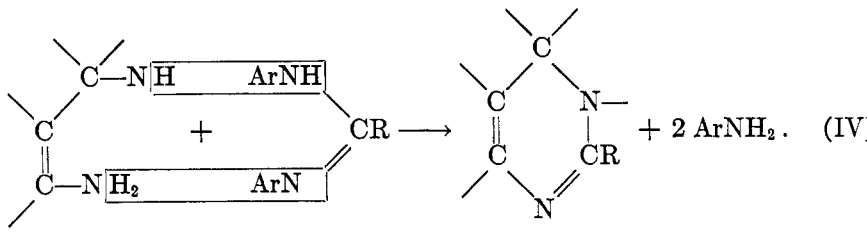


(II)

The expectation that these reactions might be duplicated by use of amidines has been realized for certain of the N,N′-diaryl formamidines and acetamidines, the essential changes being ammonia-system counterparts of (I) and (II), viz.,

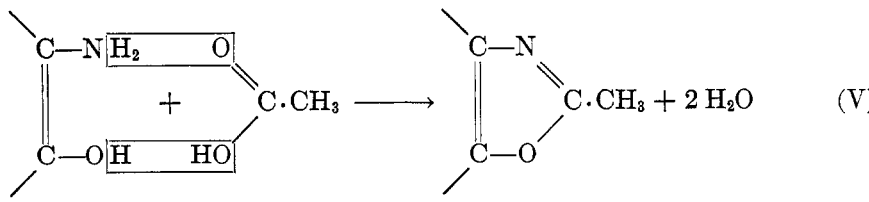


(III)

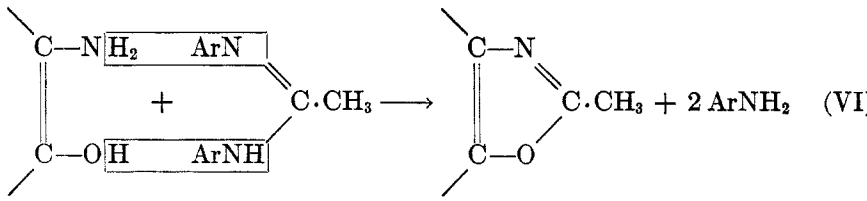


(IV)

Similarly the formation of the oxazole ring by acetic acid (anhydride) was duplicated by use of diaryl acetamidine:



(V)



(VI)

It appears that formamidines enter into such reactions more readily than do amidines of homologous or other acids. Acetamidines were used in a few trials, successfully in reactions (III) and (VI) and unsuccessfully in reaction (IV). Preliminary experiments indicated diphenylbenzamidine to be unreactive according to equation (III) under conditions favorable to reactivity of formamidines and acetamidines.

Reactions with amidines were carried out in general by simple fusion of the reactants, used either in equivalent amounts or with the amidine in excess. The following reactions are described in the experimental section.

I. Formation of imidazole ring (reactions I and III): (a) Conversion of *o*-phenylenediamine to benzimidazole by formic acid and by diarylformamidines; (b) Conversion of *o*-phenylenediamine to 2-methylbenzimidazole by acetic anhydride and by diphenylacetamidine.

II. Formation of pyrimidine ring (reactions II and IV): (a) Conversion of *o*-aminobenzylarylamines to 3,6-disubstituted dihydroquinazolines by formic acid and by diarylformamidines; (b) Conversion of anthranilanilides to 3-substituted-4-ketoquinazolines by formic acid, by ethyl orthoformate and by diarylformamidines; (c) Conversion of 1,8-diaminonaphthalene to perimidine by formic acid and by diphenylformamidine.

III. Formation of oxazole ring (reactions V and VI): Conversion of *o*-aminophenol to 2-methylbenzoxazole by acetic anhydride and by diphenylacetamidine.

In two other cases preliminary experiments showed formamidines to react like formic acid or ethyl formate, viz., (a) Conversion of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by formic acid (3) and by di-*p*-tolylformamidine, a reaction whose course is as yet obscure; and (b) Conversion of phenylbiguanide to a single product (m.p. 230°, and presumably a *sym*-triazine derivative) by either ethyl formate (4) or diphenylformamidine.

EXPERIMENTAL

The required *o*-aminobenzylarylamines were prepared by the procedure described in a previous paper (5). The anthranilanilides were made from isatoic anhydride and suitable amines by the method of Kolbe (6). Diarylformamidines were made by interaction of arylamines and ethyl orthoformate (7). Diarylacetamidines were

prepared from arylamines, N-arylacetamides and phosphorus trichloride by a modification of the method of Sen and Ray (8). The other compounds were Eastman Kodak Company chemicals. Diaminonaphthalene was obtained also by hydrogenation of 1,8-dinitronaphthalene in an Adams and Vorhees apparatus, using Raney nickel, about thirty pounds per square inch pressure of hydrogen, and dioxane as solvent. The hydrogenation was slow and incomplete, the yield of diamine as hydrochloride being 55%. The reduction liquid was intensely purple in color, and yielded a dark blue by-product.

I. Formation of imidazole ring

Ring-closure by acids. Benzimidazole was obtained in 85% yield from *o*-phenylenediamine and formic acid by the method of Wundt (9), described in modified form in Organic Syntheses (10). Methylbenzimidazole was obtained from *o*-phenylenediamine and acetic anhydride in dilute hydrochloric acid by the method of Phillips (11). The yield of crude material was nearly quantitative, and was decreased to 85.5% after crystallization from water (m.p. 176° obs.), with 7.8% recoverable from the mother liquor as picrate (m.p. 212–215° obs.) (12).

Ring-closure by amidines. Benzimidazole was obtained by heating a mixture of *o*-phenylenediamine and somewhat more than one equivalent of diphenyl- or di-*p*-tolyl-formamidine at about 125° for several hours. The mixture was submitted to steam distillation, and the distillate was acidified with hydrochloric acid and evaporated to dryness to recover as hydrochloride the amine liberated in the reaction.[2] The residual liquid in the flask was made alkaline with sodium hydroxide and steam distillation was resumed, in order to decompose unused amidine and remove the resultant amine. The liquid was then acidified slightly with acetic acid, neutralized with sodium bicarbonate, digested with charcoal, filtered, and concentrated by evaporation. When the solution was chilled, benzimidazole separated as crystals of m.p. 171° obs., raised to 172° by recrystallization from water. A further small quantity of benzimidazole could be recovered as picrate (m.p. 223° obs.) from the first mother liquor.

By this procedure 1.08 g. (0.01 mole) of *o*-phenylenediamine and 3.0 g. (about 0.015 mole) of diphenylformamidine gave benzimidazole in 81.4% yield, with 3.9% more recovered as picrate; total indicated yield 85.3%. The aniline liberated in the reaction (2.84 g. of aniline hydrochloride) was 83% of the theoretical. The yield of benzimidazole was 63% when one equivalent of diphenylformamidine was used.

2-Methylbenzimidazole. A mixture of 1.08 g. (0.01 mole) of *o*-phenylenediamine and 3.15 g. (0.014 mole) of phenyl-*o*-tolylacetamidine was heated for two hours at 180°. The mass was treated with sodium hydroxide and the mixture submitted to steam distillation to remove aniline and *o*-toluidine. The liquid in the flask was acidified with acetic acid, made barely alkaline with ammonium hydroxide, digested with charcoal, filtered hot, and then chilled. The methylbenzimidazole weighed 0.84 g. (63.6% of the theoretical), melted at 176° obs., and was identified by mixed melting point test.

II. Formation of pyrimidine ring

(*1*) *Formation of substituted dihydroquinazolines from* o*-aminobenzylarylamines.* Ring-closure by formic acid or orthoformic ester. By heating the *o*-aminobenzyl-

[2] Steam distillation in absence of acid or alkali does not decompose these diarylamidines appreciably.

arylamine with excess of 90% formic acid on the water-bath (13) small yields (20 to 39%) of the corresponding dihydroquinazolines were obtained (14), viz.,

3-*p*-tolyl-6-methyldihydroquinazoline, m.p. 160° obs.,

3-*p*-chlorophenyl-6-chlorodihydroquinazoline, m.p. 186–7°, obs.,

3-*p*-bromophenyl-6-bromodihydroquinazoline, m.p. 200° obs.

Ethyl orthoformate was used similarly by v. Walther and Bamberg (13), who reported a 70% yield of 3-tolyl-6-methyldihydroquinazoline from 2-amino-5-methyl-N-tolyl-benzylamine.

Ring-closure by diarylformamidines. A mixture of the *o*-aminobenzylarylamine (0.01–0.02 mole), slightly more than one equivalent of the diarylformamidine and about 0.2 equivalent of the corresponding amine hydrochloride was heated on the water-bath for four hours or in an oil-bath at 130–140° for about two hours. The mixture was made alkaline with sodium hydroxide and was subjected to steam distillation. The residual solid was crystallized from dilute alcohol, and the mother liquor treated to recover a further quantity of product as picrate. Results were as follows:

o-AMINO-N-ARYLBENZYLAMINE	FORMAMIDINE	DIHYDROQUINAZOLINE	
		Yield %	m.p. C.°
2-Amino-5-methyl-N-(*p*-tolyl)-benzyl-amine	Diphenyl	78	161 obs.
2-Amino-5-chloro-N-(*p*-chlorophenyl)-benzylamine	"	69	186.5 "
	Di-*p*-chlorophenyl	69	187 "
2-Amino-5-bromo-N-(*p*-bromophenyl)-benzylamine	Diphenyl	48	198 "

In these reactions the amine hydrochloride was probably dispensable, as appears elsewhere in the experimental section. Its use in these early experiments was suggested by analogous use of amine salts in reactions which involve initial cleavage of methylene-N,N′-bis-arylamines (15).

An attempt to effect this ring-closure by means of an acetamidine was unsuccessful. After heating a mixture of 2-amino-5-methyl-N-(*p*-tolyl)-benzylamine and diphenylacetamidine in equivalent amounts for two hours at 190–200°, there was no steam-volatile oil present, and apparently little or no reaction had occurred. Most of the aminobenzylarylamine was recovered, in the form of its benzal derivative, and the other isolable compound was unchanged acetamidine.

(*2*) *Formation of substituted dihydroquinazolones from anthranilamide and anthranilanilides.*

Ring-closure by formic acid or ethyl orthoformate. Anthranilanilide, when heated with excess of formic acid or ethyl orthoformate for an hour at refluxing temperatures, yielded in either case 3-phenyldihydroquinazolone-4, m.p. 136° obs., or 139° corr., and identical with the product made by heating anthranilic acid and formanilide under open reflux for three hours at 130–140° (16). The picrates also were identical.

3-Phenyldihydroquinazolone-4 picrate. On mixing concentrated alcoholic solutions of 0.5 g. of the base and 1.10 g. of picric acid (slightly more than two equivalents), there separated 0.95 g. of the salt, a 94% yield of the 1:1 picrate. After crystallization from ethyl alcohol, the pure picrate melted at 177° obs., or 180.6° corr.

Ring-closure by formamidines. A mixture of the amide (0.01 mole) and diaryl-

formamidine (slightly more than 0.01 mole) was heated under reflux for two to three hours at temperatures which ranged from 130° to 160°. The reaction mixture was subjected to steam distillation to remove amine liberated in the reaction, and the residual crude product was dissolved in hot dilute alcohol and obtained by crystallization. Results are as follows:

AMIDE	FORMAMIDINE	DIHYDROQUINAZOLONE	
		Yield %*	m.p. C°
Anthranilamide	Di-*p*-tolyl	56	213 obs.
Anthranilanilide	Diphenyl	82	140 "
"	Di-*p*-chlorophenyl	82	137 "
p'-Bromo- "	Diphenyl	75	190 "

* Including product recovered as picrate.

An attempt to effect this ring-closure by means of an acetamidine was unsuccessful: no isolable quinazolone was obtained after heating anthranilanilide with 1.5 equivalents of diphenylacetamidine at 190° for two hours.

3,4-Dihydroquinazolone-4 picrate. When alcoholic solutions of 0.37 g. of dihydroquinazolone and 1.20 g. of picric acid (1.15 g. is two equivalents) were mixed 0.81 g. of the salt separated, an 85.3% yield of the 1:1 picrate. The melting point was 204° obs., with a color change from orange to yellow at 180–190°.

(*3*) *Formation of perimidine from 1,8-diaminonaphthalene.*

Ring-closure by formic acid. The procedure of Sachs (17) gave 78.7% and 79.7% of perimidine as light olive-green plates. The melting point ("about 222°") reported by Sachs could not be duplicated with certainty. On heating the substance in a capillary tube obvious decomposition was in progress around 220°. In several trials a drop separated around 226°. The nearly black mass appeared to be wholly liquid at 233° to 238°, with brown oily droplets on the walls of the tube. On the Dennis bar the melting point was equally uncertain, but was judged to be in the neighborhood of 238°. The picrate, reported by Sachs to melt at 226°, was found to decompose with effervescence around 249–250°. To establish more firmly the identity of the product with that described by Sachs it was analyzed for nitrogen: calc'd.: 16.6%; found: 16.3%.

Ring-closure by diphenylformamidine. A mixture of 1.58 g. of diaminonaphthalene (0.01 mole) and 2.0 g. of diphenylformamidine (0.01 mole) was heated at 160° for 90 to 150 minutes. Water was added to the cooled mass, which was submitted to steam distillation, the aniline being recovered and weighed as aniline hydrochloride. The solid residue in the flask was dissolved by addition of the minimum necessary hydrochloric acid. The solution was digested with charcoal, filtered, and the filtrate was treated with concd. hydrochloric acid in moderate excess (about one-fifth volume). The greenish-yellow crystalline perimidine hydrochloride thus salted out weighed 1.65 g. (80.7%). The aniline of reaction (1.97 g. of hydrochloride) was 79.7% of the theoretical. In other experiments the crude product (after the steam distillation) was crystallized from dilute alcohol, using decolorizing carbon, in some cases after first dissolving the crude material in dilute hydrochloric acid, digesting with charcoal, and precipitating by addition of sodium hydroxide and then sodium bicarbonate. The yields so obtained were comparable with the values above.

Perimidine thus obtained was similar in appearance and properties to the com-

pound made by use of formic acid, and a mixture of the two showed in the melting point determination the same behavior as either substance separately. The picrate of the base made by use of diphenylformamidine decomposed with effervescence at 247°, and a mixture with the picrate of the perimidine made by use of formic acid decomposed at the same temperature. The identity of the compounds made in the two ways was supported by the physical appearance of crystals obtained by sublimation. These were yellow-green needles, showing identical colors in polarized light, and a like extinction angle of about 14°.

III. Formation of the oxazole ring

Preparation of 2-methylbenzoxazole. The method of Ladenburg (18), which involves heating *o*-aminophenol with acetic anhydride, was used in the modification described by Phillips (19).

The same ring-closure was effected by use of diphenylacetamidine (instead of acetic anhydride), but the yield could be determined only approximately because of difficulty in separating the methylbenzoxazole from the aniline liberated in the reaction. The boiling points for these compounds (202° and 184°) appear to be favorable for separation by distillation, but this proved to be not feasible because of the high vapor pressure of methylbenzoxazole near the boiling point of aniline. Methylbenzoxazole was estimated by taking advantage of its ready conversion to *o*-acetaminophenol by mild acid hydrolysis (18), the acetaminophenol being obtained by chilling the solution. The procedure was as follows.

A mixture of *o*-aminophenol (0.02 to 0.05 mole) and slightly more than an equivalent amount of diphenylacetamidine was heated under reflux at 190–195° for two hours. The leek-like odor of methylbenzoxazole became noticeable after a short time and was finally strong. The methylbenzoxazole and aniline were removed together by distillation (184–205°). The mixture was suspended in water and treated with enough acetic acid to effect complete solution. The liquid was boiled gently for about thirty minutes, some charcoal was stirred in, and the mixture was filtered and the filtrate chilled. The acetaminophenol separated as colorless plates; m.p. 207° obs.; yield 56%. The filtrate smelled strongly of methylbenzoxazole, but after further boiling, and concentration by evaporation, no more acetaminophenol was obtained. By working up the mother liquor some *o*-aminophenol was isolated, corresponding to 4% of methylbenzoxazole, from which it had presumably been formed by complete hydrolysis.[3]

The *o*-acetaminophenol, after crystallization from dilute alcohol and then from 95% alcohol, melted at 208° obs., or 209.6° corr. It was identical with a specimen of *o*-acetaminophenol made from methylbenzoxazole prepared by the method of Phillips.

2-Methylbenzoxazole picrate. A solution of 2.7 g. (0.02 mole) of methylbenzoxazole in a little alcohol was added to a strong solution of 5.0 g. of picric acid (4.58 g. is 0.02 mole) in alcohol. The picrate separated only upon chilling the solution. The yield was 3.04 g. (42%), the picrate being fairly soluble in alcohol, probably because of separation into its components. The melting point was 117–118° obs.; melting was accompanied by volatilization of methylbenzoxazole, the odor of which was pronounced when the determination was made on a Fisher-Johns melting point

[3] As *o*-aminophenol sublimes on heating, it is possible that the recovered substance was aminophenol which had not reacted with diphenylacetamidine and which passed into the distillate with the methylbenzoxazole and aniline.

apparatus. This value, while close to the melting point of picric acid, is apparently a reproducible constant of the picrate, a mixture of which with picric acid melted badly from 103° to 115°.

Conversion of Tetrahydroquinazoline to Dihydroquinazoline. The conversion of 3-*p*-tolyl-6-methyl-1,2,3,4-tetrahydroquinazoline to the corresponding dihydroquinazoline by heating with formic acid under pressure was reported in an earlier paper (3). The same transformation was effected also by use of diphenylformamidine instead of formic acid.

A mixture of 0.99 g. of tolylmethyltetrahydroquinazoline and 1.7 g. (about 2 equivalents) of diphenylformamidine, in a test tube provided with a reflux condenser, was heated in a metal-bath for a hour at 190–200°. The test tube was broken, and the solid mass (which gave off an isonitrile odor) was transferred to a flask, where it was treated with water and about 3 g. of sodium hydroxide. The mixture was submitted to steam distillation to remove aniline. The residue was dissolved in hot 95% alcohol; on chilling the solution there separated 0.47 g. of unchanged tetrahydroquinazoline (m.p. 139° after recrystallization from alcohol). The mother liquor was treated with picric acid, and yielded 0.75 g. of a picrate of m.p. 203° obs. A mixture of this compound with the picrate of tolylmethyldihydroquinazoline (m.p. 204° obs.) melted at 203–204° obs. The yield of dihydroquinazoline obtained in the reaction was 38%.

Interaction of phenylbiguanide and ethyl formate or diphenylformamidine. By allowing arylbiguanides and ethyl formate[4] to stand in alcoholic solution, products separate which are believed to be derivatives of *sym*-triazines (4). The compound thus obtained from phenylbiguanide and ethyl formate is a white solid, of m.p. 230–232°. Formation of the same compound by use of a formamidine instead of ethyl formate was effected as follows. A mixture of 3.54 g. (0.02 mole) of phenylbiguanide and 4.0 g. of diphenylformamidine (0.02 mole) was heated near 145° for an hour. The mixture first melted and later solidified. The odor of ammonia and that of isonitrile were detectable during the heating. The cooled mass was dissolved in hot dilute hydrochloric acid. The solution was digested with decolorizing carbon, filtered, and then neutralized by addition of sodium hydroxide solution and finally solid sodium bicarbonate. The product separated as a white powder; m.p. 227–230° obs.; yield 1.52 g. (40.6% calculated as the triazine). A mixture of this product and that made by use of ethyl formate melted at 230° obs. This and analogous compounds are the subject of continued study.

Grateful acknowledgment is made to the Faculty Research Committee of the University of Pennsylvania for a grant to assist this study.

SUMMARY

A clear functional basis for regarding amidines as ammonia-system analogs of carboxylic acids or their esters was established experimentally by effecting with several diarylformamidines and acetamidines certain ring-closures characteristically effected also by formic acid or ester or by acetic acid or anhydride. The reactions were essentially alike in type, and yielded the same products whether the reagent was acid (ester) or

[4] This reaction was called to the writer's attention by Dr. J. K. Simons, Mellon Institute, Pittsburgh, Pa.

amidine, the former splitting out water (alcohol) and the latter splitting out amine. The ring-closures studied are of the following types:

1. Closure of imidazole ring. *ortho*-Phenylenediamine, when heated with either formic acid or diarylformamidines, was converted into benzimidazole. Similarly acetic acid or diphenylacetamidine gave 2-methylbenzimidazole.

2. Closure of pyrimidine ring. N-(2-aminobenzyl)-arylamines, when heated with formic acid, ethyl orthoformate, or diarylformamidines, yielded the corresponding 3-aryl-3,4-dihydroquinazolines. Anthranilamide or anthranilanilides, heated with formic acid, orthoformic ester, or diarylformamidines, yielded the corresponding 4-ketodihydroquinazolines. Peri-diaminonaphthalene, heated with formic acid or with diphenylformamidine, yielded perimidine.

3. Closure of oxazole ring. *ortho*-Aminophenol, when heated with either acetic anhydride or diphenylformamidine yielded 2-methylbenzoxazole

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF CALIFORNIA AT LOS ANGELES]

THE FORMATION OF CHLOROANILINE DURING REDUCTION OF NITROBENZENE

G. ROSS ROBERTSON AND ROSS A. EVANS

Received August 17, 1939

It has long been known that the substitution of metallic zinc for the tin commonly used with hydrochloric acid in reducing an aromatic nitro compound to amine may introduce difficulties. Kock (1) found with nitrobenzene that nearly 25% of the quantity taken was diverted into monochloroanilines when zinc was used. With iron, no chloroaniline appeared. Apparently no explanation has been offered for the contrast in behavior of metals in such a reaction, and it is to this point that the present report is directed.

Bamberger (2) has shown that β-phenylhydroxylamine is rearranged in the presence of hydrochloric acid (through the possible intermediate N-chloroaniline) to give not *p*-aminophenol, but *p*-chloroaniline, which incidentally is the principal chlorinated by-product from the zinc process cited above. Accepting the assumption of Haber (3) that nitrobenzene is transformed into the hydroxylamine before the ultimate reduction to aniline, one finds no difficulty after all in accounting for the strange reaction in which a strong reducing agent seems to be able to replace hydrogen with chlorine. The proportions of aniline and chloroaniline obtained from the zinc process therefore depend largely upon the relative efficiencies of the two reactions, reduction and rearrangement, which compete for the transient supply of phenylhydroxylamine.

This plausible mechanism still offers no direct explanation of the fact that different metals yield greatly different fractions of chloroaniline. Accordingly, a long series of simple reduction experiments was carried out with numerous variations in choice of metallic reagent and conditions to suit various hypotheses.

EXPERIMENTAL

In each experiment a small sample of nitrobenzene was treated with concentrated hydrochloric acid and a quantity of metal somewhat more than the theoretical requirement to reduce the nitro compound completely to aniline. Reaction mixtures were usually cooled by hand in tap water. If the reduction was not complete, the excess of nitrobenzene was expelled from the acid solution by steam distillation. The aniline was isolated in the usual manner described in elementary manuals, save

that no final distillation was made, since it was desirable to preserve and sample the entire amine product for analysis.

Weighed samples of the aniline mixtures were heated in alcoholic sodium ethoxide, and chloride ion estimated in the resulting solutions by the Volhard method. The table shows the percentages of chloroaniline in the amine products in a group of significant experiments.

TABLE

CHLORINATED COMPOUNDS IN THE ANILINE PRODUCTS

METAL	PER CENT CHLOROANILINE	METAL	PER CENT CHLOROANILINE
Iron	0	Cu-Zn alloy (1.2% Cu)	3.9, 4.35
Tin	2.75, 3.47	Cadmium	23.1, 24.3
Tin, rod, rotated	7.5	Aluminum	No reduction
Zinc	26.07, 27.08	Calcium	No reduction
Zinc, rod, rotated	9.46, 11.46	Magnesium	No reduction
Zinc, rod, rot., temp. 25°	2.6, 3.5	Magnesium, below 0°, (solid CO_2)	62.0, 66.4
Zinc-tin alloy (90% Zn)	23.06		
Zinc-tin alloy (10% Zn)	6.7		

Note.—Metals were in the form of mossy fragments, or turnings, except in three experiments, in which cylindrical rods of the metals were rotated rapidly in the acid solution by mechanical stirrer during the reactions.

These analytical values, like those of Kock, are at best only approximate. There were so many variables, such as purity, size and form of metallic fragments, temperature, concentration, methods of stirring and cooling, etc., that it was scarcely possible to line up the experiments by rigorous standards. Results with different metals were so widely variant, however, that general trends are evident.

The suggestion that certain metals have peculiar valence-shell configurations responsible for a specific, perhaps catalytic, effect on chlorination was rejected as intangible and improbable. Too many metals cause entry of chlorine. It seemed preferable to seek a correlation of chlorination behavior with some definite and known gradation of properties.

Admitting the existence of competition between the reactions of reduction and rearrangement one would naturally expect metals of high reduction potential to accelerate the former reaction and thus cut down the yield of chloroaniline. A comparison of the above table, however, with the electromotive series reveals no correlation which supports this hypothesis.

In like manner the theory that metals of high hydrogen overvoltage might effect reduction more rapidly, and thus minimize chlorination, met no better success, as tables of overvoltage will show. After all, any of the base metals under consideration has ample potential to effect any of the steps of reduction involved with nitrobenzene, and an explanation depending on thermodynamics is not convincing.

The fact that tin and iron exist as reducing agents in the form of ions of lower valence, while zinc does not, suggested the possibility of the better reduction in the former cases by such ions. Unfortunately, however, the addition of ferrous or stannous ions to a zinc-nitrobenzene reacting mixture does not prevent the chloroaniline reaction. Ferrous ion in particular seems to have no significance here.

Numerous additional variations, more or less backed by hypotheses, were tested without significant results. These introduced such features as organic solvents, impressed external electric potentials, high temperatures, amalgamated metals and metal powders. Although almost any variation affected chlorine content, the actual changes did not seem to be related in any consistent and convincing way to the specific variable chosen.

There is one correlation, however, which seems to be valid, namely: the fraction of nitrobenzene diverted into chloroaniline varies directly with the velocity of the reaction producing hydrogen gas. The tabular data for tin, zinc and magnesium illustrate this assumption consistently. This relation naturally suggests two postulates, (a) that the chloroaniline rearrangement is favored by a high rate of elimination of hydrogen ion, or (b) by an excessive output of hydrogen gas.

The well known fact that reduction of nitrobenzene stops at the hydroxylamine stage in neutral solution throws light on option (a) above. In a mixture of hydrochloric acid and metallic fragments there is one location where the neutral state is attainable, namely just at the surface of the metal, where the content of acid has been largely eliminated by the metal itself. The more active the metal, the more thorough this neutralization of the interfacial layer of electrolyte. Substantial quantities of phenylhydroxylamine should then be formed from the droplets of nitrobenzene which reach this layer. Agitation now removes part of the hydroxylamine to regions which are out of reach of the additional metal needed to complete the reduction. Such outer regions, while devoid of metal, contain ample hydrochloric acid which promptly effects the Bamberger rearrangement to chloroaniline. Less active metals, like iron, are unable to maintain the neutral zone, and accordingly the complete reaction to aniline proceeds smoothly with iron and nitrobenzene as prime reagents in close contact. This agrees with the common industrial knowledge that iron will reduce nitrobenzene in the presence of much less than the equivalent amount of hydrochloric acid.

Confirmation of this hypothesis of reduced activity is seen not only in the relatively high chloroaniline yield from active metals, but also from the experiments with rotated metallic rods. With zinc the sharply reduced yields of 9 to 11% suggest that the neutral zone of electrolyte tends to be forcibly stripped off, admitting more of the nitrobenzene globules to the active metal surface in the presence of strong acid. Continuation of the rotating rod technique, and reduction of temperature with consequent reduction in activity of the metal, virtually transforms zinc into a metal comparable with tin at a higher temperature, and the resulting figures of 2.6 to 3.5% show the added advantage.

Alloying of tin with zinc has no significance beyond an interpolative effect, but addition of a noble metal (copper) to the zinc is another matter. In the latter case the usual coating of copper mud promptly forms, and the undesirable reaction $2H_3O^+ \rightarrow H_2$ gas $+ 2H_2O$ occurs on the surface of copper instead of zinc, as in the voltaic cell. It is thus reasonable to expect less tendency for a neutral solution to form at the surface of the zinc. Zinc is free to react directly with nitrobenzene, and the amine product is almost all aniline, as shown in the table.

Postulate (b) is a question of reaction time. If a nitrobenzene molecule, in contact with a moderately active metal, does not have time to get beyond the phenylhydroxylamine stage before a lively outburst of hydrogen gas pushes it away, chloroaniline would naturally result. It would not matter whether a zone of neutral solution had been present. Zinc and cadmium are good illustrations.

If now an extremely active metal be chosen, such as magnesium, postulate (b) might predict so vigorous an evolution of hydrogen that nitrobenzene could not

even reach the metal surface. No reduction would occur, as indeed experiments indicate. As a test of this reasoning, the usual nitrobenzene-acid mixture was chilled with solid carbon dioxide until the reaction with magnesium was greatly retarded. A slow, inefficient and incomplete reduction of nitrobenzene was then attained. The high chloroaniline yield (62–66%) suggests that the magnesium was forced to play a rôle more like that of zinc, and that a large fraction of the nitrobenzene molecules was unable to maintain contact with the metal long enough to get past the phenylhydroxylamine stage.

Postulate (a) operates counter to (b) in the experiment of reduction with motor-driven rods. Since the motor action in the case of zinc actually causes a *lowering* of chloroaniline content, one is inclined here to credit postulate (a). With tin, however, rotation causes *greater* chloroaniline content. Tin is relatively inactive, and is scarcely able to maintain a neutral zone. Accordingly one may well expect the operation of the motor would enhance chlorination by the mechanism of postulate (b). It must be admitted at least that neither (a) nor (b) alone will explain experimental results in general.

We wish to thank Messrs. S. Tierney, L. S. Trimble, and V. Morgan for assistance in laboratory tests of various methods.

SUMMARY

The formation of chloroaniline as a by-product in the preparation of aniline from nitrobenzene in the usual manner apparently varies directly with the rate of the wasteful reaction of metal with acid to yield hydrogen. This correlation is explained by assuming either that a zone of neutral solution is maintained at the surface of a more active metal, hindering complete reduction of the nitro group, or that the excessive output of hydrogen drives the nitrobenzene away before it is completely reduced. Incompletely reduced molecules are then rearranged to *p*-chloroaniline. Experimental data are given showing the great differences in yields of chloroaniline.

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[COMMUNICATION NO. 745 FROM THE KODAK RESEARCH LABORATORIES]

THE ACTION OF HEAT ON CERTAIN BROMONITRO COMPOUNDS

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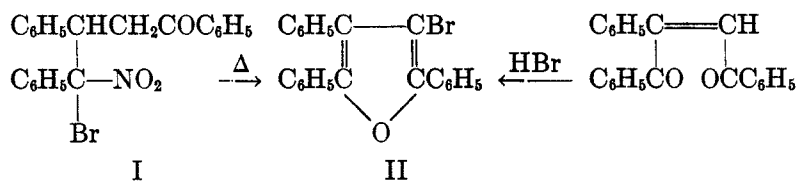
When either stereoisomeric form of γ-bromo-γ-nitro-β,γ-diphenylbutyrophenone (I) was heated slightly above the melting point, gas was evolved; the late Professor Kohler suggested to the senior author that a study of its decomposition would be of interest. In this paper are described the results secured when these and other bromonitro compounds are pyrolyzed.

Both forms of the nitro ketone (I) gave off a brown gas and yielded the same chemically inactive, white substance, $C_{22}H_{15}BrO$, formed by a loss of nitrogen dioxide and water. From the empirical formula and nonreactivity, it was assigned the structure, 2,3,5-triphenyl-4-bromofuran, (II) and the correctness of this was shown by



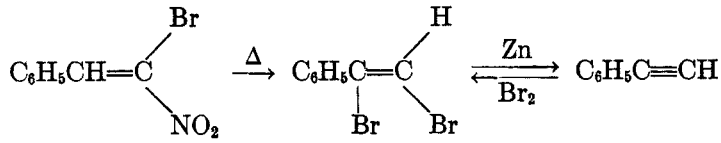
I II

a synthesis from α,β-dibenzoylstyrene and hydrogen bromide (1). In a similar manner homologs were secured from other corresponding bromonitro ketones.

γ-Nitro-β,γ-diphenylbutyrophenone (I, H for Br) also decomposes on heating, with evolution of oxides of nitrogen. The other products are benzaldehyde and benzalacetophenone. This decomposition is of an entirely different nature from that of the bromonitro ketone; the products are what one would expect if the nitro ketone dissociated into its components, phenylnitromethane and the unsaturated ketone, the former being the source of the aldehyde and oxides of nitrogen.

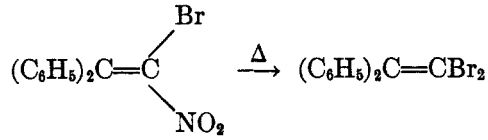
β-Bromo-β-nitrostyrene (III) was next submitted to pyrolysis. It, too, evolved nitrogen dioxide when heated above its melting point. In this case the reaction was not as clean, considerable carbonaceous matter being

formed, but the principal product was α,β-dibromostyrene, IV; there was also a small amount of benzoic acid. The structure of the dibromide (2) (IV) was shown by repeating Nef's procedure, namely, debromination with zinc dust to yield phenylacetylene and synthesis from the latter and bromine.



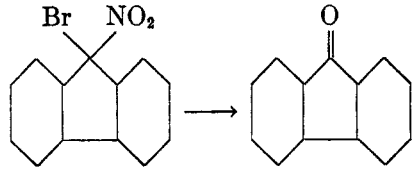
III IV

When β-bromo-β-nitro-α,α-diphenylethylene (V) was pyrolyzed, it gave β,β-dibromo-α,α-diphenylethylene (VI) as shown below. The latter was identified by comparison with a specimen secured by a known procedure (3).



V VI

A search of the literature revealed a few additional instances of the decomposition by heat of bromonitro compounds in which the bromine atom and the nitro group are on the same carbon atom. 9-Bromo-9-nitrofluorene (VII) yields fluorenone (4); several aryl bromonitrocyanomethanes yield

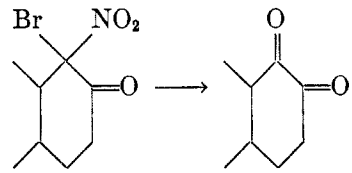


VII

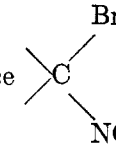
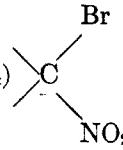
aroyl cyanides (5);

VIII

bromonitromalonic ester gives oxomalonic ester (6); polynuclear *o*-bromo-*o*-nitro ketones give *o*-quinones (7);



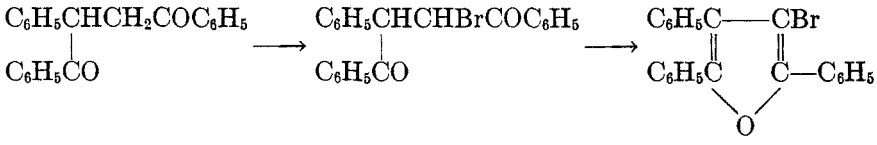
and a nitrobromo ketone (a) in the benzene series gives a toluquinone (8), (b) in the camphor series gives camphorquinone (9), and (c) in the pyrazolone series gives a pyrazoldione (10).

A considerable number of liquid halonitro compounds of the aliphatic series has been described, many of which decompose on distillation or cannot be distilled. The nature of the decomposition products has seldom been determined and no distinction has been made between bromine and nitrogen dioxide, both possible and both reddish-brown gases. A careful study of chloropicrin has shown that it slowly decomposes at its boiling point, and that the products are phosgene and nitrosyl chloride, $CCl_3NO_2 \rightarrow COCl_2 + NOCl$.[1] Even with bromonitroethane (VIII), which is recorded in the literature as distilling without decomposition, it has been found that during the distillation enough gas is evolved to color iodo-starch paper deeply, indicating the presence of nitrogen dioxide and/or bromine. It will be seen that in practically all the instances in which the nature of the products has been determined, the net result of the decomposition has been to replace  by  and that the formation of a ketone "appears to be characteristic for secondarily bound groups (4)  ". That this conclusion cannot be wholly correct is evident from the variety of examples described in this paper.

The formation of the bromofuran (II) from the bromonitroketone (I) would, at first sight, seem to be of an entirely different nature. One would

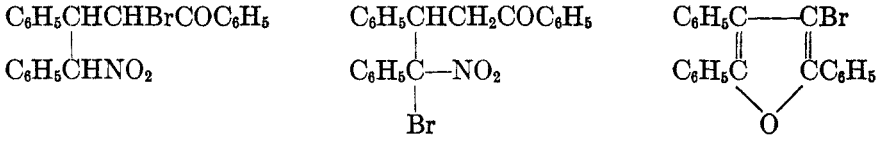
[1] Gardner and Fox, *J. Chem. Soc.*, **115**, 1189 (1919). The nitrosyl chloride was not identified, but the gases evolved passed through concentrated sulfuric acid to absorb nitric oxide. "Hydrogen chloride was either allowed to escape or in some experiments collected in copper sulfate solution."

expect to find desylacetophenone (IX). However, it has been shown (11) that when desylacetophenone is brominated, the only product is triphenylbromofuran (II), except under special experimental conditions. Thus, the production of the bromofuran would be expected if the intermediate step of the pyrolysis were the ketone IX, and it may be safely assumed that the reaction proceeds in this manner. On comparison of the formulas



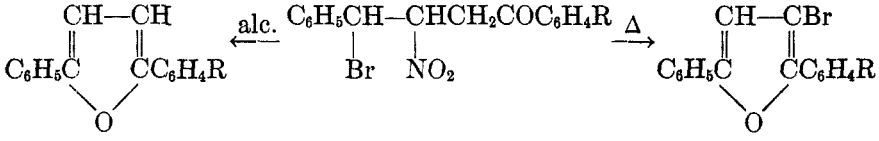
IX II

I and II, it will be noted that in the bromofuran the bromine atom appears in combination with the carbon atom that was alpha to the carbonyl group in the bromonitro ketone. This might seem to indicate that the bromine was always there and never in the gamma position. Other evidence excludes this possibility. The bromonitro ketone was secured by bromination of the nitro ketone in the form of its sodium derivative; it has been shown by Hantzsch (12) that in aliphatic nitro compounds only the hydrogen atom in the alpha position to the nitro group is replaced by bromine when the salt of the *aci*-nitro compound is so treated. Further, the four possible stereoisomeric α-bromo-γ-nitro ketones (XII) are all known and different in melting points and reactions (13).



XII I II

A few other instances of the formation of 4-bromofurans by heating bromonitro ketones (X) are known; these ketones are of a different type, however. In boiling alcoholic solution they give the unbrominated furans



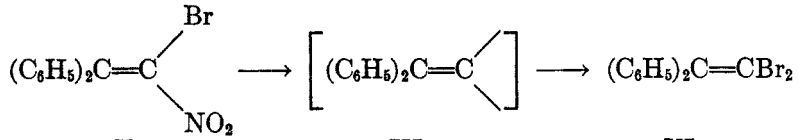
X

(14), which may indicate that ring closure precedes bromination during the pyrolysis. However, this reaction is not strictly parallel to the one under discussion. The formation of 2,5-diphenyl-3-bromo- and -3,4-dibromo-

furans by heating an acetic acid solution of γ-bromo-γ-nitro-γ-phenylbutyrophenone is readily accounted for by the mechanism proposed for the triphenylbromofuran II.

The ethylenic bromonitro compounds, III and V, fall into a different category. If the pyrolysis took the same course, ketenes or their reaction products (e.g., diphenylacetic acid) should result. There is no evidence that such is the case, since none of the anticipated substances was found. Their non-isolation, however, is inconclusive, as the decompositions were not quantitative, and there was in these instances a considerable amount of tar.

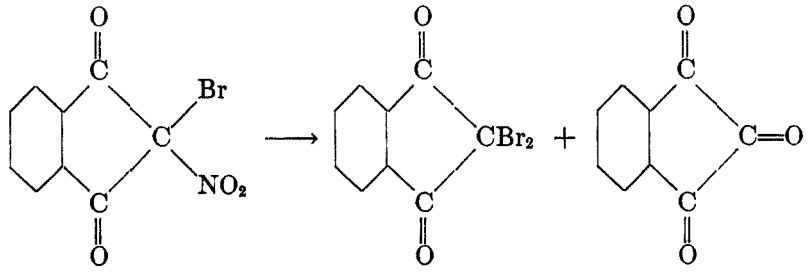
The assumption of the transitory existence of a bivalent free radical during the pyrolysis enables one to account for the products in a more satisfactory manner. Thus, the diphenylbromonitroethylene (V) would yield radical XI; the latter might combine with either the bromine or oxygen present. Addition of the former would yield the dibromide (VI) actually found, whereas oxygen should give diphenylketene. If this



V XI VI

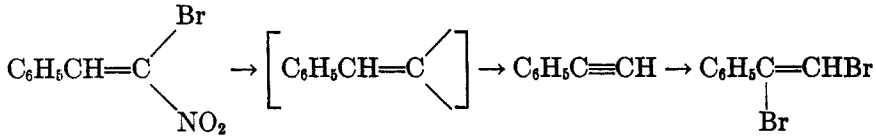
mechanism were applied to 9-bromo-9-nitrofluorene, one might expect to isolate the known 9,9-dibromofluorene, whereas fluorenone is actually obtained. Further, 9-nitrofluorene pyrolyzes to fluorenone (4) which may indicate that oxidation rather than bromination occurs with the saturated bromonitro compounds.

2-Bromo-2-nitroindandion-1,2 (XIX) and the 2-chloro analog decompose when heated; in this instance not only is the expected ketone ninhydrin (XX) formed (15), but also a larger amount of 2,2-dibromoindandion-1,3 (XXI), the combined yields accounting for nearly all of the starting material. These results would lead one to prefer the mechanism involved in the intermediate formation of a bivalent radical, which then combines with either bromine or oxygen, or both, as in this example.



XIX XXI XX

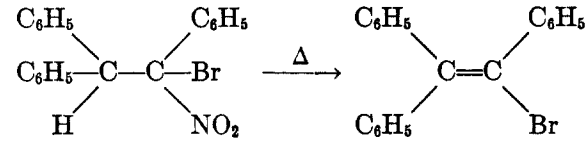
In the case of the bromonitrostyrene (III), the intermediate radical would undoubtedly be even less stable, since it has a hydrogen atom that could rearrange to yield a more stable form, phenylacetylene. The addition of bromine to this would furnish the dibromostyrene actually found and also independently synthesized by this very reaction.



III IV

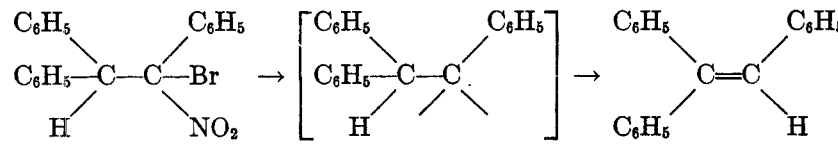
β,β-Dibromo-α,α-diphenylethylene (VI) is unchanged at the temperature of the pyrolysis; this may indicate that the bromine adds to the bivalent radical (XI) before it has time to rearrange, i.e., that a phenyl group migrates less readily than a hydrogen atom. When this dibromo derivative is heated in boiling benzene with metallic sodium, it loses the bromine and tolane results (26), showing that the radical is capable of rearrangement. Tolane has also been secured from the monobromodiphenylethylene by the action of sodium hydroxide at high temperature (16). Since the monobromide undergoes a Wurtz synthesis, a reaction that is known to proceed *via* radicals, it is evident that a fragment of this type is capable of transitory existence; hence, there is sufficient basis for the assumptions above as to the nature of the intermediates in the pyrolysis reaction.

When 1,1,2-triphenyl-2-bromo-2-nitroethane (XIII) is heated, the product is bromotriphenylethylene (XIV) (17). This behavior is different from that of all the other bromonitro compounds. The authors explain



XIII XIV

it as a simple loss of HNO_2. However, it can be accounted for by the bivalent radical mechanism following a sequence of reactions similar to that for bromonitrostyrene. The radical XV has an available hydrogen



XIII XV XVI

for rearrangement and the rearranged product, XVI, might be easily brominated to XIV.

If bivalent radicals of this nature were intermediary in the case of the bromonitro ketones, the products anticipated would be of an entirely different nature from those actually found. Hence, this mechanism, if correct, is only of limited application.

In view of the many above instances, it would seem that "the transformation of phenylbromocyanonitromethane into its metabromo isomeride" is not a "case of intramolecular meta migration" (27) but a bromination, the bromine coming from the decomposition of a second molecule.

EXPERIMENTAL

A. Bromonitro ketone series.—The general procedure for securing the γ-nitro ketones was as follows: a mixture of 2 g. of phenylnitromethane, an equivalent quantity of unsaturated ketone, and 17 cc. of methanol was made alkaline with concentrated sodium methoxide; an immediate white precipitate formed—this usually

TABLE I

PROPERTIES OF ADDITION PRODUCTS

NO.	NITRO KETONE γ-NITRO-β,γ-DIPHENYL-	M.P., °C.	FORMULA	CALC'D %		FOUND %	
				Br	N	Br	N
XXIII	-4-Chloro-butyrophenone	171	$C_{22}H_{18}ClNO_3$		3.7		3.6
XXIV	-4-Chloro-butyrophenone	116	"		3.7		3.7
XXV	-2-Methyl-5-i-propylbutyrophenone	147	$C_{26}H_{27}NO_3$		3.5		3.4
XXVI	-4-Phenylbutyrophenone	180	$C_{28}H_{23}NO_3$		3.3		3.3
XXVII	-4-Bromobutyrophenone	180	$C_{22}H_{18}BrNO_3$	18.9		18.6	
XXVIII	-4-Bromobutyrophenone	125	"	18.9		18.7	

gradually dissolved with refluxing. After an hour, or sooner, if the flask contents solidified, the whole was acidified with 3 cc. of acetic acid in 17 cc. of methanol. After boiling for 5 minutes and cooling, the addition products were triturated and filtered. When the stereoisomers were separated, the high-melting form crystallized first, in yields of 60–80%; the yield of the low-melting form, which was slowly deposited from the filtrate, was 5–15%. γ-Nitro-β,γ-diphenylbutyrophenone (13), the *p*-methoxy (18) and one stereoisomeric form of the *p*-bromo (19) homologs have already been described. The properties of the other addition products are collected in Table I.

Since benzal-4-phenylacetophenone was insoluble in hot methanol, the reaction was carried out in 25 cc. of dioxane, and the solvent evaporated on the steam-bath.

The bromonitro ketones (I) were prepared by suspending 3 g. of the addition product in 40 cc. of hot methanol, adding slightly over one equivalent of concentrated sodium methoxide, and stirring until dissolved; an excess of methoxide was avoided. The solution was then chilled in ice-water and bromine was added until a permanent color resulted; after standing for some time sodium bromide separated. Water

(15 cc.) was added, the whole shaken vigorously, and the excess bromine removed by a little sodium bisulfite. The crude bromination product was filtered and washed with methanol; the yield was practically quantitative. Recrystallization was from chloroform-methanol. In most instances the mixture of stereoisomers was used for pyrolysis. Two have been described previously (13, 18). γ-Nitro-γ-bromo-β, γ-diphenylbutyro-(4-chloro)-phenone, m.p. 126° (XXIX), γ-nitro-γ-bromo-β,γ-diphenylbutyro-(4-bromo)-phenone, m.p. 157° (XXX), and γ-nitro-γ-bromo-β,γ-diphenylbutyro-(2-methyl-5-i-propyl)-phenone, m.p. 138° (XXXV) are new.

Anal. Calc'd for $C_{22}H_{17}BrClNO_3$ (XXIX): N, 3.1; for $C_{22}H_{17}Br_2NO_3$ (XXX): Br, 31.8; for $C_{26}H_{26}BrNO_3$ (XXXV): N, 2.9.

Found: (XXIX) N, 2.8; (XXX) Br, 31.5, 31.6; (XXXV) N, 2.7.

Pyrolysis.—The bromonitro ketone (20 g.) was heated in a wide-mouthed flask at 180–200° as long as gases were evolved (15–20 minutes). If pyrolysis was in a closed system, the brown gas at first given off soon became colorless, but was re-oxidized to nitrogen dioxide when air was blown through. A few water-drops collected and an odor similar to benzonitrile was noted. The cooled melt was dissolved in chloroform and filtered into 3 volumes of methanol; the bromofuran soon separated in rosettes of needles. The yields were 60–70%, being much lower when air was

TABLE II

NO.	GROUP IN POSITION 5	M.P., °C.	FORMULA	ANALYSES					
				Calc'd %			Found* %		
				C	H	Br	C	H	Br
II	Phenyl	129	$C_{22}H_{15}BrO$	70.4	4.0	21.4	70.1	4.0	22.0
XXXI	4-Xenyl	193	$C_{28}H_{19}BrO$			17.7			17.4
XXXII	4-Bromophenyl	157	$C_{22}H_{14}Br_2O$			35.2			35.1, 35.3

* These substances were very difficult to burn, or destroy by fuming nitric acid.

excluded during the pyrolysis. In one instance a trace of benzoic acid was isolated. Three of the bromofurans have been described previously (1); the properties of the others are collected in Table II. Whenever possible the identity was assured by comparison with the original specimens and mixed melting points (4-chloro, 4-bromo, 4-methoxy). Both stereoisomeric forms of the bromonitro ketones gave the same furan in the same yield. 2,3-Diphenyl-5-(4′-xenyl)-4-bromofuran (XXXI) was also synthesized from the corresponding dibenzoylstyrene (1).

B. Bromonitrostyrene series.—The pyrolysis of β-bromo-β-nitrostyrene (20) was carried out in the same manner, at 190–200°; when gas was no longer evolved, the liquid was distilled, leaving a considerable carbonaceous residue. The distillate (3 g. from 5 g. of the styrene) had an odor resembling benzonitrile, and contained small amounts of benzoic acid. On redistillation the greater portion was found to be α,β-dibromostyrene, b.p. 253–4°.

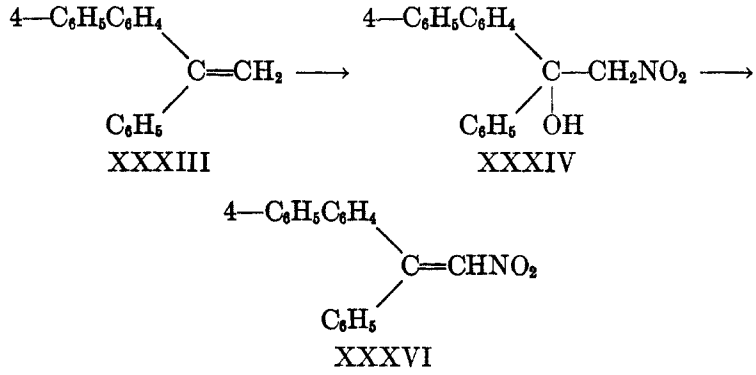
Anal. Calc'd for $C_8H_6Br_2$: C, 36.6; H, 2.3. Found: C, 36.2; H, 2.4.

When 75 g. of the bromonitrostyrene was submitted to pyrolysis, 29 g. of crude dibromostyrene and 1.3 g. of benzoic acid were obtained; 2.5 g. of the starting material was recovered. It was not possible to isolate or identify benzonitrile from any fraction of the distillate.

The bromine was removed from the dibromostyrene by zinc, following Nef's

procedure (2), and the phenylacetylene converted into the characteristic bright yellow copper derivative. A portion of the dibromostyrene was oxidized to benzoic acid by potassium permanganate, showing that no bromine had entered the nucleus.

C. Diphenylethylene series.—The necessary β-nitro-α,α-diphenylethylene was secured by Lipp's procedure (21); though the yields were erratic (48–57%), the method proved to be consistently better than the apparently simpler methods (22). β-Nitro-α-phenyl-α-(4-xenyl)ethylene (XXXVI) was obtained as follows:



Six grams of the hydrocarbon XXXIII (23) in 35 cc. of carbon tetrachloride was chilled to −10–0°, and the gases, generated by dropping concentrated sulfuric acid upon solid sodium nitrite and dried by phosphorus pentoxide, were passed through for 4 hours. The temperature was not allowed to rise above 0°. The solution was then washed with 25 cc. of water, dried with calcium chloride, and the solvent allowed to evaporate spontaneously. The resulting semi-solid mass was triturated with ether-petroleum ether, and filtered. The carbinol XXXIV separated from ether, on dilution with petroleum ether, in fine white needles, m.p. 136°.

Anal. Calc'd for $C_{20}H_{17}NO_3$: N, 4.4. Found: N, 4.3.

The solvent was evaporated from the residual solution from the isolation of the above carbinol, and the gum taken up in 25 cc. of acetyl chloride. After refluxing for an hour, the mixture was decomposed by iced sodium carbonate, the sticky, insoluble product taken up in ether and dried by potassium carbonate. Petroleum ether was then added to incipient cloudiness; on chilling, yellow crystals of the nitroethylene (XXXVI) separated. They crystallized from petroleum ether or methanol in fine prisms, m.p. 134°. The filtrate deposited a mixture of both possible geometrical isomers, which was separated mechanically; the low-melting form crystallized in needles, m.p. 114°.

Anal. Calc'd for $C_{20}H_{15}NO_2$: C, 79.7; H, 5.0; N, 4.7.
Found: (134°) C, 79.6; H, 5.1; N, 4.4; (114°) C, 79.8; H, 5.3; N, 4.7.

That the nitro group was not on one of the aromatic nuclei was shown by oxidation of the unsaturated nitro compound to the known phenyl-4-xenyl ketone, by refluxing an acetone solution with excess potassium permanganate for 15 minutes, destroying unused oxidizing agent by alcohol, filtering, evaporating, and recrystallizing the ketone from methanol; the melting point was 101°, and was not depressed on admixture with an authentic specimen (24).

β-Bromo-β-nitro-α,α-diphenylethylene (*V*).—Three lots, of 5.1 g. each of β-nitro-α,α-diphenylethylene (XXII) were dissolved separately in 10 cc. of chloroform, and 5 g. of bromine in 10 cc. of the same solvent added. There was no immediate

action, but after several hours hydrogen bromide was slowly given off. After 24 hours, the solutions were combined, unused bromine was removed by sodium bisulfite solution, and the solvent was evaporated from the washed and dried (sodium sulfate) solution. The residue was taken up in methanol, and, on addition of water to incipient crystallization, 14 g. of yellow prisms separated. Purification from methanol gave 9 g. (43%) of pure compound, m.p. 91°.

Anal. Calc'd for $C_{14}H_{10}BrNO_2$: N, 26.3; Br, 4.6. Found: N, 26.0; Br, 4.7.

Pyrolysis.—The procedure was, in general, the same as with the other bromonitro compounds. Gas bubbles first appeared at 145–150°, and the highest temperature of the bath was 300°; 8 g. of substance lost 1 g. in weight. The residue was removed by ether and methanol, and steam-distilled; only 0.2 g. of product was carried over while 2 liters of water was being collected. The residual mixture was extracted with ether, and this solvent replaced by methanol; the latter was treated with Darco and the filtrate diluted by 1 cc. of water. On standing for some time, 1.5 g. of the dibromoethylene (VI) was obtained as fine, white needles, m.p. 83.5°.

Anal. Calc'd for $C_{14}H_{10}Br_2$: Br, 47.3. Found: Br, 47.3, 47.4.

It was compared with an authentic sample secured by the directions of Goldschmiedt (3); the melting points and mixed melting points were 83.5°.

Pyrolysis of γ-Nitro-β,γ-diphenylbutyrophenone.—The nitro ketone (3.5 g.) was heated in an oil bath in the same manner as described under the bromonitro compounds; oxides of nitrogen, and steam, were given off. After one hour, the cooled melt was taken up in alcohol-chloroform, and treated with Darco and Norit. The oil that remained after evaporation of the solvent smelled strongly of benzaldehyde; since it failed to crystallize, the aldehyde was removed by steam distillation. The oily residue was removed, a portion dissolved in methanol and converted into the 2,4-dinitrophenylhydrazone of benzalacetophenone (25), m.p. 245°.

α-Bromo-α-nitroethane.—There is no mention in the literature of any decomposition of this substance during distillation. However, when 8 g. was distilled in the ordinary manner, using a water condenser, starch-iodide paper was turned deep blue, even at the outlet of the receiving flask, throughout the distillation. This indicated that decomposition was occurring.

SUMMARY

1. Pyrolysis of γ-bromo-γ-nitro ketones yields bromofurans.

2. With ethylenic bromonitro compounds, the products are α,β- or β,β-dibromostyrenes.

3. Mechanisms have been proposed to account for both reactions.

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THE RELATION BETWEEN THE ABSORPTION SPECTRA AND THE CHEMICAL CONSTITUTION OF DYES. XV. THE INFLUENCE OF SULFONIC ACID GROUPS IN AMINOAZO DYES.

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Absorption spectra studies of monoazo dyes (1) have been extended to simple aminoazo dyes sulfonated in one or both of the aryl nuclei. The dyes chosen for this study were those normally obtained by coupling benzenediazonium chloride and its three monosulfonic acid derivatives to 1- and 2-naphthylamine and their monosulfonic acids. Of the forty-eight dyes prepared and studied, thirty-six are listed together with their structural formulas in Figures I and II. The twelve dyes omitted from

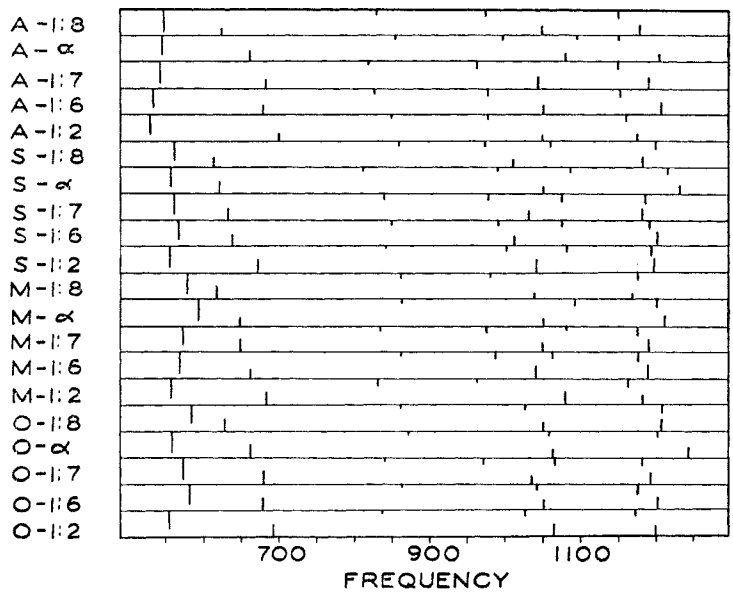


FIGURE I. FREQUENCIES OF THE PRINCIPAL MAXIMA OF DYES OF TYPE I

In Figures I and II the lengths of the lines are relative measures of the intensities of the maxima which they represent. Lines pointing upward represent neutral maxima; suspended lines represent acid maxima. A, S, M, and O indicate aniline, sulfanilic, metanilic, and orthanilic acids diazotized and coupled to *alpha-* or *beta-*naphthylamine (α or β) and the indicated sulfonated *alpha-* and *beta-*naphthylamines (1:2, 2:3, etc.).

this listing are those prepared by the coupling of the indicated benzene intermediate to the 3-, 4-, and 5-monosulfonated *alpha*-naphthylamines, where coupling takes place in the 2 position. The coupling of the dyes listed in Figure I is in the 4 position.

These dyes were prepared in the usual manner from purified intermediates.[1] The dyes containing two sulfonic acid groups were purified by the diphenyl guanidine method of Rose (2). The remainder were purified by recrystallization from appropriate solvents. All of the sulfonated dyes were obtained as their sodium salts.

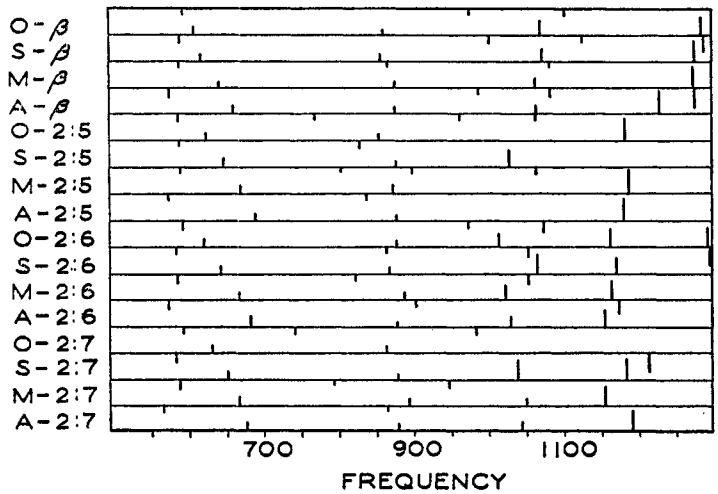


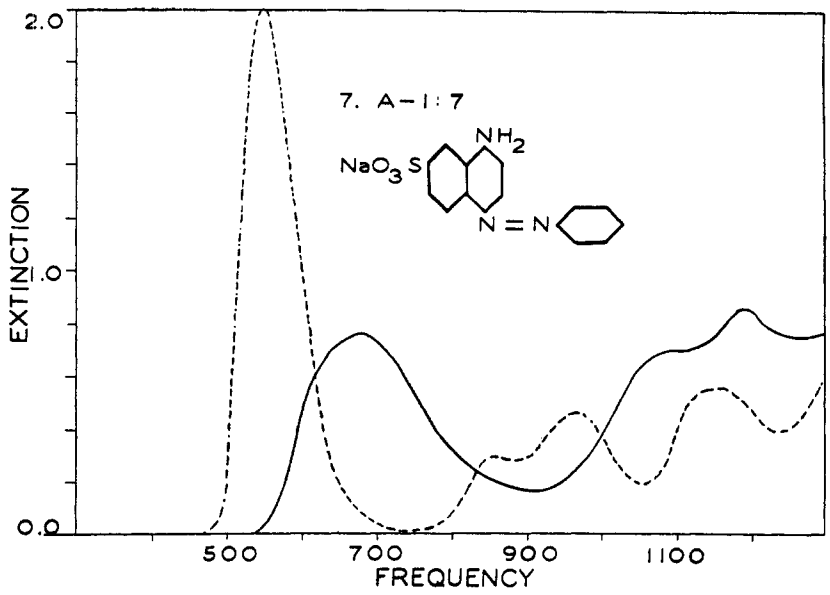
FIGURE II. FREQUENCIES OF THE PRINCIPAL MAXIMA OF TYPE III DYES, SHOWING THE EFFECT OF VARYING THE POSITION OF SULFONIC ACID GROUP SUBSTITUTION IN THE BENZENE NUCLEUS

The absorption spectra measurements were made with a Bausch and Lomb spectrophotometer in the visible range, and with a Hilger sector photometer and Bausch and Lomb spectrograph in the ultraviolet, according to methods already described (1a). Only two solvents, hydrochloric acid and water, were used. The concentration of acid was chosen to bring out the full acid color.

GENERAL DESCRIPTION OF CURVES

In this series of dyes the relationship between azo and amino groups produces three different dye types, namely: Type I, derivatives of 1-naphthylamine-4-azo-

[1] Part of the intermediates were donated by the Jackson Laboratory of E. I. duPont de Nemours & Co., Inc. of Wilmington, Del.



FIGURES III to VIII, inclusive, are representative samples of the three dye-types. The solid lines in each case represent neutral absorption curves, the broken lines acid absorption curves. Both acid and neutral curves represent dye concentrations of 1×10^{-4} mole per liter, and a cell thickness of 0.5 cm.

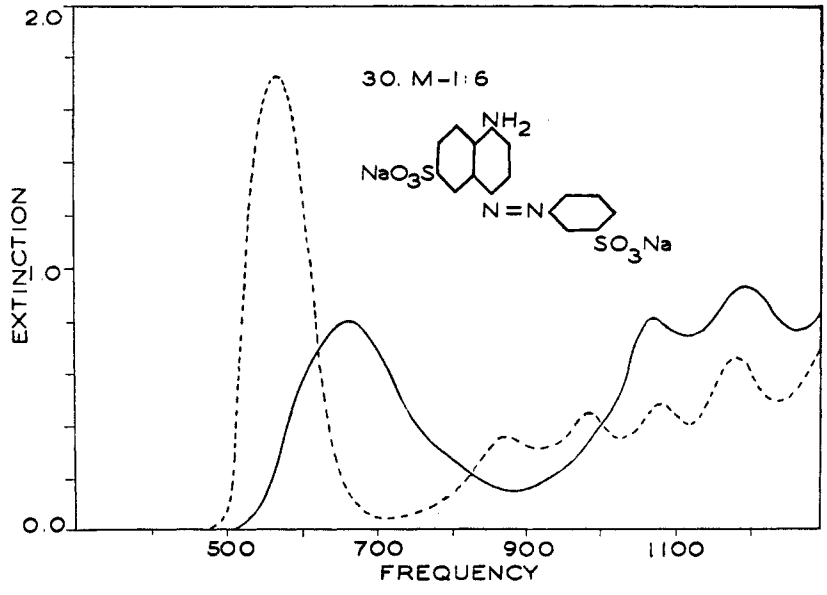


FIGURE 4

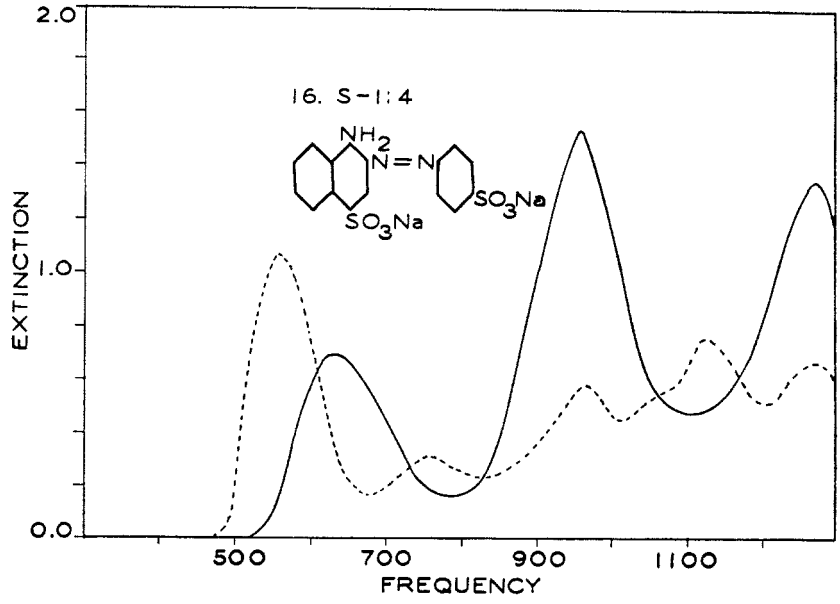


FIGURE 5

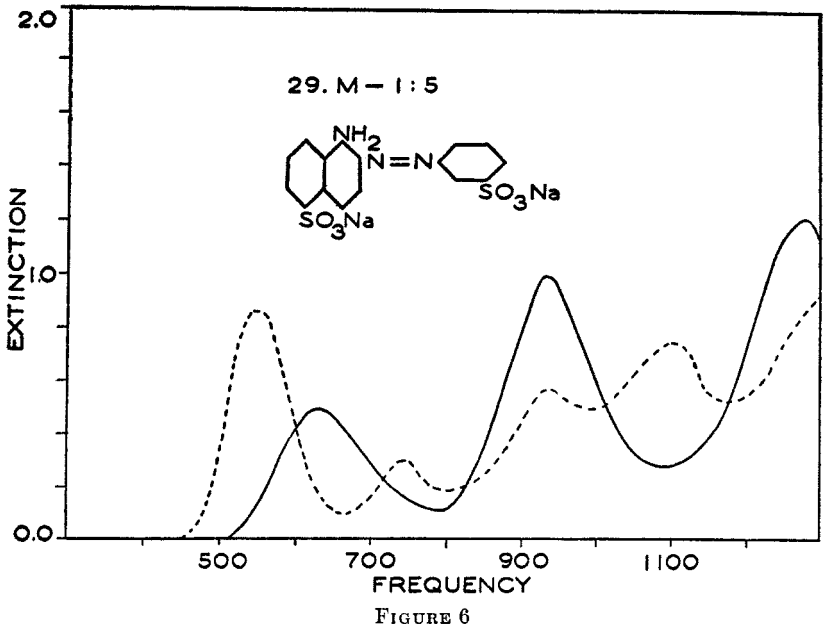


FIGURE 6

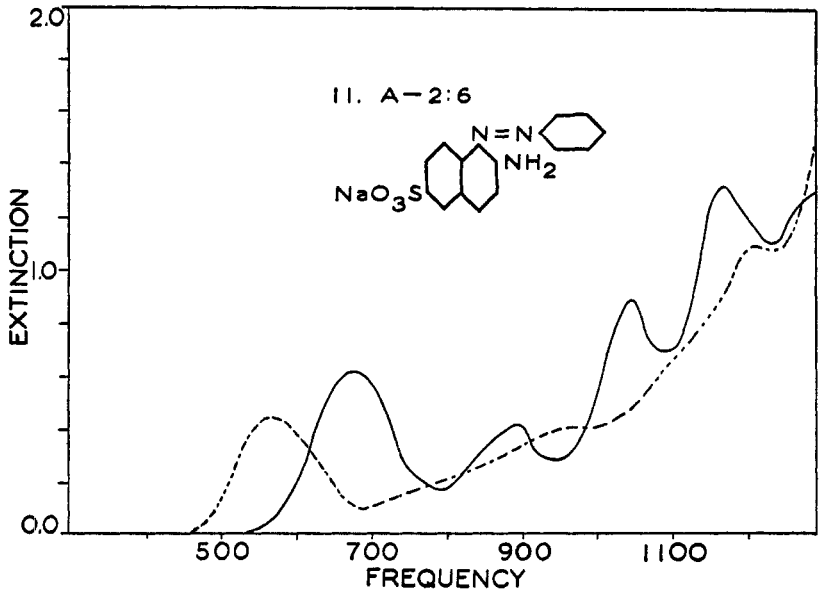


FIGURE 7

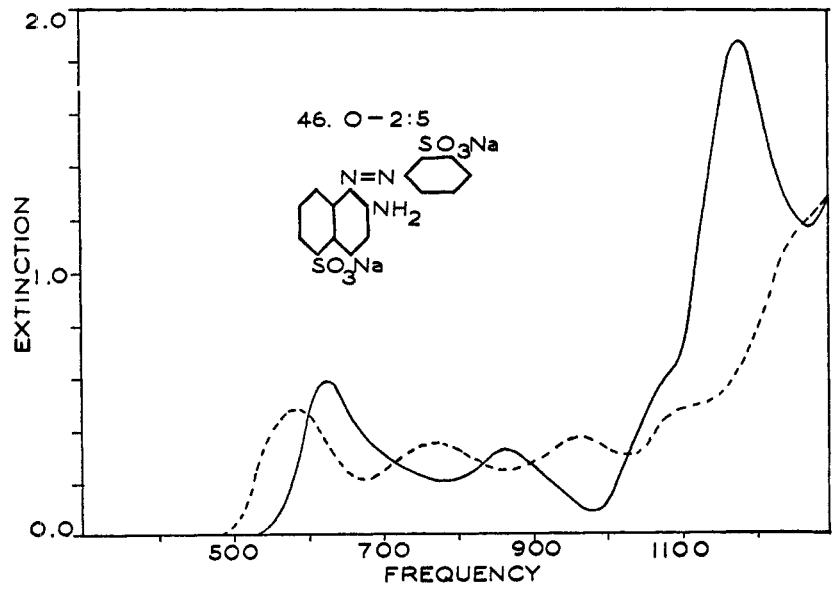
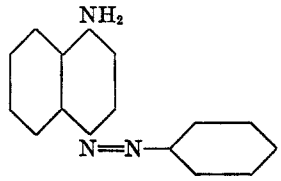
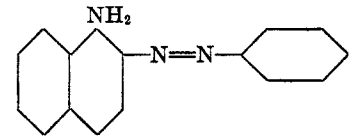


FIGURE 8

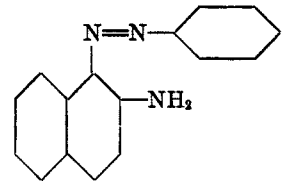
benzene; Type II, derivatives of 1-naphthylamine-2-azobenzene; and Type III, derivatives of 2-naphthylamine-1-azobenzene.



Type I



Type II



Type III

The absorption spectra curves of the dyes of any particular type are quite different from those of dyes of either of the other types. Dyes of Type I are characterized by their rather intense absorption in the visible and near visible range as compared to that in the ultraviolet. Shift to acid solvent increases the intensity of this primary band several fold over that of the same band in neutral solvent. Change of solvent has comparatively little effect on the intensities of the primary bands of the other dye types. Dyes of Type II show in both solvents more absorption in the ultraviolet than those of Type I, the neutral curves being characterized by three intense and well separated bands. Dyes of Type III show weak primary bands in both solvents, while farther into the ultraviolet the absorption rapidly increases until, in the frequency range beyond 1000 fresnels, the absorption becomes intense and general in character. Examples of these curves are given in Figures III to VIII.

DISCUSSION OF DATA

From a study of the charts of absorption maxima (Figures I and II) and of the curves themselves, it is evident that the substitution of a sulfonic acid group in a simple azo dye has, in general, considerable effect on the position of absorption bands, and that the nature and magnitude of this effect is influenced by the position of attachment and substitution. Thus, in dyes of Type I, introduction of a sulfonic acid group into the naphthalene nucleus at position 8 produces a pronounced bathochromic effect (absorption shifted towards red) while substitution in position 2 produces as strong a hypsochromic effect (absorption shifted towards blue). Substitution in positions 6 and 7 is moderately hypsochromic. In Type II dyes, the order of decreasing bathochromic effect is positions 5, 4, and 3. The unsubstituted parent dye of Type II was not available for study. The substituted dyes of Type III are all distinctly hypsochromic with respect to the parent dye, the 5 position averaging the highest frequency with 6 and 7 positions intermediate and of about equal value. Substitution of sulfonic acid groups in the diazo component invariably produced bathochromic effects, the magnitude of these effects again depending upon which dye type undergoes substitution. A para substitution in dyes of Types I and II

produces the greatest bathochromic effect with meta second and ortho least, although dyes from 1-naphthylamine-3- and 1-naphthylamine-4-sulfonic acids show but slight change as the sulfonic group is rotated about the benzene nucleus. Type III dyes show effects markedly different from those exhibited in Types I and II. The order of decreasing bathochromic effect is ortho, para, and meta with the bands distinctly and evenly separated.

Meuly (3) and Dinner (4) have investigated the absorption spectra in the visible only of a large number of sulfonated disazo and trisazo dyes. They found that the introduction of sulfonic acid groups produced a bathochromic effect. Para substitution was more effective than either ortho or meta. The lack of agreement between their results and the data herein reported may be due to the very strong effects of the additional azo groups in their dyes. They also reported that shift to acid solvent reversed the order of effect, that is, substitution of sulfonic acid groups produced hypsochromic rather than bathochromic effects. This effect was found to be but partially true with our simpler dyes. In general, dyes of Type I showed this reversal of trend. Dyes from 1-naphthylamine-8-sulfonic acid are more bathochromic in neutral solution but a change to acid solution shifts the frequency a relatively small amount. On the other hand, dyes from 1-naphthylamine-2-sulfonic acid are less bathochromic in neutral solvent but the frequency shift is very large, making them the more bathochromic in acid solution. The other dye types show in general the same frequency trends in both solvents. However, this reversal of trend is again exhibited when dyes differing only in the position of substitution in the diazo component are compared, the dyes derived from aniline being more hypsochromic in neutral solvent and more bathochromic in acid solvent. The effects just discussed have concerned the primary band in the visible only. However, extension to a consideration of the bands in the ultraviolet shows that many of the same effects are also produced there. The close proximity of various bands in this region prevents the exact determination of the positions of their maxima, so that relationships are less evident.

The intensities of the primary absorption bands show the same general relationships as their frequencies. The intensity variations are greater in acid medium than in neutral. In the latter medium, dyes from 1-naphthylamine-8-sulfonic acid as the second component show the greatest average absorption intensities of the entire group. Shift to acid increases the intensities of the bands of dyes of Type I, the 1,8 derivative again showing the least increase. Dyes from sulfanilic acid and from orthanilic acid produce the greatest intensity of color.

In an earlier paper in this series (1c) it was pointed out that for simple benzeneazophenol dyes there appeared to be a definite mathematical relationship between the frequencies of the observed bands in a given solvent. Dyes of Type II (-2-azo-1-naphthylamine) exhibit in water three well-separated bands which appear to be multiples of two times, three times, and four times a fundamental frequency of 310 to 330 fresnels. Other absorption curves do not show such good agreement, possibly in part because of the difficulty of accurately locating bands which are influenced by closely adjacent bands.

SUMMARY

A spectrophotometric study has been made of forty-eight dyes of the benzeneazo-1- and benzeneazo-2-naphthylamine series containing not more than one sulfonic acid group in each of the aryl nuclei. The data obtained permit the following conclusions.

Introduction of a sulfonic acid group into an aminoazo dye of the type studied has a definite effect upon its absorption spectra. The nature of this effect is dependent upon both the position of entrance of such a group and the position of the azo group with respect to the amino group.

Sulfonic acid groups introduced into the naphthylamine component usually produce a hypsochromic effect which is greatest for dyes from 1-naphthylamine-2-sulfonic acid. Only dyes from 1-naphthylamine-8-sulfonic acid are bathochromic. Introduction of sulfonic acid groups into the diazo component produces only bathochromic effects which are greatest for para substitution, least for ortho, and intermediate for meta, except when the second component is a derivative of 2-naphthylamine, in which case the ortho shows the greatest influence and meta the least.

Change of solvent from neutral to acid produces a nearly complete reversal of frequency trend for dyes of the 1-naphthylamine-4-azo type but not for dyes of either the 1-naphthylamine-2-azo or the 2-naphthylamine-1-azo types. For the diazo component, the frequency trend is reversed with change of solvent. The greatest decrease in frequency occurs with dyes from 1-naphthylamine-2-sulfonic acid on the basis of the second component and from aniline on the basis of the diazo component.

Intensity of absorption follows the same general trends as frequency. Substitution in the 8 position in the naphthalene nucleus and in the 4 or para position in the benzene nucleus produces the greatest intensity.

The dyes derived from 1-naphthylamine-2-azobenzene exhibit absorption curves in neutral solution in which the frequencies of the three principal maxima are consistently two, three, and four times that of a fundamental frequency of 310 to 330 fresnels.

COLUMBUS, O.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

RELATION BETWEEN CHAIN LENGTH AND ORIENTATION IN THE ACYLATION OF PHENOL

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Although considerable work has been done upon the acylation of phenol, the question of the influence of the length of the hydrocarbon chain of the acylating agent upon orientation has not been systematically studied. Auwers and Mauss (1) state that the Friedel–Crafts acylation of most phenols gives *p*-acyl phenols. Nencki and Stoeber (2), and Coulthard, Marshall and Pyman (3) reported a 2% yield of *o*-hydroxyacetophenone and 7% of *p*-hydroxyacetophenone by the action of glacial acetic acid upon phenol in the presence of zinc chloride.

The work of Skraup and Poller (4), and later of Cox (5), suggests that a correlation exists between the Fries rearrangement of phenolic esters to hydroxy aromatic ketones and the Friedel–Crafts reaction of acyl chlorides with phenol. These authors contend that the mechanism of the Fries rearrangement is a scission of the ester to yield the acyl chloride, in which case the reaction is quite correlated to a Friedel–Crafts acylation. This contention finds support in the work of Rosenmund and Schnurr (6) who stated that in many instances the synthesis of ketones from phenols occurs with an initial formation of the phenyl esters.

Since there is strong evidence in support of the belief that the mechanism of the Fries rearrangement is a cleavage followed by an acylation, the relative yields of isomers reported for the rearrangement of the phenyl esters should approximate those obtained in the acylation of phenol. Hartung, Munch, Miller and Crossley (7) studied the action of aluminum chloride upon phenyl propionate. These investigators reported a 33.2% yield of *o*-hydroxypropiophenone and a 45.8% yield of *p*-hydroxypropiophenone from this reaction. Coulthard, Marshall and Pyman (3) reported a 60% yield of *o*-*n*-butyryl phenol and a 19% yield of *p*-*n*-butyryl phenol by the action of aluminum chloride upon phenyl butyrate. They also reported a 50% yield of *o*-*n*-hexoyl phenol and a 58% yield of *o*-*n*-heptoyl phenol by the action of aluminum chloride upon phenyl hexoate and phenyl heptoate, respectively. No mention was made of the yield of the para isomer which was obtained in either of these examples. Edkins and Linnell (8) obtained a 40.4% yield of *p*-hydroxyacetophenone by the action of aluminum chloride upon phenyl acetate. In their study of the Fries

isomerization of the fatty acid esters of *m*-cresol, Baltzly and Bass (9) reported that the formation of the *o*-hydroxy ketones greatly exceeded that of the para isomers and that this tendency becomes more marked with the esters of the higher acids. These authors stated that the nature of the migrating group exercises a constant effect, and that larger groups tend to go to the ortho position. This is modified, however, by the statement that this effect is small when compared to the effect of the structure of the phenol and the temperature of the reaction.

A consideration of the previous work shows that very little has been done concerning the influence of the chain length of the acylating agent upon orientation in the Friedel–Crafts reaction of acid chlorides upon phenol. The data upon the influence of the chain length upon orientation in the Fries isomerization are somewhat more complete but in both reactions the observations have not been extended over a sufficient range.

The question whether the Friedel–Crafts reaction and the Fries isomerization yield similar products as regards the relative proportion of isomers formed has not been answered. It is the purpose of this study to determine the influence of the chain length of the acylating agent upon the orientation in the Friedel–Crafts reaction between phenol and acyl halides, and also to determine whether the directing influence of the chain length of the acyl group in the Fries isomerization and the Friedel–Crafts reaction is similar. If the products are found to be similar it lends weight to the belief that both reactions involve acylation by acyl halides. This paper reports the first part of this work, namely, the determination of the influence of the chain length of the acylating agent upon orientation in the Friedel–Crafts acylation of phenol. The work comparing the Friedel–Crafts reaction and the Fries isomerization is now under way and will be reported at a later date.

In summarizing the earlier work, it appears that the para position is favored in the Friedel–Crafts acylation of phenol with acyl chlorides of low molecular weight. As the molecular weight of the acylating agent increases there is evidence supporting the belief that the tendency towards the formation of the ortho isomer is substantially increased. In this work we have studied the acylation of phenol with caprylyl, lauroyl, myristoyl, palmitoyl, and stearoyl chlorides. The isomers were separated by the method employed by Baltzly and Bass (9), which method depends upon the preferential solubility of the para isomers in alkaline solutions. Identification of the para isomers was made by oxidation of the ketones with nitric acid. A number of oxidizing agents such as alkaline permanganate, chromic acid, etc., were investigated but were found to be unsatisfactory.

The data presented in Table I show that the total yield of ketone is essentially independent of the chain length of the acylating agent for the

compounds studied. No formation of *meta*-hydroxy ketones was observed. There was a marked preference for the ortho position with hydroxycaprylophenone, which became less with hydroxylaurophenone. The amount of para isomer exceeded the amount of ortho isomer for hydroxymyristophenone and hydroxypalmitophenone and was approximately equal in hydroxystearophenone. It appears, therefore, that the tendency to orient ortho decreases as one goes from eight to eighteen carbon atoms. Previous work indicates a preference for the formation of the para isomers in acylations with acid chlorides of low molecular weight. This preference appears to become less with increasing molecular weight and is evidently reversed as one studies the hydroxy ketones of higher molecular weight.

EXPERIMENTAL

Preparation of hydroxylaurophenones. Phenol (14 g., 0.15 mole) was dissolved in 30 cc. of tetrachloroethane previously cooled to 10°. Anhydrous aluminum chloride (20 g., 0.15 mole) was added at such a rate that the temperature did not rise over 15°. The cooling bath was removed, and lauroyl chloride (22 g., 0.1 mole) was added through a dropping-funnel, over a period of thirty minutes. The resulting mixture was heated and stirred at 55–60° for six hours, and was hydrolyzed by pouring onto ice. The product was steam distilled to remove the solvent and excess phenol.

Separation of isomeric hydroxylaurophenones. The low-melting solid (weight 28 g.) was separated and washed free of mineral acids. It was further washed with a solution of 3 g. of sodium hydroxide and 40 cc. of ethyl alcohol in 160 cc. of water. The insoluble portion was separated by filtration (weight 10 g.). This product gave a deep red-violet coloration with a solution of ferric chloride. The alkaline filtrate was acidified with hydrochloric acid and the solid filtered (weight 14 g.). This product gave no coloration with ferric chloride. This separation is in accordance with the findings of Baltzly and Bass (9) who stated that the ortho isomers are precipitated by excess alkali and give colorations with ferric chloride whereas the para isomers are alkali-soluble and give no colorations with this agent.

The alkali-insoluble product was crystallized from Skellysolve "B" and gave 9.05 g. of white, flaky crystals melting at 43–45°. Recrystallization gave a compound which melted at 44–45.5°.

The alkali-soluble product was dissolved in 200 cc. of Skellysolve "B". The product crystallized at room temperature, and 6.85 g. of colorless crystals melting at 71–72° was obtained. These crystals were assumed to be *p*-hydroxylaurophenone. Further cooling of the filtrate gave crystals of lauric acid.

Identification of the isomeric hydroxylaurophenones. One-half gram of the alkali-soluble compound (m.p. 71–72°) was dissolved in 20 cc. of acetone containing a small amount of sodium hydroxide (0.1 g.). The solution was cooled to 10° and dimethyl sulfate (0.5 g.) added. The mixture was heated for one hour, diluted with water, and the white solid filtered. Crystallization from alcohol gave a white solid (pearly plates) melting at 57–59°. This compound showed no depression in melting point when mixed with a sample of *p*-methoxylaurophenone which was prepared by the Friedel–Crafts acylation of anisole.

The oxidation of both the *p*-methoxy- and the *p*-hydroxy- laurophenones was attempted using neutral and alkaline permanganate, sodium hydroxide fusion, chromic acid, and various concentrations of nitric acid. Heating the methoxy com-

pound with 50% by volume nitric acid was the only satisfactory oxidation method found. The following procedure was used: One-half gram of the *p*-methoxylaurophenone was heated for 20 hours in 30 cc. of 50% nitric acid until the oily layer on the surface had disappeared. The solution, on cooling, deposited white, needle-like crystals which melted at 181–184° after one recrystallization from water. This product proved to be identical with anisic acid.

The 2,4-dinitrophenylhydrazones were prepared by refluxing 0.5 g. of the hydroxylaurophenones dissolved in 20 cc. of alcohol with 0.3 g. of 2,4-dinitrophenylhydrazine. A few drops of concentrated hydrochloric acid were added, and the mixture again heated for 5 minutes, cooled, and filtered. The 2,4-dinitrophenylhydrazones were crystallized from alcohol. The *o*-hydroxylaurophenone gave a 2,4-dinitrophenylhydrazone (orange flakes), which melted at 92–93°. The *p*-hydroxylaurophenone gave a 2,4-dinitrophenylhydrazone (dark red needles) melting at 150–151°.

Preparation and separation of hydroxycaprylophenones. The acid chloride used was prepared by the action of phosphorus trichloride upon caprylic acid. Aluminum chloride (66 g., 0.5 mole) was added over a period of one-half hour to 75 cc. of tetrachloroethane which contained 50 g. of phenol (0.52 mole). The temperature was held at 10° during the addition of the aluminum chloride. The mixture was allowed to come to room temperature and caprylyl chloride (40.5 g., 0.25 mole) was added through a dropping-funnel over a period of one and one-half hours. The mixture was then heated and stirred at 55° for four hours, after which it was hydrolyzed by pouring onto ice, and the solvent and excess phenol were removed by steam distillation.

The oily layer was separated and treated with 500 cc. of a 25% alcohol solution containing 4 g. of sodium hydroxide. The insoluble portion was extracted with petroleum ether and acidified by heating with hydrochloric acid. The solution was washed with water and dried with anhydrous sodium sulfate. The solvent was removed and the product was distilled, giving a water-white liquid (36 g.) boiling at 100–104° at 1 mm. The product was redistilled and a fraction (27.5 g.) boiling at 97–99° at 1 mm. was obtained.

The alkali-soluble compound was removed from solution by acidification with hydrochloric acid, followed by extraction with petroleum ether. Crystallization from petroleum ether gave white, pearly plates (6.8 g.) which melted at 62.5–63.5°.

The 2,4-dinitrophenylhydrazones were prepared as previously described. The constants were as follows: *o*-hydroxycaprylophenone-2,4-dinitrophenylhydrazone, orange crystals, m.p. 140–141°, *p*-hydroxycaprylophenone-2,4-dinitrophenylhydrazone, red needles, m.p. 176–178°.

Preparation and separation of hydroxymyristo-, hydroxypalmito-, and hydroxystearo-phenones. The myristic acid used for the preparation of the myristoyl chloride was purified by crystallization from acetone. The melting point was 53–54°. The myristoyl chloride prepared from this acid and phosphorus trichloride boiled at 119.5–123° at 1 mm. The hydroxymyristophenones were prepared, separated, and identified by the same procedure used for the hydroxylaurophenones. The hydroxypalmito- and hydroxystearo- phenones were prepared in a similar manner. The palmitoyl chloride boiled at 139–140° at 1 mm. and the stearoyl chloride at 186–190° at 5 to 6 mm.

The physical characteristics and melting points of the 2,4-dinitrophenylhydrazones were as follows: *o*-hydroxymyristophenone-, orange plates, m.p. 92–92.5°; *p*-hydroxymyristophenone-, dark red needles, 142–143°; *o*-hydroxypalmitophenone-, yellowish-orange plates, 94–95°; *p*-hydroxypalmitophenone-, dark red needles, 141–

142°; *o*-hydroxystearophenone-, yellow powder, 96–97°; *p*-hydroxystearophenone-, dark red needles, 139.5–140°.

Table I shows the relative yield of isomeric hydroxyphenyl ketones obtained.

Table II shows the melting or boiling points and the analyses of the various isomeric hydroxyphenyl ketones.

TABLE I

COMPARATIVE YIELDS OF ISOMERIC HYDROXYPHENYL KETONES

COMPOUND	YIELD (%)	
	Ortho	Para
Hydroxycaprylophenone	50	12
Hydroxylaurophenone	32.6	24.6
Hydroxymyristophenone	31.9	36.7
Hydroxypalmitophenone	25.4	28.5
Hydroxystearophenone	27.8	28

TABLE II

MELTING POINTS AND ANALYSES OF ISOMERIC HYDROXYPHENYL KETONES

COMPOUND	M.P. (°C.)	ANALYSES[a]			
		Calc'd (%)		Found (%)	
		C	H	C	H
o-Hydroxycaprylophenone	b.p. 97–99 at 1 mm.	76.32	9.15	76.13	9.15
o-Hydroxylaurophenone	44 –45.5	78.21	10.21	78.40	10.30
o-Hydroxymyristophenone	52 –55	78.89	10.59	78.70	10.41
o-Hydroxypalmitophenone	54 –56	79.51	10.92	79.70	10.67
o-Hydroxystearophenone	64 –66	79.94	11.18	79.78	10.86
p-Hydroxycaprylophenone	62.5–63.5	76.32	9.15	76.57	9.06
p-Hydroxylaurophenone	71 –72	78.21	10.21	78.01	9.93
p-Hydroxymyristophenone	78 –80	78.89	10.59	79.22	10.33
p-Hydroxypalmitophenone[b]	84.5–85	79.51	10.92	79.73	10.78
p-Hydroxystearophenone	87 –89	79.94	11.18	79.68	10.90

[a] Analyses by Dr. T. S. Ma, University of Chicago.

[b] Previously prepared by Auwers, *Ber.*, **36**, 3891 (1903).

SUMMARY

1. The yield of *ortho*- and *para*-hydroxy ketones has been determined in the Friedel–Crafts acylation of phenol with caprylyl, lauroyl, myristoyl, palmitoyl, and stearoyl chlorides.

2. The ortho position is favored for the lower members of this series, but the ratio of the *ortho*- to *para*-hydroxy ketones decreases as the molecular weight of the acylating group is increased.

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[CONTRIBUTION FROM THE ANIMAL HUSBANDRY DIVISION, UNITED STATES DEPARTMENT OF AGRICULTURE[1]]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. II. THE REACTION OF 1,3,5-HEXATRIENE WITH 1,4-NAPHTHOQUINONE[2]

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Although most of the known naturally occurring steroids are non-benzenoid, the total synthesis of this type has not yet been accomplished. It should be possible to build up a large variety of such compounds by means of successive Diels-Alder diene additions. The Diels-Alder reaction has the great advantage that it always proceeds stereoselectively to give polycyclic compounds with *cis* configuration at the ring junctions, and furthermore two successive additions lead exclusively to one of the possible *cis,cis* isomers (1). Dane and collaborators (2) have employed this reaction for the synthesis of steroids containing one benzene ring, and Cook and Lawrence (3), Meggy and Robinson (4), Butz (5), Goldberg, and Müller (6), and others have reported applications of the reaction which might be extended to the synthesis of steroids.

We have explored some of the possibilities making use of compounds which contain an open chain of six carbon atoms as the basis of the synthesis. From these, the angular tetracyclic skeleton of the steroids might be built up by successive diene additions according to the schemes in diagrams A, B, and C, in which the broken lines represent new carbon-to-carbon links. 1,3,5-Hexatriene, 1,3-hexadien-5-yne, 1,5-hexadien-3-yne, and their derivatives would be examples of six-carbon chains potentially capable of adding successively two molecules of dienophile.[3] We have found that both 1,3,5-hexatriene and 2,5-dimethyl-1,5-hexadien-3-yne form adducts of interest in this connection. This paper will present only the results obtained with hexatriene and a single dienophile, 1,4-naphthoquinone.

[1] This work was supported by an appropriation from Bankhead-Jones funds (Bankhead-Jones Act of June 29, 1935), and is part of an investigation of the animal metabolism of substances related to the steroid hormones being carried out under the Physiology of Reproduction Project, a coöperative project of the Bureau of Animal Industry and the Bureau of Dairy Industry.

[2] A part of the work reported here was presented before the Chemical Society of Washington, May 11, 1939.

[3] There is need for such a word. Several writers have used "philodiene," but "dienophile" seems better.

One scheme for the synthesis of a steroid from 1,3,5-hexatriene is illustrated by formulas I–IV; III is an anticipated by-product. For a successful outcome, the following requirements must be fulfilled: (a) The hexatriene must react with suitable dienophiles at temperatures where side reactions, *e.g.*, polymerization, do not occur to any considerable extent. (b) The 3-vinylcyclohexene system in the primary adduct (I) must be mobile, so that isomerization to II will occur. (c) Isomerization must not proceed exclusively to III, unless III can rearrange to II under the conditions of the second diene addition leading to IV. (d) Further isomerization of III to cyclohexadiene derivatives must not be considerable, for these add dienophiles, though possibly not at temperatures where addition to II would readily occur (7).

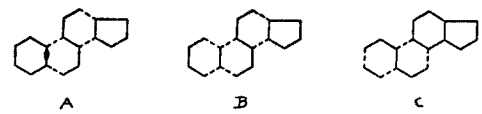


FIGURE 1

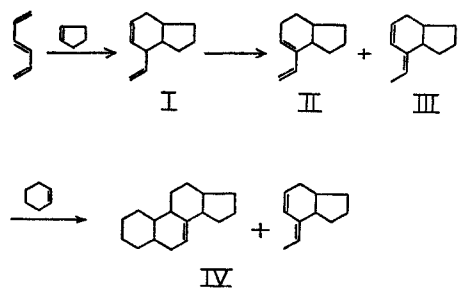


FIGURE 2

There is no very pertinent information in the literature on which can be based a prediction how far all of these requirements will be met. Prior to our work,[4] hexatriene had been added only to maleic anhydride (8). An unsuccessful attempt to add it to 3-methyl-2-cyclohexenone had been reported (9). Farmer and Warren (8) found that *trans*-1,3,5-hexatriene combined with maleic anhydride at 100° to give, in nearly quantitative yield, 6-ethylidene-1,2,3,6-tetrahydrophthalic anhydride (V). *Cis*-1,3,5-hexatriene gave, after extensive manipulation of the crude reaction-products, the same anhydride. We have been able to add 4-acetoxy-2,5-toluquinone and cyclopentene-1-aldehyde (5), and, more recently,

[4] The addition of hexatriene to itself and to allyl chloride has recently been reported [Kharasch and Sternfeld, *J. Am. Chem. Soc.* **61**, 2318 (1939)].

several other cyclohexene and cyclopentene derivatives. Most of these additions occur at low temperatures and give good yields of adducts, so that the first requirement is fulfilled.

Information on the mobility of the hydrogen atoms in derivatives of 3-vinylcyclohexene is very meager. Moreover, such information as is available on this and related systems refers almost entirely to hydrocarbons, whilst we have to deal with compounds containing the carbonyl and other groups, which may exhibit quite different equilibria. Levina and Levina (10) have found that 3-vinylcyclohexene itself gives a mixture of ethylcyclohexane and ethylbenzene when passed over a platinum-carbon catalyst at 200°. Slobodin (11) states that 4-vinylcyclohexene isomerizes only with difficulty in the presence of floridin even at 240°. On the other hand, 6-vinyl-1,2,3,6-tetrahydrophthalic anhydride (VI) might, from the work of Farmer and Warren (8), be expected to isomerize readily, since they isolated none of this isomer from the reaction-products of hexatriene with maleic anhydride at 100°. If the analogous compounds, XI

V VI

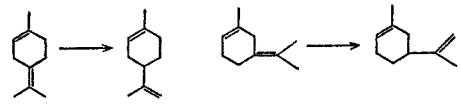
FIGURE 3

and XII, from naphthoquinone and hexatriene are similarly unstable, the isolation of XIII and XIV can be expected.

Whether requirements c and d will be fulfilled can not be predicted. In simple systems, such as that of the isomeric butenes (12) an equilibrium mixture is formed in the presence of catalysts at temperatures ranging from 26° to 300°. This mixture can contain up to 66% of a vinyl isomer at 100° in the presence of one catalyst and 31% of a vinyl isomer at 300° with another catalyst; but it is doubtful to what extent these results apply to the more complicated compounds I, II, and III. It seems probable from a study by Lyubarskii (13), that under the conditions obtaining during the high-temperature production of Russian turpentine, *p*-terpinolene (VII) is converted to dipentene (VIII), and *m*-terpinolene (IX) to sylvestrene (X). The isomerization of abietic acid (14) and terpenes containing a pair of isolated double bonds (15) to compounds containing a conjugated system has been observed on heating with dienophiles. The isomers formed are probably derivatives of cyclohexadiene, and the isomerization is influenced by the presence of water and acids in the case of the terpenes.

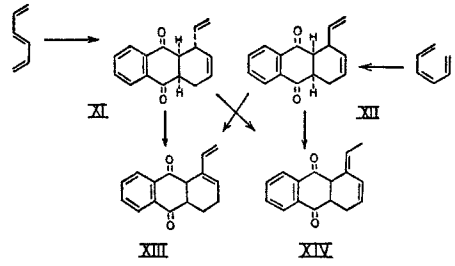
If the observations of Farmer and Warren (8) concerning the product of

reaction between hexatriene and maleic anhydride were correctly interpreted by them, it is essential to determine whether other primary adducts from hexatriene (3-vinylcyclohexenes) isomerize so readily to the ethylidene compounds (III) exclusively. If this tendency proved to be general and unavoidable, the project of using hexatriene for synthesis might well be abandoned. If, on the contrary, an adduct containing the vinyl group were obtained, we should then be in a position to investigate systematically its ability to isomerize and to add a second molecule of dienophile. 1,4-Naphthoquinone was chosen because it has been shown (16) that this quinone reacts with dienes to give tetrahydroanthraquinones which are easily oxidized in alcoholic potassium hydroxide by air to readily characterizable anthraquinones. 1-Vinyl-9,10-anthraquinone had not previously been prepared, but this should be easily converted to known com-



VII VIII IX X

FIGURE 4



XI XII XIII XIV

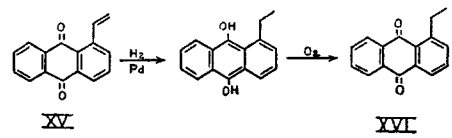
FIGURE 5

pounds. 1,4-Naphthoquinone has the additional advantage that it is symmetrical about the reactive double bond, and hence can lead to only two primary products, *cis*-1-vinyl-*cis*-1,4,4a,9a-tetrahydro-9,10-anthraquinone (XI) and *trans*-1-vinyl-*cis*-1,4, 4a,9a-tetrahydro-9,10-anthraquinone (XII). The relative quantities of *cis*- and *trans*- isomer formed might be influenced by the composition of the hexatriene used, which probably contained both *cis*- and *trans*- hexatriene.

When hexatriene and naphthoquinone in ethanol were heated together at 50°, two products were obtained, a liquid of the expected composition $C_{16}H_{14}O_2$ in 70% yield, and a colorless crystalline compound, m.p. 134–136°[5], of the same composition, in 25% yield. The liquid was converted

[5] All the melting points reported in this paper are corrected unless it is otherwise stated.

in ethanol to the red potassium enolate, and this was oxidized with air to a yellow compound, $C_{16}H_{10}O_2$, m.p. 163–164°. This is the new substance, 1-vinyl-9,10-anthraquinone (XV), for catalytic hydrogenation gave a tetrahydro derivative which was oxidized, without being isolated, to 1-ethyl-9,10-anthraquinone (XVI), identical with a sample prepared from 1-acetylanthracene by the method of Waldmann and Marmorstein (17). Further evidence for the structure of the yellow substance of m.p. 163–164° was provided by ozonization and hydrolysis, followed by oxidation of the unstable product (9,10-anthraquinone-1-aldehyde?) to the known 9,10-anthraquinone-1-carboxylic acid. Since the yield of pure vinylanthraquinone obtained from the liquid $C_{16}H_{14}O_2$ is 85% of the calculated quantity, and since this liquid will be shown later to contain 10% of the solid isomer, the liquid contains 85–90% of vinyl derivatives. It is unlikely that the vinyl group would be formed by isomerization of an ethylidene or ethyl derivative during the oxidation, which was carried out at 30° in fifteen minutes. Therefore, with naphthoquinone and hexatriene at 50°, in contrast to maleic anhydride (8) and hexatriene at 100°, vinyl compounds, and not an ethylidene compound, are the principal products.



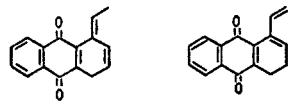
XV XVI

FIGURE 6

The crystalline product of m.p. 134–136° also gave a red enolate with potassium hydroxide in ethanol, and the enolate was oxidized by air to a brilliant yellow compound, but in this case, with the composition $C_{16}H_{12}O_2$. The oxidation had stopped at the dihydroanthraquinone stage. This resistance to further dehydrogenation was reminiscent of that of 1,1,3-trimethyl-1,4-dihydro-9,10-anthraquinone investigated by Diels and Alder (18), and suggested that the 1-carbon atom in the compound $C_{16}H_{12}O_2$ carried no hydrogen. This consideration would limit the possible structures to XVI, XVII and XVIII. The structure XVI was excluded by the behavior of the compound when heated. There was no visible change up to 187°, where the substance rapidly decomposed without melting, with evolution of gas and formation of a nearly colorless product which melted at 281–283° (uncorr.). 1-Ethylanthraquinone (17) has the melting point 96°. A final choice between XVII and XVIII, implying structures XIV and XIII respectively for the solid $C_{16}H_{14}O_2$, was not possible, although we preferred XIV and XVII because it seemed likely that the dehydrogenation of XIII would have proceeded all the way to 1-vinylanthraquinone if XVIII were an intermediate. The solid product from the

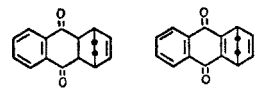
decomposition of the compound $C_{16}H_{12}O_2$ was shown to be 9,10-anthraquinone, and the gas was ethylene. Both were formed in quantitative yield. The ethylene was determined by elementary analysis and further identified by the preparation of a solid derivative. An attempt was made to formulate a mechanism for the decomposition of a substance XVII to give anthraquinone and ethylene.

At this stage in the work, it was pointed out to us that the melting point of the solid compound $C_{16}H_{14}O_2$ and the behavior of its yellow dehydrogenation product toward heat were identical with the properties of a compound prepared by Diels and co-workers (19) from cyclohexadiene and naphthoquinone. On heating the compound $C_{16}H_{12}O_2$ they obtained ethylene and a quantitative yield of anthraquinone. The method used for the identification of the ethylene was not stated. When a similar dehydroadduct from α-phellandrene and naphthoquinone was heated, these investigators



XVII XVIII

FIGURE 7



XIX XX

FIGURE 8

showed that the gas eliminated was isopropylethylene by conversion to the dibromide. The structures assigned to the two compounds by Diels were XIX and XX, and the failure of XX to dehydrogenate further to a compound $C_{16}H_{10}O_2$ was explained by an increased stabilization of the H-C bonds at positions 1 and 4 by the endo-ethylene bridge.

Preparation of the solid adduct of m.p. 135° from cyclohexadiene and naphthoquinone according to the method of Diels, and comparison with the compound from our hexatriene demonstrated that the two were indeed identical. Therefore, either the hexatriene isomerized in part during the reaction with naphthoquinone, or our hydrocarbon contained cyclohexadiene. The hydrocarbon we used was prepared by heating 1,5-hexadien-3-ol, obtained from allylmagnesium bromide and acrolein, with phthalic anhydride, and it is possible that a rearrangement-product such as 2,4-hexadien-1-ol underwent a cyclodehydration or that hexatriene was cy-

clized at the temperature of its formation. A decision between these various possibilities requires further experimental work.

The possibility that our hexatriene contained cyclohexadiene and the fact that the liquid $C_{16}H_{14}O_2$ prepared from the hydrocarbon is not pure do not affect the finding that the principal product of the reaction of hexatriene with naphthoquinone is a vinylcyclohexene derivative or a mixture of several isomeric vinylcyclohexenes. Indeed, one can now predict, on the assumption that hexatriene does not give cyclohexadiene at 50° in the presence of naphthoquinone and ethanol, that pure hexatriene would give a quantitative yield of vinyl isomers of composition $C_{16}H_{14}O_2$. It will be interesting to test this prediction by employing hexatriene prepared by the new low-temperature method of Kharasch and Sternfeld (20).

The considerable stability of the vinyl linkage in the liquid $C_{16}H_{14}O_2$ was demonstrated by heating in a bath at 200–236° and at 2.5 mm. for one hour. Three products were obtained; a nearly colorless solid (10%),

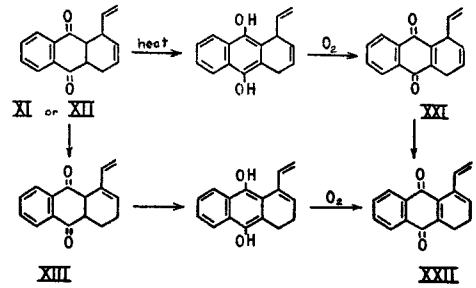


FIGURE 9

a yellow crystalline solid (50%), and an oil. The oil no longer gave an insoluble quinone by oxidation in alcoholic potassium hydroxide, and was not further investigated. The nearly colorless solid was oxidized by ferric chloride to the quinone XX of Diels and Alder, and was therefore probably the corresponding 1,4-diphenol formed by enolization of XIX. The principal product separated from the xylene mother liquors from this diphenol after several days in contact with air. The substance melted at 97–99°, and elementary analysis indicated the probable[6] composition $C_{16}H_{12}O_2$. These properties suggested that the compound might be 1-ethyl-9,10-anthraquinone which melts at 96° (17). However, a mixed melting point determination showed a depression of 20–25°. We have not observed the formation of ethylanthraquinone or an ethyldihydroanthraquinone at any time, although we anticipated that these might be

[6] Three separate determinations gave discordant results, one set of which corresponded to the composition given. See experimental part.

found as a result of the isomerization and oxidation of compounds such as XI. The substance gave 1-vinyl-9,10-anthraquinone when oxidized in ethanolic potassium hydroxide and therefore contains the vinyl group. The most probable structure is XXI, which could be formed from XI or XII by enolization and oxidation. Structure XXII is not excluded by the available evidence. The conception of the principal thermal reaction as an enolization is supported by the isolation of the same yellow compound of m.p. 97–99° by treating the liquid $C_{16}H_{14}O_2$ with hydrogen bromide in acetic acid and oxidizing the product with air, and is further supported by the observation of Bergmann and Bergmann (21), who record the formation of a 1,4-diphenol during a Diels–Alder addition to a quinone at 150–170°.

EXPERIMENTAL

1,3,5-Hexatriene was prepared by heating 1,5-hexadien-3-ol with phthalic anhydride. In our hands the procedure described below gave more consistent yields than the methods (22) previously described.[7]

1,5-Hexadien-3-ol. This alcohol has been prepared by Le Heux (22b) and by Levene and Haller (23). We prepared it by the interaction of allylmagnesium bromide and acrolein. As a satisfactory yield depends heavily on conditions, these will be given in detail. To 30.5 g. (1 mole) of dried magnesium turnings were added 300 cc. of anhydrous ether, a crystal of iodine, and 5 g. of allyl bromide. The allyl bromide, obtained from the Eastman Kodak Company, was shaken with phosphorus pentoxide for five minutes. After decanting, the fraction which distilled at 70–71° was collected. The reaction was started by careful warming until spontaneous refluxing occurred. When the refluxing became slower, 75 g. of allyl bromide (0.5 mole) in 1800 cc. of ether was added at a rate such that steady refluxing was maintained; the time from the beginning of reaction to the completion of the addition of allyl bromide was four to five hours. The best yields were obtained when the mixture presented a milky-white appearance throughout the reaction period. If it became gray to blue-gray, possibly because of too slow addition of bromide, the yields were smaller. The reaction-mixture was refluxed gently for thirty minutes, after which 20.6 g. of acrolein (0.28 mole) was added during thirty minutes. Stirring was continued fifteen minutes after the addition of acrolein and the mixture allowed to stand overnight. The acrolein, containing preservative, was used as received from Eastman Kodak Co., since it was found that freshly distilled acrolein was less satisfactory. On the following day the mixture was decomposed in the usual way with ice, followed by just enough dilute sulfuric acid to dissolve the sludge. After removal of the ether and volatile products (biallyl?), the crude alcohol boiled at 45–65° at 25 mm. The yield was 74–79% based on the acrolein taken, 41–44% based on the allyl bromide. About 90% of this product had the b.p. 130–137° and 42–48°/17 mm.

If a theoretical proportion of acrolein was used the yield was only 35–40% (based on acrolein), and twice the theoretical quantity gave only about 20%.

1,3,5-Hexatriene. A one-liter distilling flask was used for the dehydration of

[7] The new method of Kharasch and Sternfeld (*loc. cit.*) appeared after the preparation of this paper.

the hexadienol. The side arm of the flask should be 0.3 inch in diameter and be attached 9.6 inches from the bottom of the flask. A mixture of 22.7 g. of phthalic anhydride, a few crystals of hydroquinone, and 15 g. of hexadienol, b.p. 130–137°, was placed in the flask. The flask was placed in a Wood's metal-bath, previously heated to 130°, to such a depth that two-thirds of the contents of the flask was immersed. The products of pyrolysis were condensed in a water-cooled condenser, and then received in a tube cooled to −50°. During the first hour the temperature of the bath was gradually increased to 160°. After the first half hour the flask should be insulated with an asbestos shield, since air cooling decreases the yield of hexatriene. After the first hour the temperature of the bath was gradually raised until at about 1.5 hours distillation accompanied by a crackling sound began, and the vapor temperature rose to 80°. The bath temperature at this point was 190–200°. Thereafter heat was applied at such a rate that the vapor temperature remained between 80° and 90°. The total period of heating ranged from 3.75 to 4.5 hours.

The two-phase distillate was separated by freezing the lower layer and decanting; the upper layer was dried with calcium chloride and distilled; 5.5 g. boiled at 70–95°. Redistillation over sodium then gave 4 g. (32.7%) of hexatriene[8], b.p. 80–82°/757 mm., d_4^{20} 0.7754, n_D^{18} 1.4924, MR 29.96. Previously reported constants are: hexatriene from 1,5-hexadien-3,4-diol diformate (22a), b.p. 78.5–80°/766 mm., d_{10} 0.7565, n_D^{10} 1.49856; *trans*-hexatriene purified through a dibromide (22c), b.p. 80–80.5°/755 mm., d_4^{14} 0.740, n_D^{14} 1.517; *cis*-hexatriene, containing probably 2–2.5% of the *trans* isomer (24), b.p. 78.5°/760 mm., d_4^{20} 0.7175, n_D^{20} 1.4577.

Reaction of 1,3,5-hexatriene with 1,4-naphthoquinone. Six and six-tenths grams of naphthoquinone, 5 g. (1.5 moles) of hexatriene, and 25 cc. of ethanol were heated in a sealed tube at 50° for 6 hours. Heating for 23 hours did not affect the yield or character of the products. After cooling to −15°, crude crystals were separated. One recrystallization of these from ethanol gave 2.7 g. (27%) of a nearly colorless product. Two more crystallizations, first from hexane and then from ethanol, gave a colorless solid, m.p. 134–136°.

Anal.[9] Calc'd for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88.
Found: C, 80.91, 80.96; H, 5.96, 5.70.

The ethanol was removed from the mother liquors from the crystalline product, the residual oil was dissolved in hexane at 50°, the solution separated from a small quantity of dark insoluble oil, and the hexane was evaporated. The residue was a pale amber oil (XI or XII) of the composition $C_{16}H_{14}O_2$. The yield was 7 g. (70%). Sublimation at a low pressure (below 0.5 mm.) removed about 1% of naphthoquinone. The crude undistilled liquid was analyzed, since distillation at 2.5 mm. resulted in partial decomposition.

Anal. Calc'd for $C_{16}H_{14}O_2$: C, 80.67; H, 5.88.
Found: C, 80.12, 80.10; H, 5.63, 5.72.

Oxidation of the liquid $C_{16}H_{14}O_2$ to 1-vinyl-9,10-anthraquinone. One cubic centimeter of ethanol saturated with potassium hydroxide was added to a solution of

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[8] The product may contain 1,3-cyclohexadiene as it gives the same adduct (in 30% yield) with 1,4-naphthoquinone as does cyclohexadiene. The higher density points to the same conclusion. D_4^{20} for 1,3-cyclohexadiene, 0.8404 [Willstätter and Hatt, *Ber.*, **45**, 1464 (1912)].

[9] All the microanalyses were done by the Arlington Laboratories, Arlington, Virginia. The authors are grateful to the Arlington Laboratories for carrying out the special analysis of the gas from the decomposition of XX.

1.87 g. of the liquid $C_{16}H_{14}O_2$ in 25 cc. of ethanol, and air was drawn through the mixture at 30°. After 5–10 minutes the reaction was completed. The supernatant liquid remained dark red or brown and crude yellow quinone was precipitated. Thorough washing with water and drying gave 1.5 g. of 1-vinyl-9,10-anthraquinone, m.p. 163–164°, from acetone.

Anal. Calc'd for $C_{16}H_{10}O_2$: C, 82.05; H, 4.27.
Found: C, 82.34, 81.91; H, 4.50, 4.35.

Conversion of 1-vinyl-9,10-anthraquinone to 9,10-anthraquinone-1-carboxylic acid. The vinylanthraquinone (0.362 g.) in 100 cc. of acetic acid was saturated with ozone, the products refluxed for five minutes with 20 cc. of water and allowed to stand overnight. Concentration to 10 cc. gave 0.174 g. of yellow substance (dried over potassium hydroxide) which melted partially at 167–169°. The acetic acid mother liquor yielded 0.2 g. more of less pure product. Chromic acid (0.14 g.) in 4.5 cc. of acetic acid and 1.5 cc. of water was added to 0.14 g. of the substance m.p. 167–169°, suspended in 1.5 cc. of acetic acid, at 60–80°. It was held at this temperature for ten minutes, then raised to 80–90° for five minutes. At this point yellow solid began to separate. The mixture was cooled, let stand one hour, the solid filtered out, washed thoroughly with water, dried, and recrystallized from acetic acid. From the total products of ozonization, there was thus obtained 0.205 g. of anthraquinone-1-carboxylic acid, m.p. 288–290° (uncorr.).

Anal. Calc'd for $C_{15}H_8O_4$: C, 71.43, H, 3.19.
Found: C, 71.40, 71.34; H, 3.56, 3.24.

Conversion of 1-vinyl-9,10-anthraquinone to 1-ethyl-9,10-anthraquinone. Vinylanthraquinone (0.150 g.) in 17 cc. of acetic acid absorbed, in the presence of 0.018 g. of a commercial palladium black (from A. H. Thomas Co.), four atoms of hydrogen in one-half hour, after which the rate of absorption decreased. The products of hydrogenation were then oxidized with chromic acid. The acetic acid solution was concentrated to 6 cc., 0.064 g. of chromic acid in 5 cc. of acetic acid and 2 cc. of water was added, the mixture held at 30° for fifteen minutes, and then evaporated to 2 cc. on a steam-bath. After cooling, addition of 10 cc. of water precipitated a yellow solid, which, after drying and crystallization from ethanol and ligroin, had the m.p. 95–97°, and showed no depression with a sample of 1-ethylanthraquinone prepared according to Waldmann and Marmorstein (17).

Oxidation of the solid $C_{16}H_{14}O_2$ to the quinone XX of Diels and Alder. Nine cubic centimeters of *N* potassium hydroxide in ethanol was added to 0.45 g. of the solid tetrahydroanthraquinone, m.p. 134–136°, suspended in 8 cc. of ethanol. Aeration of the red solution for two minutes decolorized it and precipitated a brilliant yellow crystalline solid. This was washed thoroughly with water and recrystallized from acetone. It decomposed at 187–188° to a nearly colorless solid which melted at 281–283° (uncorr.). The yield was 0.387 g.

Anal. Calc'd for $C_{16}H_{12}O_2$: C, 81.36; H, 5.09.
Found: C, 81.40, 81.71; H, 5.14, 5.19.

Effect of heat on the vinyltetrahydroanthraquinones (XI and XII). (a) Five-tenths gram of the liquid $C_{16}H_{14}O_2$ in 5 cc. of ethanol was heated in a sealed tube at 50–55° for fourteen days. Cooling and concentration of the solution gave no crystals of the solid isomer. Oxidation of the heated material gave 0.33 g. of vinylanthraquinone. This is a 67% yield; the unheated liquid $C_{16}H_{14}O_2$ gave 70–85% yields of vinylanthraquinone in a series of preparations.

(b) Liquid vinyltetrahydroanthraquinone (5.7 g.) was heated without solvent in a bath at 200–236° for one hour at 2.5 mm. pressure. Less than 10% distilled. The residue was extracted with hot xylene, in which all but 0.6 g. was soluble. The

insoluble part, after recrystallization from xylene, was colorless, decomposed at 147–150°, and became reddish when exposed to air. This substance was oxidized by ferric chloride in boiling ethanol (0.5 hour) to a yellow compound which was identical with XX, and is therefore probably the corresponding diphenol. The xylene extract of the residue from the pyrolysis, on standing five days in contact with air, deposited a yellow crystalline compound, m.p. 97–99°, from ethanol. This is not identical with 1-ethyl-9,10-anthraquinone (17) m.p. 94°, mixed m.p. 70–75°. In all, 2.8 g. of the new compound was isolated from the xylene solution. Elementary analysis gave discordant results.

Anal. Calc'd for $C_{16}H_{12}O_2$: C, 81.36; H, 5.09.

Found: C, 82.85, 83.71, 81.32; H, 5.22, 5.27, 4.99.

The xylene mother liquor from this substance gave an oil which did not yield an insoluble quinone when oxidized in ethanolic potassium hydroxide with air. The oil was not examined further. Similar oxidation of the yellow compound, m.p. 97–99°, gave a yellow substance of m.p. 163–164°, which did not depress the m.p. of 1-vinyl-9,10-anthraquinone. This demonstrates that it contains the vinyl group. In contrast to the liquid (XI and XII) and solid $C_{16}H_{14}O_2$ (XIX), the vinyl-dihydro compound with potassium hydroxide in ethanol gave an evanescent green solution which rapidly changed to red.

9,10-Anthraquinone from compound XX. When the temperature of 310 mg. of XX was gradually raised, evolution of gas began at 160° and the brilliant yellow color had vanished after five minutes, when the temperature was 165°. The temperature was then raised to 250° during fifteen minutes to ensure complete reaction[10]. The nearly colorless residue weighed 270 mg. (calc'd 272.8 mg.) and melted at 281–283° (uncorr.) to a nearly colorless liquid. The mixed m.p. was 282–284° with a commercial sample of anthraquinone once recrystallized from acetone, and having the melting point 282–283° with charring.

Anal. Calc'd for $C_{14}H_8O_2$: C, 80.76; H, 3.87.

Found: C, 80.52, 80.87; H, 4.05, 4.02.

*Ethylene-bis-*p*-tolyl-disulfone from the quinone (XX).* XX (310 mg.) was heated slowly up to 250°. Change of color and evolution of gas began at 160°. The gas entered two tubes, in series, containing 10 cc. and 20 cc. of a solution of bromine in ether (40 mg. Br/cc.). The tubes were cooled to −15° and atmospheric moisture was excluded. The total period of heating from 160° to 250° was 15 minutes. The absorption tubes were disconnected after 5 minutes at 250°, when bubbling of gas had stopped. The two portions of ether solution were combined, washed with sodium thiosulfate solution and water, and dried over sodium sulfate. The ether solution was then refluxed with 580 mg. of p-$CH_3C_6H_4SO_2Na + 2H_2O$ in 20 cc. of ethanol for 8 hours. The solvents were evaporated, and the residue dried over phosphorus pentoxide. The solid residue was extracted repeatedly with ether, the ether was evaporated from the extract, and the residue crystallized from hot ethanol. The product melted at 201–202° (corr.); the m.p. of a mixture with a sample of disulfone, prepared according to Otto (25), was 200–201° (corr.). The yield was very small, about 5%. Otto prepared the disulfone in 65% yield by heating ethylene bromide and sodium p-toluenesulfinate in ethanol. We obtained 40%, starting from 200 mg. of ethylene bromide, but when an equal volume of ether was added to the mixture before refluxing, the yield was decreased to 5%. It would probably have been better to absorb the ethylene in bromine without solvent, but the reaction is hardly suitable for the quantitative determination of small amounts of ethylene.

[10] This was subsequently shown to be unnecessary. When heated quickly, the substance decomposes completely at 187–188°.

Elementary analysis of the gas from the quinone (XX). XX was heated at 160–180° for 20 minutes. Gaseous products were passed through a trap cooled to −55°, to remove any condensable material, and were then burned by the usual microanalytical procedure.

Anal.	Weight of XX taken	48.70 mg.
	" " anthraquinone formed	
	Calc'd:	42.92 mg.
	Found:	42.93 "
	Weight of gas (by difference)	5.77 "
	" " CO_2	18.21 "
	" " H_2O	7.62 "
	" " gas (from CO_2 and H_2O)	5.76 "

Calc'd for C_2H_4: C, 85.71; H, 14.28.
Found: C, 86.06; H, 14.67.

Reaction of cyclohexadiene with naphthoquinone. Naphthoquinone (1.8 g.), 1.4 g. of cyclohexadiene (26) (1.5 moles), and 4 cc. of ethanol were heated in a sealed tube for 6 hours at 50°. There was isolated 1.9 g. (70% yield) of crude crystals, which after two crystallizations from ethanol melted at 134–136°. The melting point was not depressed when this product was mixed with the solid, $C_{16}H_{14}O_2$, obtained from the hydrocarbon prepared from 1,5-hexadien-3-ol.

SUMMARY

1. A crude 1,5-hexadien-3-ol, on dehydration with phthalic anhydride, gave a hydrocarbon consisting chiefly of 1,3,5-hexatriene, but which may contain as much as 35% of 1,3-cyclohexadiene.

2. This hydrocarbon reacted with 1,4-naphthoquinone to give 1-vinyltetrahydro-9,10-anthraquinones in 60% yield.

3. The 1,4-endo-ethylene-1,4,4a,9a-tetrahydro-9,10-anthraquinone of Diels and Alder was formed at the same time in 30% yield. This indicates either that the hydrocarbon consisted in part of 1,3-cyclohexadiene, or that 1,3,5-hexatriene was cyclized at 50° in the presence of the napthoquinone.

4. Oxidation of the 1-vinyltetrahydro-9,10-anthraquinones gave the new substance 1-vinyl-9,10-anthraquinone.

5. The vinyl group in the 1-vinyltetrahydroanthraquinones is quite stable to heat. Atmospheric oxidation of the thermal rearrangement products gave a new compound which is probably 1-vinyl-1,4-dihydro-9,10-anthraquinone.

6. The product of the addition of naphthoquinone to hexatriene is probably a mixture of *cis-* and *trans-* 1-vinyl-*cis*-1,4,4a,9a-tetrahydro-9,10-anthraquinones. The ability of this product to rearrange to the 1-vinyl-3,4,4a,9a-tetrahydro isomer and subsequently add dienophiles is under investigation.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE FRICK CHEMICAL LABORATORY OF PRINCETON UNIVERSITY]

MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. VII. THE REARRANGEMENT OF OPTICALLY ACTIVE ALKYL PHENYL ETHERS[1]

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The early work carried out in this laboratory and published in Parts I, II, and III (1) of this series has demonstrated that in molecular rearrangements of the Curtius, Lossen, and Hofmann types involving optically active radicals, the optically active group maintains an asymmetric configuration during rearrangement. It has also been shown that no appreciable racemization occurs during such transformations.

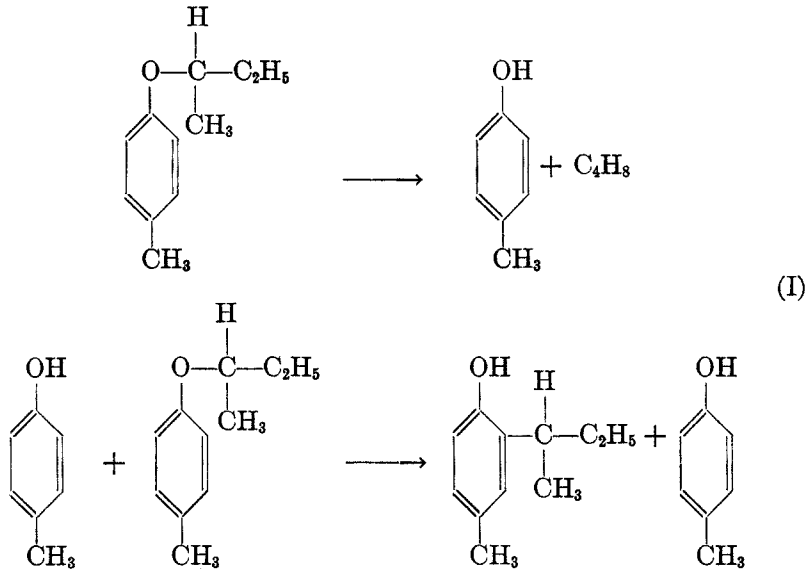
The mechanism by which the radical originally attached to the carbon atom migrates to the nitrogen atom has been the subject of much discussion.[2] Its electronic nature has also been variously interpreted. In Part IV (2) of this series, however, experiments were described which clearly show that the migration of the optically active group *does not take place in any free form, either as a positive carbonium ion, a negative carbanium ion or a neutral free radical.*

At first thought, this might suggest that the electronic nature of the tercovalent group plays no vital part in the production of optical stability or instability during rearrangement. For, if the migrating group is never completely free either as a negative ion, positive ion, or neutral free radical, but by some means is always within the sphere of influence of the rest of the molecule during the rearrangement process, then, regardless of whether or not the asymmetric carbon atom is without its complete octet of electrons, it might happen that the rearrangement would take place in a manner that insured an asymmetric configuration in all stages of the reaction. A study of the literature, however, strongly suggests that this is not the case. Experimental facts have been recorded which demonstrate quite conclusively that the optical stability of a tercovalent group (3) is dependent on its electronic nature.

[1] The experimental results herein described were placed before the Society in a paper read before the Division of Organic Chemistry at the Society's meeting in Boston, September 11–15, 1939. Present address of W. I. Gilbert, Western Maryland College, Westminster, Md.

[2] For references see earlier papers in this series.

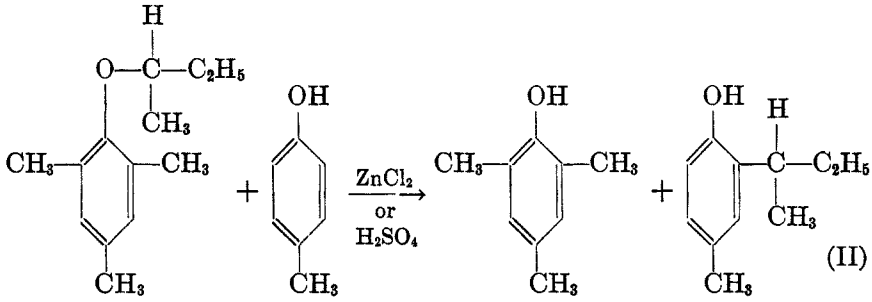
In Part V (4) of this series Sprung and Wallis studied from this point of view the nature of the products formed in the Claisen rearrangement of *d*- and *l*-*s*-butyl *m*-cresyl, and *d*, and *l*-*s*-butyl *p*-cresyl ethers. Although they found that the substituted phenols so obtained always were optically active, they did observe that the rearrangement is accompanied by partial racemization. Their results, together with those of other investigators in allied fields, indicated to them that a particular electronic arrangement of the migrating group was of fundamental importance in maintaining optical stability, and that consequently the stability was not wholly determined by some other phenomenon such as solvation or the like. In their discussion these authors did point out, however, that another explanation involving a bimolecular process had to be considered, especially in the light of certain experiments described by Short and Stewart (5) and by Sowa, Hinton and Nieuwland (6). They formulated such a possible mechanism as depicted in formulation I.



(I)

In this paper we wish to describe the results of certain experiments which were devised to test this mechanism, and to determine whether an alkyl radical containing an asymmetric carbon atom is actually able to enter a foreign nucleus without resultant loss of optical activity. For this purpose *d*-, and *l*-*s*-butyl mesityl ethers were prepared and the nature of their rearrangement products was determined. If the above metathetical mechanism is responsible for the optically active products obtained by Sprung and Wallis, then the reaction of *d*-, or *l*-*s*-butyl mesityl ether

with *p*-cresol in the presence of either zinc chloride or sulfuric acid should lead to the formation of an optically active 4-methyl-2-*s*-butylphenol, as shown in formulation II.



(II)

Preliminary experiments with racemic *s*-butyl mesityl ether showed that when a mixture of it with *p*-cresol was allowed to react in acetic acid solution in the presence of zinc chloride at 115°, only small yields of 4-methyl-2-*s*-butylphenol were obtained. The main products were butylene, mesitol, the unchanged mesityl ether, *p*-cresol, and *s*-butyl acetate. When sulfuric acid was substituted for zinc chloride, better yields of the 4-methyl-2-*s*-butylphenol were produced.

Similar treatment of *d*-*s*-butyl mesityl ether ($[\alpha]_D^{22}$ + 6.97°) gave in all cases *d*,*l*-4-methyl-2-*s*-butylphenol. The crystalline acetic acid derivative was also inactive. The same results were of course obtained with the incompletely resolved *l*-ether ($[\alpha]_D^{19}$ − 3.94°). Therefore it can be definitely concluded that an intermolecular mechanism of the above type can not be used to explain the retention of optical activity in the experiments reported by Sprung and Wallis, and their alternative mechanism is much the more probable.

Recently Hurd and Pollack (7) have suggested an oxonium type of mechanism to explain the rearrangement of alkyl phenyl ethers by the use of acidic catalysts. The first phase of the reaction is the combination of the ether with a proton to give an oxonium salt. This salt then rearranges and finally gives off a proton to form the rearranged product. To us, however, the most interesting step of the process is the one in which the actual rearrangement occurs, for it is to be noted that in the formulation of their mechanism, the alkyl group, because of resonance phenomena at the double bond in the benzene nucleus, must migrate with its full quota of electrons. It is also to be concluded from their formulation that the group *is at all times within the sphere of influence of the molecule as a whole*, this latter conclusion again illustrating a principle so often stressed by us in this laboratory.

With the above reasoning in mind, the formation of inactive products

which we have observed in the present investigation is easily explained. A scission of the *s*-butyl mesityl ether occurs to give butylene and mesitol. This is then followed by the reaction of the butylene with *p*-cresol to give *d, l*-*s*-butyl *p*-cresyl ether. The last compound then rearranges to give *d,l*-4-methyl-2-*s*-butyl phenol.

In order to make certain that the experimental facts are not to be explained on the basis of some other type of bimolecular reaction, we prepared isopropyl phenyl ether and inactive *s*-butyl *p*-cresyl ether and rearranged them in the presence of each other by means of sulfuric and acetic acids. If a bimolecular reaction occurs, one would expect to find products resulting from the exchange of isopropyl and *s*-butyl radicals between the phenol and *p*-cresol residues respectively. However, if an intramolecular reaction occurs, then one would expect only the normal products, namely, isopropylphenol and 4-methyl-2-*s*-butylphenol. We were able to isolate and identify as products of the reaction only *o*-isopropylphenol and 4-methyl-2-*s*-butylphenol. No other products could be isolated and identified. The rearrangement was carried out in the same manner as the previous reactions and the products worked up in the usual way. The phenols were identified by means of their acetic acid derivatives.

We are of the opinion, therefore, that the true course of the alkyl phenyl ether rearrangement is by way of an intramolecular path, and it appears that at present an oxonium electronic mechanism best explains the existing facts.

EXPERIMENTAL PART

Preparation of mesitol. Mesitylene was converted to mesitylene sulfonic acid by treatment with sulfuric acid at room temperature (8). The sulfonic acid so prepared was fused with powdered potassium hydroxide and converted into the phenol. The fused mass was leached with water. The solution was then acidified and steam distilled. Recrystallization of the product from petroleum ether gave crystals which melted at 69°.

It was found that larger quantities of mesitol could be more easily obtained from the "Remington Phenols" which were procured from the E. I. du Pont de Nemours Co. When this crude mixture was chilled, a large portion of the mesitol present crystallized. The crude product was filtered and recrystallized several times from petroleum ether. When pure it melted sharply at 69°.

Preparation of d, l-*s-butyl mesityl ether.* Fifteen-hundredths mole of *s*-butyl bromide and 0.15 mole of mesitol were dissolved in 900 cc. of absolute alcohol. To this solution was added an equivalent amount of sodium ethoxide dissolved in 100 cc. of alcohol. The mixture was refluxed on the steam-bath for eight hours, after which it was concentrated at reduced pressure to about 100 cc. The reaction-product was then added to 75 cc. of a 10% solution of potassium hydroxide and the mixture was extracted with ether. The ether solution was worked up in the usual manner and the product purified by distillation at reduced pressure.

d, l-s-Butyl mesityl ether is a liquid which can not be distilled at atmospheric pressure without decomposition. It boils at 72–73° at 1 mm.: d_{20} 0.9268, n_D^{20} 1.49886; M.R. (calc'd) 60.64; M.R. (obs.) 60.90.

Anal. Calc'd for $C_{13}H_{20}O$: C, 81.19; H, 10.48.
Found: C, 81.1; H, 10.37.

Preparation of the optically active s-*butyl mesityl ethers.* *s*-Butyl alcohol was resolved through its phthalic acid ester according to the method of Pickard and Kenyon (9) using the time-saving steps suggested by Sprung and Wallis. The *d-s*-butyl alcohol so obtained had a rotation $[x]_D^{24}$ +11.67° (pure liquid 1 dm.) as compared with $[\alpha]_D^{20}$ +12.0° reported by Sprung and Wallis. The mother liquors gave an *l-s*-butyl alcohol $[\alpha]_D^{20}$ −10.84° (pure liquid 1 dm.).

The active alcohols were converted to the corresponding bromides by saturation at 0° with dry hydrogen bromide gas according to the method of Levene and Marker (10). The dextrorotatory alcohol gave a bromide of rotation $[\alpha]_D^{22}$ −23.13° (pure liquid 1 dm. tube) as compared with $[\alpha]_D^{25}$ −13.79° reported by Levene and Marker and $[\alpha]_D^{22}$ −19.77° reported by Sprung and Wallis.

The levorotatory alcohol gave a bromide of $[\alpha]_D^{20}$ +12.71° (pure liquid 1 dm. tube).

The corresponding *d-*, and *l-s*-butyl mesityl ethers were prepared according to the procedure described above for the racemic modification. The mesityl ether from the bromide ($[\alpha]_D^{22}$ − 23.13°) had a rotation $[\alpha]_D^{22}$ +6.97° (pure liquid). The ether which was prepared from the bromide ($[\alpha]_D^{20}$ +12.71°) had a value $[\alpha]_D^{20}$ −3.94° (pure liquid).

Experiments with d, l-s-*butyl mesityl ether.* (a) Rearrangement in the presence of *p*-cresol with zinc chloride and acetic acid.

1. In a typical experiment 48 g. (0.25 mole) of ether and 27 g. (0.25 mole) of pure *p*-cresol were placed in a 500 cc. round bottom flask and shaken with gentle warming until the mixture was homogeneous. To this solution was added 250 g. of a zinc chloride solution prepared by dissolving 75 g. of anhydrous zinc chloride in 200 cc. glacial acetic acid. A reflux condenser and a gas measuring burette with reservoir were connected to the flask and the mixture heated gradually in an oil-bath. At 105° gas was evolved rapidly. The temperature was raised to 115° and kept there until no more butylene was evolved. At this temperature considerable gas absorption occurred. The heating was discontinued when a decrease in volume began to take place.

2. Treatment of reaction product. The procedure used in working up the products of the reaction was essentially that described by Sprung and Wallis. The reaction-mixture was treated with ice-cold alkali until only very slightly acid. Then it was extracted with ether. The ether extract was washed repeatedly with 100-cc. portions of 4% sodium hydroxide solution until the alkaline layer was no longer colored. After the ether solution was washed with a 5% solution of sodium carbonate, and finally with water, it was dried with sodium sulfate and the ether distilled. The residue (56.5 g.) was distilled at reduced pressure in an atmosphere of nitrogen. The fractions collected are described in Table I.

3. Identification of products. None of the above fractions could be induced to crystallize, but crystalline acetic acid derivatives were prepared according to the directions of Niederl and Natelson (11). Fractions I, II, and III gave a product that melted at 144–145° and gave no depression of the melting point when mixed with an authentic sample of mesitoxyacetic acid (m.p. 145°). Fraction IV gave a product that melted at 74–75° and was found to be identical with an authentic specimen of 4-methyl-2-*s*-butylphenoxyacetic acid (m.p. 75–76°). From the material in the trap it was possible to isolate 11.2 g. of pure *s*-butyl acetate.

4. Material soluble in 4% alkali. The alkaline extract obtained above was acidified and extracted with ether. On working up the ether solution, 37.2 g. of residue was obtained. Distillation of this material at 2 mm. gave 23.4 g. of pure *p*-cresol and 2.8 g. of pure mesitol.

(b) Rearrangement of *d, l-s*-butyl mesityl ether in the presence of *p*-cresol by means of sulfuric and acetic acids. A procedure was used similar to that described above. Twenty grams of the inactive ether and 11.2 g. of *p*-cresol were treated with 28.5 cc. of Niederl's reagent (12.5 cc. of conc'd sulfuric acid was dissolved in an amount of glacial acetic acid sufficient to make the total volume 62.5 cc.) for one hour at 120–125°. The mixture was then refluxed for an additional half hour. Gas evolution took place, and 375 cc. of butylene was collected. The reaction-product was worked up in the usual manner and gave (1) 12.6 g. of material soluble in 4% alkali of which 5.5 g. was *p*-cresol and 7.1 g. was mesitol; (2) 18.0 g. of product in-

TABLE I

FRACTION	BOILING RANGE AT 1 MM., °C.	WT., G.
I	65–75	8.9
II	75–80	16.6
III	80–85	6.0
IV	85–95	1.2
Residue		2.3
Trap		16.3

TABLE II

FRACTION	BOILING POINT RANGE 2 MM. PRESSURE, °C.	WT., G.
I	73–80	2.6
II	80–85	3.0
III	85–90	2.6
IV	90–110	4.4
Residue		1.5
Trap		2.5

soluble in 4% alkali. This latter fraction on distillation yielded the fractions described in Table II. Fractions I and II were found to be mesitol as shown by their acetic acid derivatives (m.p. 143° and 142° respectively). Fraction III was a mixture of mesitol and 4-methyl-2-*s*-butylphenol. The mixture of their crystalline acetic acid derivatives, on fractional crystallization, gave two products. The less soluble melted at 143° and gave no depression when mixed with a sample of mesitoxyacetic acid. The more soluble fraction melted at 73° and was identical with the acetic acid derivative of 4-methyl-2-butylphenol. Fraction IV was practically pure 4-methyl-2-butylphenol. *s*-Butyl acetate was the principal constituent in the trap. From the original aqueous solution it was possible to isolate some sodium-*p*-cresol sulfonate.

Rearrangement of d-s-*butyl mesityl ether in the presence of* p-*cresol with sulfuric and acetic acids.* A mixture of 4.5 g. of the dextrorotatory ether $[\alpha]_D^{22}$ +6.97°, and 2.53 g. of *p*-cresol was treated in the usual manner with 7.2 cc. of Niederl's reagent.

The following products were obtained: (a) 49.2 cc. of butylene; (b) 3.4 g. of material insoluble in 4% alkali; (c) 2.7 g. of material soluble in 4% alkali (d) 1.4 g. of sodium *p*-cresol sulfonate; (e) a very small amount of *s*-butyl acetate. All products were optically inactive. As in the previous experiments, the material insoluble in 4% alkali was found to be a mixture of mesitol and *d*, *l*-4-methyl-2-*s*-butylphenol. Completely inactive products were also obtained when the *l*-ether $[\alpha]_D^{20}$ −3.94° was used.

Rearrangement of isopropyl phenyl ether and s-*butyl* p-*cresyl ether in the presence of each other.* The isopropyl phenyl ether was prepared from isopropyl bromide and phenol by the method of Smith. The *s*-butyl *p*-cresyl ether was prepared by the action of *s*-butyl bromide on sodium cresolate by the method of Sprung and Wallis (4).

Forty-five grams (.275 mole) of *s*-butyl *p*-cresyl ether and 37.4 g. of isopropyl phenyl ether were treated with 153 cc. of Niederl's reagent. The reaction-mixture was heated slowly to 115°, where gas was very vigorously evolved. The temperature was held at 115–120° for one hour, after which the solution was gently refluxed for an additional hour. The following products were obtained: (a) 3004 cc. gas (a mixture of propylene and butylene); (b) 21.0 g. of material soluble in 4% alkali; (c) 40 g. of material insoluble in 4% alkali; and (d) 2.3 g. of sulfonates.

TABLE III

FRACTION	BOILING RANGE AT 4 MM., °C.	WT., G.
I	105–109	6.1
II	109–120	9.6
III	120–124	6.4
Residue		8.0
Trap		4.7

The material insoluble in 4% alkali was distilled and gave the fractions described in Table III.

Fractions I and II formed crystalline acetic acid derivatives which melted at 130° and 128–130° respectively. Smith gives 130° as the melting point of the acetic acid derivative of 2-hydroxy-1-isopropylbenzene.

Fraction III was combined with the residue and fractionally distilled at atmospheric pressure. The fraction so obtained gave acetic acid derivatives which melted at 73–75°, the melting point observed for the acetic acid derivative of 2-*s*-butyl-*p*-cresol.

A careful examination of the mother liquors from the derivative preparations, and from the recrystallizations, yielded no crystalline products corresponding in melting point to the compounds one would expect to be formed if an exchange of alkyl groups between the two molecules in question takes place.

We wish to take this opportunity to express our thanks to Merck and Company for the analyses published in this article.

SUMMARY

Optically active *s*-butyl mesityl ether has been prepared and rearranged in the presence of *p*-cresol by treatment with a mixture of sulfuric and acetic acids.

In all the cases studied, optically inactive 4-methyl-2-*s*-butylphenol was produced.

Isopropyl phenyl ether and *s*-butyl *p*-cresyl ether have been prepared and rearranged in the presence of each other. There was no evidence of an intermolecular exchange of alkyl groups.

A discussion of these facts is given in the light of certain mechanisms for the reaction.

PRINCETON, N. J.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

INVESTIGATIONS ON LOCO WEEDS. I. THE ISOLATION OF α- AND β-EARLEINE FROM *ASTRAGALUS EARLEI*

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The occurrence of so-called "loco weeds" in the range country of the Western states has been the cause of rather serious economic losses resulting from the consumption of such weeds by grazing live stock. At the present time, knowledge of the toxic agent or agents in the weeds is meager. The general group of "loco weeds" may be conveniently divided into two classes: those containing selenium, in which part, if not all, of the toxicity is attributed to the presence of compounds of this element, and the non-seleniferous weeds, in which the toxicity is due to substances other than selenium compounds. The more extensive investigations of the seleniferous "loco weeds" have been reviewed by Trelease and Martin (1), and the less detailed work on the non-seleniferous weeds is summarized in various Government publications (2). Investigations of both classes of weed have been largely in the pharmacological and veterinary field.

We have been able to find but two records of recent chemical investigations of non-seleniferous "loco weeds." Couch (3) succeeded in freeing the toxic principle of *Oxytropis lambertii*, or white loco, from many harmless substances, but did not obtain it in crystalline form. Fraps (4) reported the isolation of an admittedly impure, although highly toxic, crystalline tartrate of an alkaloid from *Astragalus earlei*, or Big Bend loco. To the alkaloid he gave the name "locoine." To these studies may be added the earlier work of Prescott (5), Power and Cambier (6), and Crawford (7).

Through the kind cooperation of Dr. Frank P. Mathews, of the United States Department of Agriculture Loco Weed Laboratory at Alpine, Texas, we have secured considerable quantities of *Astragalus earlei*. This material served in the present investigation. At the outset, careful quantitative selenium determinations on the whole weed by the method of Williams and Lakin (8) showed that this element, if present at all, was present to the extent of less than one part per million of the dried weed. Since concentrations of selenium in excess of this amount appear to be necessary to produce selenium poisoning in animals (9), complications from this source appear to be excluded.

[1] Du Pont fellow in chemistry, 1938–1939.

At first, when the general method of Fraps (4) was applied to the extraction of the weed, the impure tartrate described by him was apparently obtained. The finely ground, dried weed was extracted with alcohol and the extract was clarified with basic lead acetate. The toxic principle was then dissolved from much resinous material by boiling absolute alcohol. Precipitation with phosphotungstic acid, followed by decomposition of the precipitate with barium hydroxide, gave an aqueous solution suitable for the preparation of salts. Further recrystallization of the crude tartrate prepared from such a solution resulted in the isolation of pure potassium tartrate. The toxic material accumulated in the mother liquors. We therefore conclude that Fraps' crude "locoine tartrate" contained potassium tartrate mixed with toxic material.

The problem of the isolation of nitrogenous organic substances was thus complicated by the presence of relatively large amounts of potassium in the weed, a difficulty rendered more annoying by the fact that the solubilities of various salts of the organic bases closely approximated those of the corresponding salts of potassium. Elimination of the troublesome potassium ions by the use of various zeolites was explored. The aqueous extract of the dried weed, after clarification with basic lead acetate, was passed through a column of "Zeo Karb H" (a zeolite manufactured specifically for exchanging hydrogen ions for alkali or alkaline earth ions), which had been activated prior to use by two per cent hydrochloric acid. The anticipated exchange of potassium ions for hydrogen ions took place, but the effluent from the column contained no detectable nitrogen, nor did it contain material precipitable with phosphotungstic acid. Elution of the column with dilute hydrochloric acid gave no better results. Better success attended the use of "Decalso" (a zeolite which exchanges alkaline earth ions for those of the alkali metals). Passage of the clarified aqueous extract of the weed over "Decalso," which had been activated previously with barium chloride solution, gave a solution which contained nitrogen and which also contained bases precipitable with phosphotungstic acid. From this solution we have succeeded in isolating two presumably pure nitrogenous bases in the form of their salts, and a considerable amount of *d*-pinite. The details of the purification of the latter, and its isolation from white loco are described in the following paper. As more information concerning the properties of the two bases accumulated, it was possible to eliminate the use of "Decalso," although it appears that this material will be helpful in the isolation of other constituents of the weed.

We suggest the names α- and β-earleine for the two nitrogenous substances. The bases are strikingly similar in their general properties, and their separation was accomplished only by chromatographing a solution of their picrates over aluminum oxide. The empirical formula of α-earleine,

as derived from analyses of the picrate, styphnate, and hydrobromide, corresponds to that of a triacidic base, $(C_{16}H_{37}N_3O_7)_x$. β-Earleine similarly appears to be a triacidic base, $(C_{16}H_{37}N_3O_4)_x$. With the amount of material available it has not been possible to determine exactly the molecular sizes of the two bases. Both substances resemble quarternary ammonium hydroxides in their general behavior, and apparently contain a methyl carbinol group, and at least one primary amine group. They are optically inactive.

In the isolation of α- and β-earleine we have used cats to follow the course of the toxic activity of the weed. Our observations in general parallel those of Fraps (4). It is necessary to feed a crude extract of from one to two kilos of dried weed in order to produce definite symptoms of locoism. The disease manifests itself by lack of muscular coördination which may result in collapse when the cat jumps voluntarily from a height as low as six inches. The hind legs seem stiff and the animal walks with a crouching gait. The eyes assume a staring appearance and the head shakes continuously. Drs. Abner Wolf and Homer Kesten, of the College of Physicians and Surgeons, have examined the gross and micropathological symptoms of a number of locoed cats. Their findings will be reported elsewhere.

Neither α- nor β-earleine appears to be toxic to cats. However, we have secured several other fractions of material from the weed which are highly active and from which impure crystalline material has been isolated. Work on these fractions as well as structural studies on the two bases here described is being continued.

We wish to express our appreciation for the kind cooperation of Dr. F. P. Mathews in collecting the weed used in this investigation, and of the Permutit Company, who generously contributed the special zeolites used.

EXPERIMENTAL

All melting points are corrected.

Extraction and isolation of α- and β-earleine. As finally developed, the procedure for the isolation of the two bases as picrates is as follows. One hundred pounds of finely ground *Astragalus earlei* was soaked overnight in 20 gal. of 70% alcohol and was then pressed out in a hydraulic press. The process was repeated twice more, the third extract being used for the first extraction of a subsequent batch. The combined extracts were concentrated at reduced pressure at 40° to a volume of about 5 l. Fifteen liters of water was added to the concentrate, and the clear, supernatant liquor was decanted from the water-insoluble portion. Ten liters more of water was added to the residue and, after agitation, the supernatant liquor was again decanted. The combined aqueous extracts were treated with excess basic lead acetate solution and the precipitate was filtered through a layer of diatomaceous earth. After removal of the excess lead with hydrogen sulfide, the solution retained practically all of the toxic activity of the original weed.

The solution was divided into four equal parts and concentrated at reduced pressure at 40° to a thick syrup. The residual water was removed by repeated concentration with absolute alcohol and benzene. Each of the resinous residues was extracted with 3 l. of commercial absolute alcohol with vigorous agitation at 55°. After standing overnight in the refrigerator, the supernatant alcoholic extract was decanted and the residual resin was again extracted with 1 l. of absolute alcohol per portion. The combined alcoholic extracts from the four portions were concentrated to about 5 l. and refrigerated. On standing, with occasional scratching, *d*-pinite gradually crystallized. After the pinite was filtered, the solution was concentrated to about 3 l. and again refrigerated. After 2 or 3 days, crystallization of pinite was substantially complete. The filtrate from the pinite was concentrated to a resin, 2 l. of water was added, and about 1 l. of solvent was removed under reduced pressure in order to remove traces of alcohol. The volume was then made up to about 7 l. with water and the solution was filtered from a slight amount of insoluble material. This solution contained the major portion of the toxic material present in the original weed.

A 24% solution of phosphotungstic acid in 4% sulfuric acid was added to the aqueous solution obtained above until precipitation was complete. The supernatant liquid was immediately decanted from the heavy curdy precipitate, which was quickly washed with five 500-cc. portions of water before it congealed. The precipitate was combined with any that had come down in the mother liquor and washings, suspended in a mixture of 1.5 l. of water and 1 l. of acetone, and then decomposed as usual in the cold with barium hydroxide. About one-half of the original toxic material was present in the solution of the decomposed phosphotungstates. This solution was concentrated to dryness under reduced pressure and the residue was dissolved in 1400 cc. of warm 95% alcohol. Saturated alcoholic picric acid solution was added until the solution was just acid to bromphenol blue. Two and eight-tenths liters of benzene was added and the solution was cooled.

This solution of picrates was passed by gravity through an adsorption column of aluminum oxide (Baker and Adamson, reagent grade) 120 cm. long and 3.3 cm. in diameter. The column gradually became completely colored and the liquid running out the bottom was yellow. After passage of all the solution, the column was sucked as dry as possible at the water-pump.

α-Earleine. The upper two-thirds of the aluminum oxide column was eluted with hot 95% alcohol. On concentration of the eluate, a picrate crystallized. The yield was about 1.5 g. per 100 lb. of dried weed. After five recrystallizations from alcohol, the picrate formed long, silky, yellow needles and melted constantly at 250°. It was optically inactive. Although the picrate appeared to be homogeneous, it apparently contained sodium and deflagrated on attempted combustion. A sodium-free picrate was obtained by dissolving the substance melting at 250° in water, acidifying the solution with sulfuric acid, extracting the picric acid with benzene, and reprecipitating the base as the phosphotungstate. α-Earleine picrate, obtained as before by decomposition of this phosphotungstate, melted constantly with some decomposition at 184° after recrystallization from alcohol.

Anal. Calc'd for $(C_{16}H_{37}N_3O_7 \cdot 3C_6H_3N_3O_7)_x$: C, 38.1; H, 4.3; N, 15.7.
Found: C, 38.3; H, 4.1; N, 15.6.

α-Earleine styphnate melted with decomposition at 186–188° after recrystallization from alcohol.

Anal. Calc'd for $(C_{16}H_{37}N_3O_7 \cdot 3C_6H_3N_3O_8)_x$: C, 36.5; H, 4.2; N, 15.0.
Found: C, 36.8; H, 4.1; N, 15.0.

α-Earleine hydrobromide was prepared by adding cold, dilute alcoholic hydrobromic acid to an alcoholic solution of the base. The hydrobromide crystallized from its strongly chilled alcoholic solution as rectangular prisms which melted at 225° with partial sublimation.

Anal. Calc'd for $(C_{16}H_{37}N_3O_7 \cdot 3HBr)_x$: C, 30.7; H, 6.6; N, 6.7; Br, 38.4.
Found: C, 31.1, 30.8; H, 6.2, 6.6; N, 7.0; Br, 40.1.

The free base, α-earleine, formed colorless prisms from absolute alcohol. It is insoluble in acetone and ethyl acetate. It is so hygroscopic that an accurate melting point determination was impossible. The analytical data are probably unreliable for the same reason.

Anal. Calc'd for $(C_{16}H_{37}N_3O_7)_x$: C, 50.1; H, 9.7; N, 11.0.
Found: C, 48.1; H, 10.2; N, 11.2.

α-Earleine is saturated as far as immediate reaction with permanganate is concerned, but is slowly oxidized by this reagent when warmed on the steam-bath. Bromine water is not decolorized by the base. Dilute ferric chloride gives neither a color nor a precipitate. The base gave a positive iodoform test, but did not react with the usual carbonyl reagents. Its behavior with nitrous acid and with benzenesulfonyl chloride indicates the presence of at least one primary aliphatic amine group. Its alcoholic solution gives a precipitate with alcoholic mercuric chloride solution. The Molisch test and biuret test were negative. The substance did not contain methoxyl groups.

β-Earleine. The solution which passed through the aluminum oxide column was concentrated, and gave about 25 g. of crude β-earleine picrate per 100 lb. of dried weed. After 5 recrystallizations from alcohol, the picrate formed bright yellow, rectangular prisms and melted constantly at 247°. Although this melting point is close to that of α-earleine picrate before removal of sodium, a mixture of the two melted at 190°. When either the sodium-containing α-earleine picrate or β-earleine picrate is chromatographed over aluminum oxide in 2:1 benzene–alcohol solution, but a single ring is formed. A mixture of the two picrates under similar conditions gives two rings. β-Earleine picrate is optically inactive.

Anal. Calc'd for $(C_{16}H_{37}N_3O_4 \cdot 3C_6H_3N_3O_7)_x$: C, 39.8; H, 4.4; N, 16.5.
Found: C, 39.8, 39.6; H, 4.7, 4.7; N, 16.6.

The styphnate melted with decomposition at 209° with sintering above 180° after recrystallization from alcohol.

Anal. Calc'd for $(C_{16}H_{37}N_3O_4 \cdot 3C_6H_3N_3O_8)_x$: C, 38.1; H, 4.3; N, 15.7.
Found: C, 37.9; H, 3.9; N, 15.5.

β-Earleine hydrobromide formed irridescent crystals on strong chilling of its alcoholic solution. It melted with decomposition at 296° on slow heating, and at 304° on more rapid heating. It is so hygroscopic that accurate analytical data could not be obtained.

The free base, β-earleine, melted with decomposition at about 187° after recrystallization by careful addition of dry acetone to its solution in absolute alcohol. The base is so hygroscopic that analytical data were impossible to obtain. It is saturated towards permanganate in the cold but is slowly oxidized by this reagent on standing. It does not decolorize bromine water. Ferric chloride solution gives a dark precipitate, and excess of the reagent dissolves the precipitate with evolution of gas. The action of nitrous acid and of *p*-toluenesulfonyl chloride indicates the presence of at least one primary aliphatic amine group. The base gives a very strong iodoform test but does not react with the usual carbonyl reagents. Precipitates were obtained with silicotungstic acid and with alcoholic mercuric chloride solution. The biuret and Molisch tests were negative. When β-earleine is heated in a test

tube, it decomposes and gives off a gas with the odor of a lower aliphatic amine. We have not had sufficient material to identify this amine, but the general behavior is characteristic of quarternary ammonium bases. Crystalline acetyl and benzoyl derivatives of β-earleine have been prepared, but in insufficient quantity for purification.

The micro-analyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

INVESTIGATIONS ON LOCO WEEDS. II. THE ISOLATION OF *d*-PINITE FROM *ASTRAGALUS EARLEI* AND FROM *OXYTROPIS LAMBERTII*

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In the preceding paper (1) the isolation of two organic bases from *Astragalus earlei*, or Big Bend loco weed, was described. At the same time considerable quantities of *d*-pinite were encountered in the weed. In addition, we have commenced a preliminary study of the constituents of *Oxytropis lambertii*, or white loco weed, which had previously been investigated incompletely by Couch (2). Inasmuch as the same sugar has been isolated from both weeds in approximately the same amounts, we are taking this opportunity to record our observations.

d-Pinite, the monomethyl ether of inosite, has been obtained chiefly from the sap of *Pinus lambertiana Dougl.* (3), and as a by-product in the preparation of coniferin (4). Griffin and Nelson (5) later made a somewhat more detailed study of the sugar and prepared a number of derivatives. The substance isolated by us from both varieties of loco weed is identical in every respect with the material of Griffin and Nelson. We were fortunate in having available samples of the original compounds prepared by Griffin and Nelson.

EXPERIMENTAL

For the isolation of *d*-pinite from *Astragalus earlei* in best yield, the procedure is slightly different from that given in the preceding paper. The extraction of the ground weed, clarification of the extract with basic lead acetate, and concentration to a resin were carried out as for the isolation of the nitrogenous components. The resin was then extracted several times with boiling commercial absolute alcohol, rather than at 55°. The combined alcoholic extracts were clarified by liberal use of Norit and diatomaceous earth. On standing in the refrigerator, with occasional scratching, the pinite gradually crystallized. The yield was about 10 g. per kilo of dried weed. More of the sugar may be obtained by concentrating the mother liquors, as well as by further extraction of the original resin.

d-Pinite, as thus obtained, melted at 188°, after recrystallization four times from alcohol. A sample of Griffin and Nelson's (5) pinite melted at 186°, and mixtures of varying amounts of the two showed no depression. The specific rotation was $[\alpha]_D^{25}$ +65° (c = 2.480 in water); Griffin and Nelson report $[\alpha]_D^{25}$ +65° for *d*-pinite.

[1] DuPont fellow in chemistry 1938-1939.

Anal. Calc'd for $C_7H_{14}O_6$: C, 43.3; H, 7.2; OCH_3, 15.7.
Found: C, 43.3; H, 7.5; OCH_3, 16.0.

Acetyl pinite prepared from our sugar melted at 98°. Griffin and Nelson's material melted at 98°, and a mixture of the two showed no depression. For our acetyl derivative, $[\alpha]_D^{25}$ +8.6° (c = 1.970 in alcohol); for Griffin and Nelson's acetyl derivative, $[\alpha]_D^{25}$ +8.7° (c = 1.960 in alcohol).

Anal. Calc'd for $C_{17}H_{24}O_{11}$: C, 50.5; H, 5.9.
Found: C, 50.7; H, 6.2.

Substantially the same procedure was used in isolating pinite from *Oxytropis lambertii* in about the same yield. The sugar was identical in all respects with pinite from the other two sources. The acetyl derivatives were also identical.

The micro-analyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

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

3-(*p*-DIMETHYLAMINOBENZAL)-6-NITROPHTHALIDE AND 3-(*p*-DIMETHYLAMINOBENZYL)-6-AMINOPHTHALIDE

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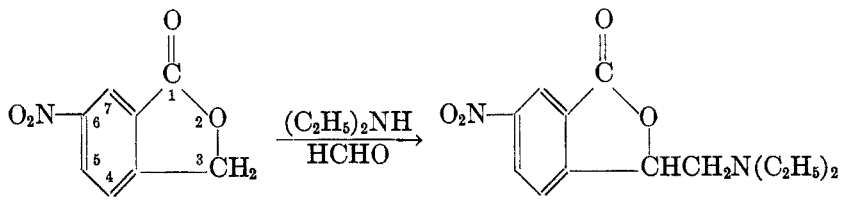
Although the methylene group in phthalide is not sufficiently reactive to condense with aldehydes, the introduction of a nitro group in the 6-position has been shown to cause the 6-nitrophthalide (I) to condense with aromatic aldehydes (1). In the present work an attempt was made to carry out the Mannich reaction (2) on 6-nitrophthalide in order to obtain the 3-diethylaminomethyl-6-nitrophthalide (II). Reduction of the nitro

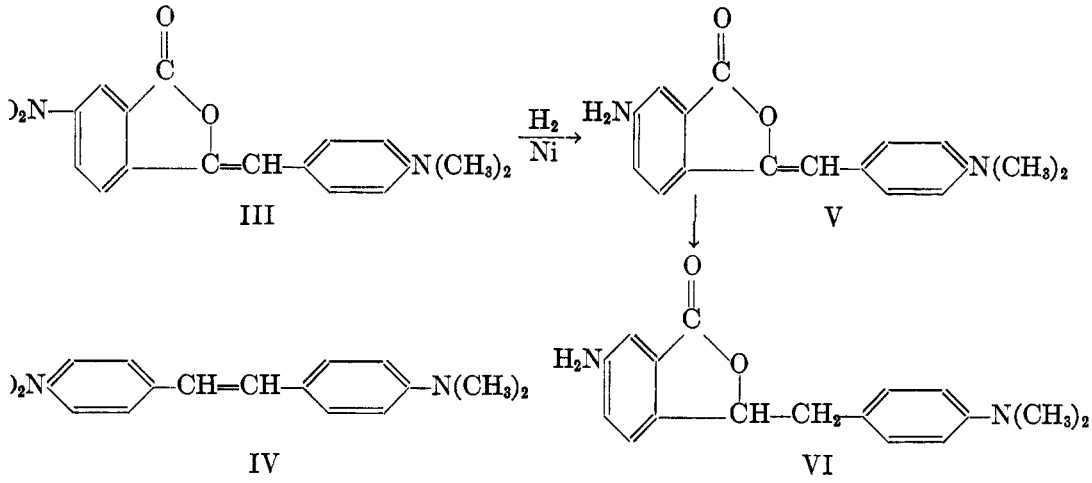


I II

group would then give a 6-amino derivative whose pharmacological properties would be very interesting. However, up to the present, it has not been possible to carry out the Mannich reaction on 6-nitrophthalide, although a variety of experimental conditions were tried. Hence, attention was turned to the products obtainable by condensation with aryl aldehydes.

6-Nitrophthalide condensed smoothly with *p*-dimethylaminobenzaldehyde in the presence of piperidine to give an 87% yield of the benzal compound III. This compound existed in three polymorphic forms. Crystallization from acetone or chloroform gave shining green hexagonal plates, while cooling of a saturated solution of the compound in benzene or dioxane yielded dark purple, almost black, plates. When the melting point of each of those forms was determined on the Köfler hot stage under a microscope, it was observed that as the melting point was approached, both changed over to a third form which consisted of reddish rhombic plates. This change was complete before melting occurred and only one melting point of the three forms was noted: *viz.* 283–284°.

The intense color of this compound is not surprising in view of its close



structural relationship to the phthaleins and the stilbene dyes (3). 4-Nitro-4′-dimethylaminostilbene (IV), which contains a system of conjugated double bonds and resonating groups identical with that in compound III, is a red dye (4).

Since the base (III) dissolved in ten per cent hydrochloric acid but precipitated on dilution, it was found possible to dye wool directly by treating the wool with a hydrochloric acid solution of the base and then washing thoroughly with water. The wool so treated was colored a bright autumn rust which was fast to washing and ultraviolet light.

Catalytic reduction of the base (III) using Raney nickel and hydrogen at a pressure of about 2000 pounds gave first the bright, irridescent, orange 3-(*p*-dimethylaminobenzal)-6-aminophthalide (V) and then, after filtering and addition of fresh catalyst, the canary yellow 3-(*p*-dimethylaminobenzyl)-6-aminophthalide (VI). Both formed acetyl derivatives on treatment with acetic anhydride.

The 3-(*p*-dimethylaminobenzyl)-6-aminophthalide (VI) is a vinylog (5) of the 6-amino compound derived from II. Its salts with mineral acids were very hygroscopic. It failed to dissolve completely in one equivalent of dilute hydrochloric acid, but yielded a clear solution with two equivalents of acid. This solution proved to be so acidic that it was extremely irritating to the eyes and skin of a rabbit. Hence, no definite pharmacological studies of its action could be made.

EXPERIMENTAL

6-Nitrophthalide. The method of Borsche, Diacont and Hanau (1) was used in the preparation of this compound. A mixture of 26.8 g. (0.2 mole) of phthalide in 30 cc. of concentrated sulfuric acid was added dropwise to a mixture of 23 g. of

potassium nitrate in 50 cc. of concentrated sulfuric acid cooled to 0°. The temperature was not allowed to rise above 5° at any time during the addition. After all of the phthalide solution had been added, the mixture stood twelve hours and was then decomposed on cracked ice. The crude product so obtained weighed 36 g. Recrystallization from dilute acetic acid yielded 28 g. (78% of the theoretical) of fine, pale yellow needles which melted sharply at 145°.

3-(p-Dimethylaminobenzal)-6-nitrophthalide. Twelve grams (0.08 mole) of *p*-dimethylaminobenzaldehyde was heated at 185-190° for one hour with 14.4 g. (0.08 mole) of 6-nitrophthalide and four drops of piperidine as catalyst. Water was evolved and the mixture became molten and turned dark purple. After cooling, the cake which formed was broken up and ground in a mortar to a fine powder. It was then extracted repeatedly with one liter of dioxane until none of the original powder was left. Concentration of the dioxane solution yielded very fine dark purple crystals amounting to 21.7 g. (87% of the theoretical). The product so prepared melted at 283–284° with decomposition. Borsche, Diacont and Hanau (1) mention this compound in a footnote and give a melting point of 270° but no additional data.

Anal. Calc'd for $C_{17}H_{14}N_2O_4$: C, 65.80; H, 4.55; N, 9.03.
Found: C, 65.98; H, 4.66; N, 9.09.

3-(p-Dimethylaminobenzal)-6-aminophthalide. A suspension of 6.2 g. (0.02 mole) of the benzal compound and 6 g. of Raney nickel in 700 cc. of purified dioxane was hydrogenated in a high pressure reducing machine (6) at a pressure of 2100 pounds at 90° for one hour. The catalyst was then filtered and the filtrate concentrated to 50 cc. Three grams (53.6% of the theoretical) of the bright orange crystals melting at 259–262° separated.

Anal. Calc'd for $C_{17}H_{16}N_2O_2$: C, 72.84; H, 5.76; N, 10.00.
Found: C, 72.80; H, 5.99; N, 10.25.

The 3-(*p*-dimethylaminobenzal)-6-aminophthalide was also prepared by catalytic reduction using platinum catalyst (7) in a 50% sulfuric acid solution under approximately three atmospheres pressure.

3-(p-Dimethylaminobenzyl)-6-aminophthalide. A mixture of 7.3 g. (0.0235 mole) of the nitrobenzal compound dissolved in 1000 cc. of dioxane was hydrogenated for one hour at a pressure of 2315 pounds, and a temperature of 100° using 6 g. of Raney nickel catalyst. The catalyst was filtered and fresh catalyst added to the highly fluorescent solution. The mixture was again hydrogenated for an hour at a pressure of 2140 pounds and a temperature of 100°. The catalyst was filtered and the dioxane distilled under reduced pressure until only about 50 cc. of liquid remained. The product separated in the form of bright yellow crystals which weighed 3.5 g. (53% of the theoretical) and melted at 204.5°.

Anal. Calc'd for $C_{17}H_{18}N_2O_2$: C, 72.31; H, 6.43; N, 9.94.
Found: C, 72.30; H, 6.66; N, 10.05.

This compound was likewise prepared by reduction in a 50% sulfuric acid solution using platinum catalyst. The aminobenzal compound was not isolated in this case but after the initial reduction of the nitro group, the catalyst was filtered and fresh catalyst added. The yields in these reductions in strong sulfuric acid were much lower, being on the order of 5%.

3-(p-Dimethylaminobenzal)-6-acetylaminophthalide. This compound was prepared by boiling about a tenth of a gram of the aminobenzal compound for one hour with acetic anhydride. The excess acetic anhydride was decomposed by pouring the mixture into boiling water. The bright orange powder thus obtained

was recrystallized by evaporation of an alcohol solution of the compound which had been diluted with a small amount of water. The light fluffy plate-like crystals melted at 287°.

Anal. Calc'd for $C_{19}H_{18}N_2O_3$: N, 8.69. Found: N, 8.44.

3-(p-Dimethylaminobenzyl)-6-acetylaminophthalide. This was prepared by a procedure similar to that followed in the preparation of the acetyl derivative of the aminobenzal compound. However, on decomposition of the excess acetic anhydride, the free base did not precipitate. Neutralization with dilute sodium hydroxide solution, however, yielded the yellow acetyl derivative. This powder was recrystallized from a water–alcohol mixture prepared by adding water dropwise to a hot alcohol solution of the compound until a slight cloudiness, which was then destroyed by addition of a drop of alcohol, was produced. The granular yellow crystals melted at 210°.

Anal. Calc'd for $C_{19}H_{20}N_2O_3$: N, 8.64. Found: N, 8.69.

SUMMARY

6-Nitrophthalide did not undergo condensation in the Mannich reaction, but did condense with *p*-dimethylaminobenzaldehyde to produce 3-(*p*-dimethylaminobenzal)-6-nitrophthalide. This compound was highly colored and was found to be a direct dye for wool.

Catalytic reduction of 3-(*p*-dimethylaminobenzal)-6-nitrophthalide produced first the substituted 6-aminophthalide, and complete reduction formed 3-(*p*-dimethylaminobenzyl)-6-aminophthalide.

URBANA, ILL.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

ACTION OF BROMINE ON VANILLIN, ISOVANILLIN, AND SOME OF THEIR DERIVATIVES, AND MODIFICATION OF THE DIRECTIVE INFLUENCE OF HYDROXYL IN THESE COMPOUNDS

L. CHAS. RAIFORD AND MELVILLE F. RAVELY

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The position taken by a radical that enters a benzene substitution product is determined largely by the character of the substituent already there. The rules formulated to cover this behavior (1) apply in general to those cases where but one substituent is present in the starting material, and they predict the structures of the chief products only. When two or more substituents are present, the position taken by a new one is less easily predicted; consequently it was desired to study compounds in which this behavior could be tested further.

In such studies another consideration is of interest, *viz.*, the extent to which the directive influence of hydroxyl may be modified or suppressed by changing its composition through acylation or alkylation[1]. The derivatives of vanillin[2] and isovanillin offered an opportunity to extend such studies.

Derivatives of vanillin. In previous work it has been found that treatment of vanillin, 3-methoxy-4-hydroxybenzaldehyde, with chlorine (2), bromine (3), iodine (4), and nitric acid (5), respectively, gives high yields of derivatives in which the entering substituent takes position 5 (CHO = 1). Since that position is ortho with respect to hydroxyl and meta with respect to the aldehyde group it might be assumed, on the basis of the above observations alone, that these radicals exercised equal influence in determining the position taken by the entering substituent. That this is probably not the case is indicated by the work of Martinsen (6), who found that ortho-para directing groups facilitate substitution in the benzene ring, while groups of the meta directing type have a retarding influence. Therefore, in the reactions cited above it would appear that the chief directive influence was probably exerted by hydroxyl. When acetylvanillin is used,

[1] Data on the behavior of alkyl derivatives of vanillin, soon to be published, have been obtained by R. P. Perry formerly of this laboratory.

[2] In recent years all the chlorine and bromine substitution products of vanillin demanded by theory have been obtained in this laboratory [*J. Am. Chem. Soc.*, **57**, 2500 (1935)].

bromination gives 87% of the 6-bromo derivative (7), while nitration gives as much as 80% of the 2-nitro compound and about 5% of the 6-isomeride (8). Benzoylvanillin gives similar results (9), indicating that acylation of hydroxyl suppresses its activity to such an extent that the directive influence in the acyl derivatives is due to the methoxyl radical[3]. Apparently, the aldehyde radical, which occupies position 1, exercises no influence in these types.

In view of these observations, it was of particular interest to study the behavior of related compounds in which position 1 was occupied by some meta-directing radical other than the aldehyde group. For this purpose vanillonitrile, vanillic acid, methyl vanillate, and 1-nitro-3-methoxy-4-hydroxybenzene [4-nitroguaiacol (OH = 1)] were selected. Treatment of these with bromine gave, in each case, the 5-bromo derivative in high yield, indicating again that the position taken by halogen must be determined chiefly by the hydroxyl group. Next, each starting material was acetylated and the products were tested with bromine as before[4]. The aldehyde, the acid, and the ester gave the corresponding 6-bromo derivatives in yields shown below. From the nitrile and the nitro compound no reaction products could be isolated, but starting material was recovered as shown in Table I.

Derivatives of isovanillin. Bromination of isovanillin was carried through in accordance with the general directions of Henry and Sharp (10), with a much larger quantity of material than they used. The product consisted of 33% of 2-bromoisovanillin and 55% of the 6-isomeride. With the hope of securing the 5-bromo compound by use of the Sandmeyer reaction, acetylisovanillin was nitrated as directed by Pschorr and Stöhrer (11), and the 5-nitro compound, which melted at 119–120.5°[5], was subjected to the action of several reducing agents. With ferrous hydroxide in the presence of ammonia water (12), the required amino compound seemed to be produced, but it could not be isolated in pure form. In another experiment sodium amalgam was used and the mixture was kept faintly alkaline by addition of hydrobromic acid. When the change seemed to be complete, the liquid was decanted from the mercury, and rendered neutral by addition of acid. The precipitate obtained was dissolved in hydrobromic acid,

[3] This difference in directive influence between acyloxyl and alkoxyl has been noted by Klemenc [*Monatsh.*, **33**, 701 (1912)] and by Cardwell and Robinson [*J. Chem. Soc.*, **107**, 256 (1915)] in the nitration of acetylguaiacol.

[4] In these experiments sodium acetate was added to the reaction-mixture to interact with the hydrogen bromide liberated and thus prevent the hydrolysis of the acetyl derivative. This precaution was found necessary by Raiford and coworkers [*J. Am. Chem. Soc.*, **49**, 1078 (1927); **53**, 1057 (1931)] in the study of closely related cases.

[5] Pschorr and Stöhrer, *loc. cit.*, reported 113°.

cooled to 0°, and diazotized with sodium nitrite. Treatment of the resulting product with a hydrobromic acid solution of cuprous bromide gave a black, resinous material from which nothing could be identified.

To obtain isovanillonitrile, isovanillin was converted to the oxime and this was changed to the acetoxynitrile by boiling with purified acetic anhydride (13),[6] as directed by Marcus and elaborated by Raiford and Potter (14). The nitrile was obtained by hydrolysis of the acetoxy derivative with normal potassium hydroxide solution at room temperature for a few hours. Treatment of the nitrile with bromine gave 32% of the 2-bromo and 15% of the 6-bromo derivative, both in purified form. Next

TABLE I

BROMINATION OF VANILLIN AND RELATED COMPOUNDS

STARTING MATERIAL	SUBSTITUENT IN POSITION 1	POSITION TAKEN BY HALOGEN	YIELD %
Vanillin	CHO	5	88
Acetylvanillin		6	87
Vanillonitrile	CN	5	85
Acetovanillonitrile		No reaction product obtained	[a]
Vanillic acid	COOH	5	82
Acetylvanillic acid		6	80
Methyl vanillate	$COOCH_3$	5	97
Methyl ester of acetylvanillic acid		6	30[b]
1-Nitro-3-methoxy-4-hydroxybenzene (4-nitroguaiacol)	NO_2	5	87
1-Nitro-3-methoxy-4-acetoxybenzene		No reaction product isolated	[c]

[a] 99% of starting material was recovered.

[b] This represents purified compound. The crude product contained considerable resin and starting material.

[c] Starting material was recovered to the extent of 88%.

the nitrile was hydrolyzed to the acid by boiling with potassium hydroxide solution, though it was subsequently found that oxidation of an acetic acid solution of acetylisovanillin with potassium permanganate was more satisfactory for the preparation of the acid. Bromination of isovanillic acid gave but one of the expected products, the 6-isomeride in a yield of 13%, while 27% of purified starting material was recovered.

[6] When the available C. P. grade was used, the acetoxynitrile obtained was contaminated with resin and was difficult to purify. In subsequent work the anhydride was purified by fractionation in an apparatus with ground glass joints, and the portion that distilled at 137.5–139° was collected for use. With some lots of C. P. grade, more than one-fourth was rejected in this way.

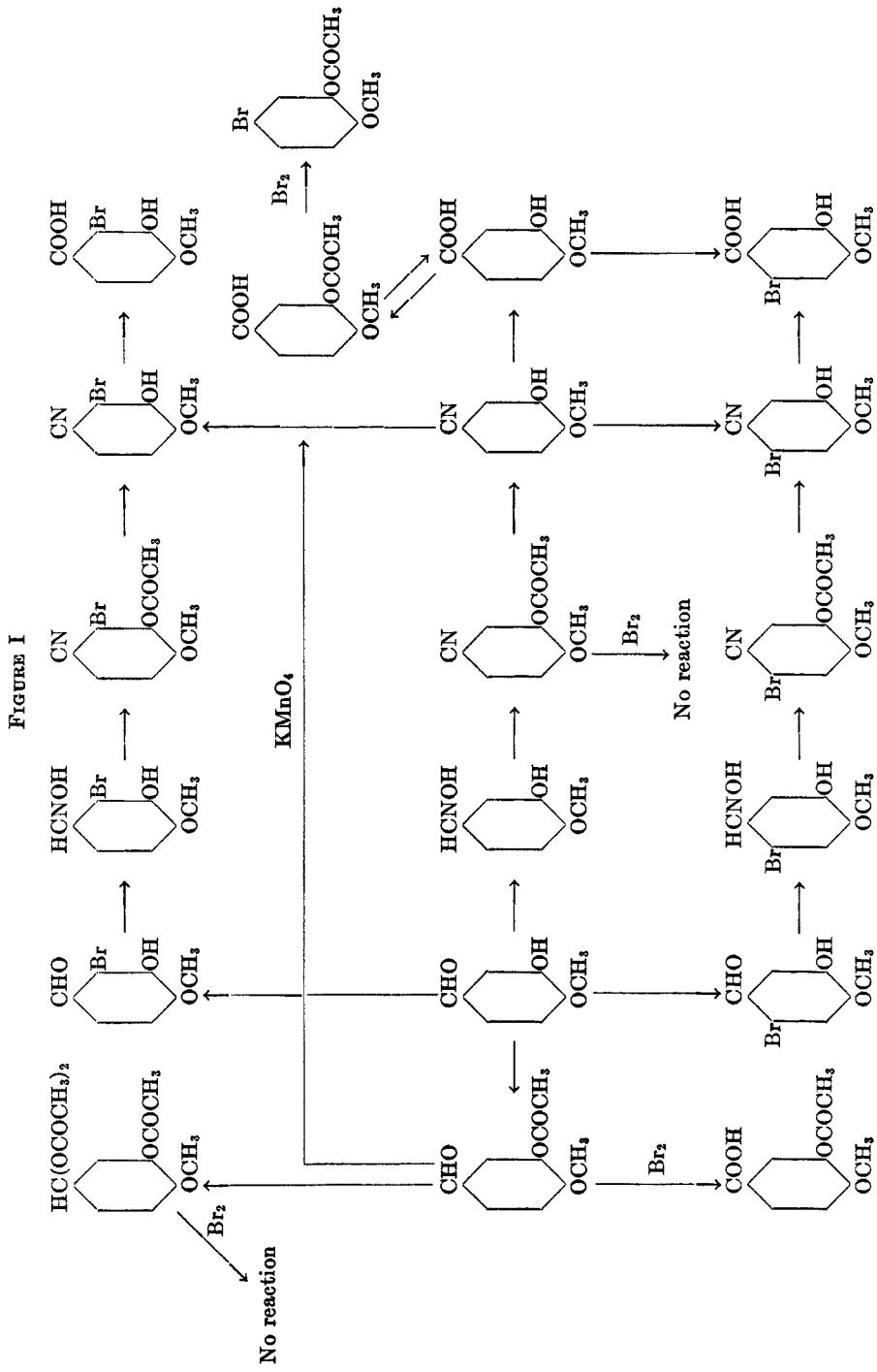
HC(OCOCH3)2
OCOCH3
OCH3
Br2
No reaction
CHO
Br
OH
OCH3
HCNOH
CN
OCOCH3
KMnO4
Br2
No reaction
COOH
Br2
COOH
OCOCH3
OCH3
Br
OCOCH3
OCH3

FIGURE I

Attempts to brominate acetylisovanillin were unsuccessful. With acetic acid solution at 50–60°, and iodine as a catalyst, starting material was recovered to the extent of 95%. When sodium acetate was present in the above mixture and bromine was added at the temperature of the steam bath, the aldehyde was oxidized[7] and acetylisovanillic acid m.p. 216–218°,[8] was obtained. In subsequent experiments attempts were made to protect the aldehyde group. Isovanillin was converted into 3-acetoxy-4-methoxybenzal diacetate (see below), and this was subjected to the action of bromine. Starting material only could be recovered.

Bromination of acetylisovanillic acid proved to be impossible under any conditions here tried. When an acetic acid solution of the acetyl acid in the presence of sodium acetate was treated with 50% excess of bromine for eight to ten hours on a steam-bath, the product turned out to be a mixture with a wide melting range. By fractional crystallization the portion containing halogen was obtained in nearly pure form in a yield of about 12%. It melted at 62–64° and was identified as 2-methoxy-5-bromophenyl acetate, previously obtained by Jona (15) by acetylation of 5-bromoguaiacol (OH = 1) and by Hindmarsh, Knight and Robinson (16) by the bromination of acetylguaiacol. In the present work the carboxyl group was replaced by halogen.

Treatment of an acetic acid solution of acetylisovanillonitrile, to which sodium acetate and iodine had been added, with 50% excess of bromine, in the cold and at the temperature of the steam-bath failed to give a bromine substitution product. About 75% of starting material was recovered. These relations are shown in Figure I.

EXPERIMENTAL

Methyl 5-bromovanillate. The methyl ester of vanillic acid, previously prepared by Matsmoto (17), who recorded no yield, was here obtained in 53% yield of purified material as follows: Gaseous hydrogen chloride was bubbled for about five hours through a boiling solution of 40 g. of vanillic acid in 200 cc. of absolute methyl alcohol under a reflux condenser, the upper end of which was protected by a drying-tube containing calcium chloride. The solution became dark brown. About two-thirds of the solvent was distilled off, the residue poured into four volumes of water, the oil that separated was extracted with ether, the solution was dried with calcium chloride, and the ether distilled. The greater portion of the oil distilled at 140–141° at 4 mm., and after several days at about −5° gave colorless needles that melted at 63–64°. Matsmoto recorded 62-63°.

A mixture of equal quantities of this ester and anhydrous sodium acetate was dissolved in about three times its weight of acetic acid, a crystal of iodine was added,

[7] Raiford and Milbery [*J. Am. Chem. Soc.*, **56**, 2729 (1934)] found that attempts to brominate acetic acid solutions of 4-benzoyloxybenzaldehyde and a number of its substitution products, in contact with air, gave the corresponding acids.

[8] Matsmoto [*Ber.*, **11**, 130 (1878)] reported 206-207°.

and slightly more than one molecular proportion of bromine was run in slowly. The mixture was allowed to stand overnight and was then diluted with 200 cc. of water, which precipitated the product. A yield of 97% was obtained. Crystallization from alcohol gave tan leaflets that melted at 152–152.5°.

Anal. Calc'd for $C_9H_9BrO_4$: Br, 30.65. Found: Br, 30.76.

Hydrolysis of the above product with caustic potash solution gave 5-bromovanillic acid that melted at 231–232°, as previously recorded by Raiford and Potter (14).

Bromination of the acetyl derivative. Ten grams of methyl vanillate was dissolved in 40 cc. of freshly distilled acetic anhydride, a drop of concentrated sulfuric acid was added, the whole was allowed to stand overnight, and the solution poured into water, which precipitated an oil. Gentle warming and stirring caused the oil to solidify. A yield of 93% was obtained. Crystallization from 50% alcohol gave colorless fibrous masses, resembling cotton, that showed a melting point of 75.5–76°. Attempts were made to analyze the compound by determination of acetyl by the method used by Freudenberg and Harder (18). Non-uniform results varying from 18.78% to 21.39% of acetyl were obtained, while the theory requires 19.20%. Analysis for carbon and hydrogen showed that the product was nearly pure.

Anal. Calc'd for $C_{11}H_{12}O_5$: C, 58.92; H, 5.35.
Found: C, 58.74; H, 5.40.

When 10 g. of the acetyl derivative was brominated as described above for the ester, and the product was poured into water, 11 g. of a solid precipitated; it contained resin and was difficult to purify. Crystallization from butyl alcohol gave 6.5 g. of colorless material that showed a melting range of 60–65°. This material was shaken with slightly warm alcohol, which removed starting material and left a residue that, after further crystallization from alcohol, separated in nearly colorless needles that melted at 95–95.5°.

Anal. Calc'd for $C_{11}H_{11}BrO_5$: Br, 26.40. Found: Br, 26.43.

Hydrolysis of this derivative with potassium hydroxide solution gave 6-bromovanillic acid that melted at 190–191° (19).

Acetylisovanillin. To a solution containing 152 g. of isovanillin and 56 g. of potassium hydroxide in 500 cc. of water, which was cooled to about 0°, a solution of 100 cc. of specially purified acetic anhydride in 100 cc. of ether was added dropwise, with constant shaking and continued cooling. The product separated as a liquid which soon solidified in colorless pellets. Crystallization from 50% alcohol gave thick colorless needles that melted at 88–89°[9]. By working up the mother liquor, a yield of 85% was obtained. Analysis indicated that our product was nearly pure.

Anal. Calc'd for $C_{10}H_{10}O_4$: C, 61.85; H, 5.15.
Found: C, 61.80; H, 5.18.

3-Acetoxy-4-methoxybenzal diacetate. Five grams of isovanillin was dissolved in 25 cc. of acetic anhydride and a drop or two of concentrated sulfuric acid was added. The liquid, which developed a dark purple color and became warm, was allowed to stand about an hour and was then poured into a solution of sodium carbonate, which precipitated a yellowish solid. Repeated crystallization from alcohol gave large, nearly colorless plates that melted at 118–119°. The yield of purified material was 62%.

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[9] Pschorr and Stöhrer [*Ber.*, **35**, 4397 (1902)] obtained, by boiling isovanillin with acetic anhydride, a product which they recorded as melting at 64° but which they reported as having the composition of the one here under consideration. Later, Pacsu and Vargha [*Ber.*, **59**, 2822 (1926)] prepared this product in two different ways but did not analyze it. They found 88° as the melting point.

TABLE II

DERIVATIVES OF ISOVANILLIN

COMPOUND	YIELD %	SOLVENT	CRYSTAL FORM	M.P. °C.	COMPOSITION	ANALYSES			
						Bromine		Nitrogen	
						Calc'd	Found	Calc'd	Found
Oxime	88	Alcohol	Colorless needles	143 –144	$C_8H_9NO_3$	—	—	8.38	8.61
Nitrile	85	Water	Colorless needles	130 –132[a]	$C_8H_7NO_2$	—	—	9.40	9.41
Acetonitrile	75	Water	Colorless needles	116 –117	$C_{10}H_9NO_3$	—	—	7.33	7.40
Acetyl-2-bromo-	72[b]	Alcohol	Colorless cubes	82 –84	$C_{10}H_9BrO_4$	29.30	29.24	—	—
2-Bromo-oxime	70[b]	Alcohol (25%)	Pale tan needles	174 –176	$C_8H_8BrNO_3$	32.52	32.49	5.69	5.68
2-Bromonitrile	74[b]	Alcohol (50%)	Colorless needles	171 –172.5	$C_8H_6BrNO_2$	35.09	34.93	6.14	6.16
Acetyl-2-bromonitrile	77[b]	Alcohol (50%)	Colorless needles	108 –109.5	$C_{10}H_8BrNO_3$	29.63	29.64	5.18	5.21
2-Bromoacid	43[b]	Water	Colorless fibrous masses	216.5–218	$C_8H_7BrO_4$	32.38	32.53	—	—
Acetyl-6-bromo-	84	Carbon tetrachloride	Colorless plates	106 –107	$C_{10}H_9BrO_4$	29.30	29.23	—	—
6-Bromo-oxime	92[c]	Alcohol	Thick colorless needles	224 –226	$C_8H_8BrNO_3$	32.52	32.46	5.69	5.68
6-Bromonitrile	86[c]	Alcohol (75%)	Small colorless needles	162 –163.5[d]	$C_8H_6BrNO_2$	35.09	35.12	6.14	6.17
Acetyl-6-bromonitrile	60[c]	Alcohol	Colorless needles	165 –167[d]	$C_{10}H_8BrNO_3$	29.63	29.54	5.18	5.20
6-Bromoacid	57	Water[e]	Tan needles	166.5–168.5	$C_8H_7BrO_4$[f]	32.38	32.62	—	—

[a] Mameli [*Gazz.*, (2) **37**, 377 (1907)] recorded 124° for a product that should have the composition and structure of the one here in question. His compound was obtained by conversion of 5-aminoguaiacol into a diazonium salt and subjection of the latter to the Sandmeyer reaction. The nitrile was obtained as brick-red needles.

[b] This represents purified material.

[c] Purification required many crystallizations and much loss of material occurred.

[d] A mixture of these products showed a melting range of 120–140°.

[e] When crystallized from water it combined with one-half molecular proportion of solvent. *Anal.* Calc'd for $C_8H_7BrO_4 + 0.5\ H_2O$: Br, 31.25; H_2O, 3.51. Found: Br, 31.75; H_2O, 3.55.

[f] Refers to anhydrous material obtained by drying to constant weight at about 110°.

Anal. Calc'd for $C_{14}H_{16}O_7$: C, 56.75; H, 5.40.
Found: C, 56.70; H, 5.50[10].

Analytical data and additional properties for other derivatives of isovanillin which were obtained by standard methods are given in Table II.

SUMMARY

1. A number of new derivatives of vanillin and isovanillin have been prepared and some of their reactions studied.

2. All attempts to prepare 5-bromoisovanillin, in which the halogen atom would be adjacent to the methoxyl group, have been unsuccessful. This failure, considered in the light of other reactions carried through in this work, shows that the alkoxyl radical tends to direct more strongly toward the para than toward the ortho position.

3. Additional data have been obtained to support the view that acylation of hydroxyl in a benzene derivative suppresses its directive influence.

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[10] After standing for one year in a glass-stoppered bottle some decomposition had taken place. This was shown by the pronounced odor of acetic acid, and by low values for the melting point and for carbon and hydrogen determinations.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

DIRECTED RING CLOSURE IN THE SYNTHESIS OF CHROMANS AND COUMARANS FROM *o*-ALLYLPHENOLS

CHARLES D. HURD AND WILLIAM A. HOFFMAN

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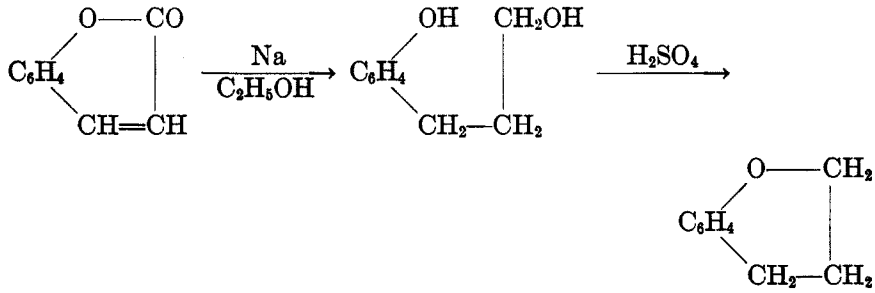
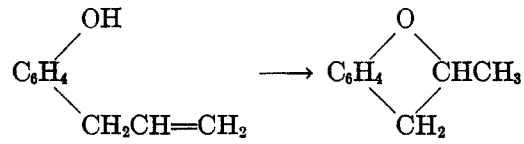
Chroman, produced by the action of phosphorus pentoxide on phenyl γ-hydroxypropyl ether (1), $C_6H_5OCH_2CH_2CH_2OH$, is a liquid with these properties; b.p. 98–99° (18 mm.), 214° (742 mm.); n_D^{20} 1.544; d_4^{20} 1.0610. The same substance is obtained from coumarin (2) by reduction and subsequent ring closure.



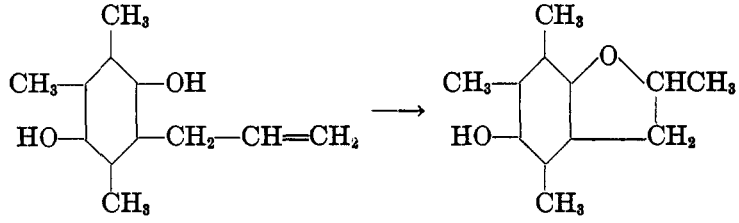
2-Methylcoumaran, its isomer, is produced by heating *o*-allylphenol with pyridine hydrochloride (3) or with other acidic reagents such as hydrogen bromide in acetic acid, or absolute formic acid. It has these properties: b.p. 82–83° (14 mm.), 197–198° (760 mm.); n_D^{22} 1.531; d_4^{24} 1.032.



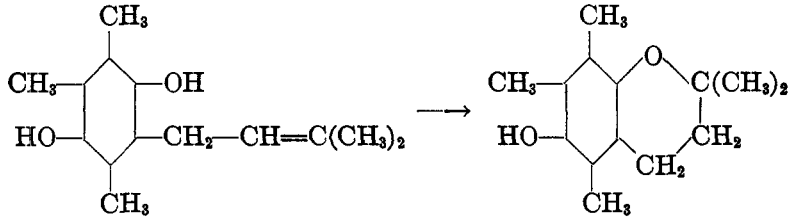
In general the chromans possess somewhat higher boiling points, higher densities, and higher indices of refraction than the isomeric 2-methylcoumarans. This correlation holds with 6-methylchroman and 2,5-dimethylcoumaran, 8-methylchroman and 2,7-dimethylcoumaran, 6-bromochroman and 2-methyl-5-bromocoumaran.

Claisen observed that a small amount of 2-methylcoumaran was formed during the pyrolytic rearrangement of phenyl allyl ether into *o*-allylphenol. Since the 2-methylcoumaran is formed from *o*-allylphenol by addition of the phenolic hydroxyl to the allylic double bond, it is significant that no chroman was formed concurrently.

Recent work in the development of the chemistry of vitamin E has shown that chromans do form by ring closure of certain substituted *o*-allylphenols, whereas the isomeric methylcoumarans come from others. For example, the methylcoumaran type was shown (4) to result from the action of acids on 2-allyl-3,5,6-trimethylhydroquinone:



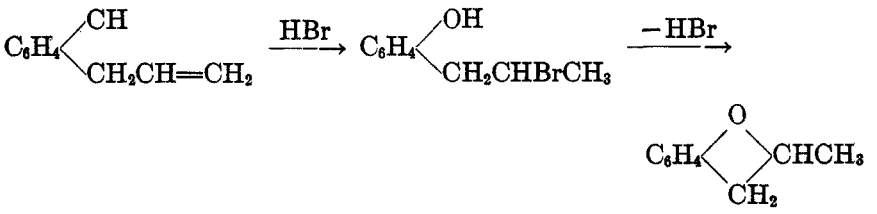
whereas the chroman type was produced in similar work with 2-(dimethylallyl)-3,5,6-trimethylhydroquinone:



The present investigation was undertaken to see if the direction of cyclization of allylphenol and related compounds to coumarans and chromans could be controlled. These types of ring closure may be regarded as a special case of addition to an olefinic double bond. The extensive studies of Kharasch and co-workers have shown conclusively that a trace of peroxide frequently governs the direction of addition of reagents to open-chain unsaturated compounds. If the "peroxide effect" were to hold with *o*-allylphenols, this would be its first application in the synthesis of cyclic or heterocyclic compounds.

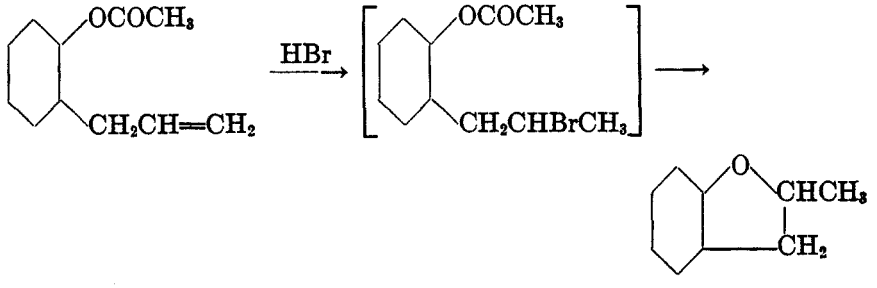
The transformation of *o*-allylphenol into 2-methylcoumaran, especially in the presence of hydrogen bromide, may be visualized as occurring in one of two ways. Addition of the phenolic function to the ethylenic double bond of the allyl group may occur directly, or perhaps the first stage of the

reaction is addition of hydrogen bromide to yield an intermediate which at once splits out hydrogen bromide to give the coumaran.

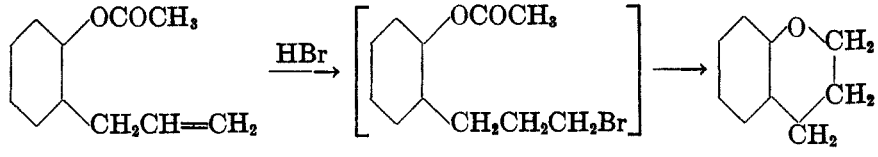


This direction of addition would be anticipated under peroxide-free conditions. Hydroquinone, a dihydric phenol, is frequently used to maintain such a condition, but it was realized that allylphenol itself might be capable of doing the same thing. As a matter of fact this was found to be true. 2-Methylcoumaran was formed from *o*-allylphenol and hydrogen bromide whether under peroxide-free conditions or not. Air, ascaridole, or benzoyl peroxide failed to promote the formation of chroman.

To eliminate the effect of the phenolic hydroxyl, which may have inhibited the effect of peroxides in these experiments, the phenols were acetylated. As before, reaction with hydrogen bromide in the presence of hydroquinone gave rise to 2-methylcoumaran, presumably by this reaction:



When ascaridole or other peroxides were present in place of the hydroquinone, the course of the reaction changed and chroman was formed.



Yields were comparably good in the two reactions.

The acetate of *o*-allyl-*p*-cresol was treated similarly. It gave rise to 2,5-dimethylcoumaran under peroxide-free conditions and to 6-methyl-

chroman when peroxides were present. It was established also that ring closure either to coumarans or to chromans could be achieved satisfactorily with *o*-allyl-*o*-cresol, *o*-allyl-*p*-bromophenol, and *o*-crotylphenol.

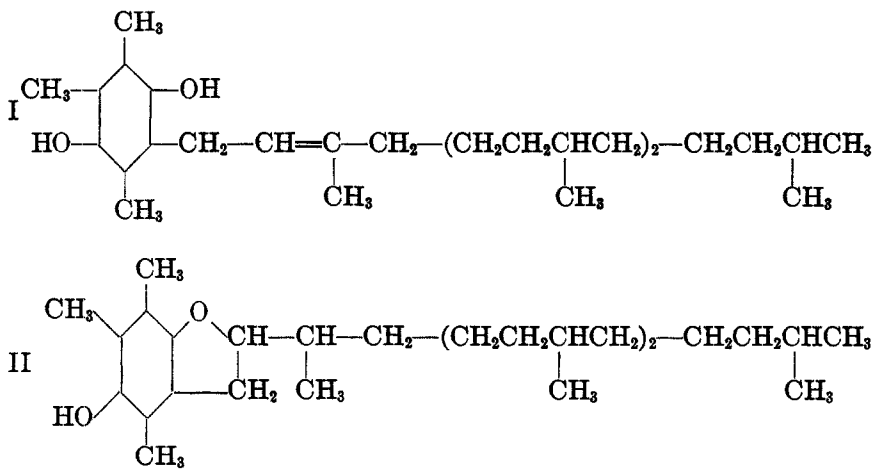
Ketene was used to acetylate the several phenols in this work. Yields in all cases were excellent, usually between 90 and 96%. This extends the reaction which was reported recently by Hurd and Roe (5). They found that although ketene and phenol were inert towards each other at room temperature, they reacted readily in the presence of a trace of sulfuric acid.

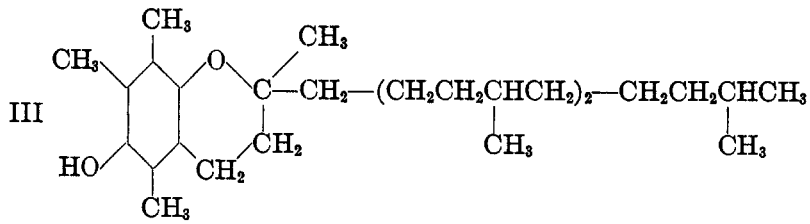
$$ArOH + CH_2{=}C{=}O \xrightarrow{H_2SO_4} ArOCOCH_3$$

Like phenol, the allylphenols were found to be inert towards ketene unless a trace of sulfuric acid was present. In this manner *o*-allylphenyl acetate, *o*-allyl-*p*-tolyl acetate, *o*-allyl-*o*-tolyl acetate, *o*-allyl-*p*-bromophenyl acetate, and *o*-crotylphenyl acetate were made, the last two of which are new compounds.

An extensive side reaction was encountered with *o*-(β-methylallyl)-phenol, $C_6H_4{<}^{OH}_{CH_2C(CH_3)=CH_2}$, in its reaction with ketene. Acetylation was cut down markedly because the sulfuric acid catalyst promoted a concurrent exothermic isomerization to 2,2-dimethylcoumaran.

Success in the directed ring closure of *o*-allyl- and *o*-crotyl- phenols to either coumaran or chroman types lent encouragement to the hope that the coumaran isomer (II) of vitamin E (III) might be synthesized from 2-phytyl-3,5,6-trimethylhydroquinone (I).





III

Instead of starting with I, however, it seemed simpler to study *o*-(γ,γ-dimethylallyl)phenol, $C_6H_4{<}^{OH}_{CH_2CH=C(CH_3)_2}$, first. Acetylation of this phenol with ketene in the presence of a trace of sulfuric acid gave a fair yield of *o*-(γ,γ-dimethylallyl)phenyl acetate but it yielded 2,2-dimethylchroman as a major product. This tendency for chroman formation was so great with *o*-(γ,γ-dimethylallyl)phenyl acetate in its reaction with hydrogen bromide that 2,2-dimethylchroman was formed regardless of whether the experiment was performed in the presence of benzoyl peroxide or hydroquinone[1]. Since coumaran formation was not obtained with *o*-(γ,γ-dimethylallyl)phenol, no experiments more closely related than this to vitamin E were carried out.

EXPERIMENTAL PART

Preparation of the Phenols

Five of the unsaturated phenols and cresols required in this study were synthesized by pyrolysis of the corresponding allyl ethers in an atmosphere of carbon dioxide[2] (6). The phenols prepared were *o*-allylphenol, *o*-allyl-*p*-cresol, *o*-allyl-*o*-cresol, *o*-allyl-*p*-bromophenol, and β-(methylallyl)phenol in yields, respectively, of 90, 80, 78, 68, 63%. It will be recalled that the yield of *o*-allylphenol was only 42% when the rearrangement was performed (7) without the atmosphere of carbon dioxide.

o-*Crotylphenol.* This substance was prepared by a modification of the Claisen and Tietze (8) procedure which consisted in condensing sodium phenoxide in anhydrous benzene with crotyl bromide (9), b.p. 13.6° (15 mm.), n_D^{20} 1.4795, at 0° with good stirring over a period of nine hours. A 41% yield of crotylphenol, b.p. 117–118° (13 mm.), n_D^{20} 1.5415, was obtained.

o-(γ,γ-*Dimethylallyl)phenol.* γ,γ-Dimethylallyl bromide (10) was prepared by addition of hydrogen bromide to isoprene. It was collected at 48–50° and 37 mm. A suspension of sodium phenoxide, prepared by refluxing in 400 cc. of anhydrous benzene for four hours 37.8 g. (0.4 mole) of phenol and 9.2 g. (0.4 mole) of metallic sodium, was cooled to 0° and to it was added, with good stirring, 59 g. (0.4 mole) of

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[1] Walling, Kharasch, and Mayo, *J. Am. Chem. Soc.*, **61**, 1711, 2693 (1939) have reported recently that dilution promotes the abnormal addition of hydrogen bromide to trimethylethylene. Similarly, dilution might be helpful in bringing about the abnormal coumaran type of ring closures, but this has not been tested yet.

[2] Dry nitrogen was used with allyl-*p*-bromophenyl ether.

the γ,γ-dimethylallyl bromide over a period of three hours. After stirring for five hours longer and then standing overnight, the solvent benzene was removed under reduced pressure and 100 cc. of water and 100 cc. of petroleum ether were added. The mixture was extracted with three 40-cc. portions of 10% sodium hydroxide solution and with 25 cc. of "Claisen's alkali." To make the latter, a mixture of 30 g. of potassium hydroxide in 25 cc. of water is diluted to 100 cc. with methanol. The combined alkaline extracts were acidified with dilute sulfuric acid, extracted with ether, and dried over anhydrous calcium chloride. Distillation gave 28.1 g. (43.8%) of the phenol, b.p. 120–122° (12 mm.), n_D^{20} 1.5365, d_4^{20} 0.9947. M.R. Calc'd. 50.46; Obs. 50.89.

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.44; H, 8.69.
Found: C, 81.06; H, 8.53.

Acetylation of Phenols by Ketene

o-*Allylphenyl acetate.* The required amount of ketene, prepared by passing acetone vapors over a red hot filament (11), was passed into 20 g. of *o*-allylphenol, b.p. 101° (14 mm.), to which had been added three drops of concentrated sulfuric acid.

TABLE I

ACETYLATIONS BY KETENE

PHENOL TAKEN	B.P., °C/MM.	GRAMS	ACETATE FORMED	B.P., °C/MM.	n_D^{20}	d_4^{20}	YIELD	
							g.	%
o-Allyl-*p*-cresol	117/15	15.4	*o*-Allyl-*p*-tolyl	126–128/16[a]	1.5085[a]		18.1	91
o-Allyl-*o*-cresol	120–122/26	30	*o*-Allyl-*o*-tolyl	127/14[b]	1.5085[b]		34.8	90
o-Allyl-*p*-bromophenol	149–150/18	19	*o*-Allyl-*p*-bromophenyl	154–155/18	1.5430	1.361	22	96
o-Crotylphenol	117–118/13	12	*o*-Crotylphenyl	132/15	1.5100	1.019	14	91

[a] Constants recorded (12b), b.p. 139°/22 mm., n_D^{20} 1.507.
[b] Constants recorded (12b), b.p. 128°/14 mm., n_D^{20} 1.507.

Reaction took place at once. The reaction-flask warmed up as the ketene was introduced, and reached 100° as the reaction progressed. The reaction-product was distilled, giving 19.7 g. of *o*-allylphenyl acetate, b.p. 110–110.5° (11 mm.), n_D^{20} 1.5085. This is 74% of the theoretical. Presumably this yield could be increased to 90–95% without difficulty (see Table I). Physical constants previously recorded (12) are: b.p. 117–118° (15 mm.), 123–124° (20 mm.), n_D^{20} 1.508. A run in which sulfuric acid was omitted gave no reaction at room temperature.

Acetylation of other phenols. The above procedure was typical of that adopted for other phenols. The reaction was exothermic in all cases, and the reaction-mixture with *o*-allyl-*p*-cresol became so hot (180°) that external cooling was advisable. Ordinarily, no solvent was employed, but with *o*-allyl-*p*-bromophenol 30 cc. of dry petroleum ether was present. The data for the acetylation of four phenols are collected in Table I. Two of these acetates are new compounds, analyzed as follows.

o-*Allyl*-p-*bromophenyl acetate: Anal.* Calc'd for $C_{11}H_{11}BrO_2$: Br, 31.47; M.R. 58.80. Found: Br, 31.34, 31.59; M.R. 58.81.

o-*Crotylphenyl acetate: Anal.* Calc'd for $C_{12}H_{14}O_2$: C, 75.76; H, 7.42; M.R. 55.20. Found: C, 75.85; H, 7.49; M.R. 55.84.

o-(*β-Methylallyl*)*phenyl acetate.* This ester was prepared by refluxing 30 g. of *o*-(*β*-methylallyl)phenol with 41.4 g. of acetic anhydride for two hours. It was then dissolved in 100 cc. of ether, extracted with 5% sodium hydroxide solution, dried, and distilled. About 27 g. was collected at 122–123° (15 mm.); n_D^{20} 1.5175. Bartz, Miller, and Adams (13) listed these constants: b.p. 98° (6 mm.); n_D^{20} 1.5177.

Acetylation was tried also with ketene. When one drop of sulfuric acid was added to 30.6 g. of *o*-(*β*-methylallyl)phenol the liquid became very warm. Ketene was passed in for two hours. Distillation at 12 mm. gave these fractions: (b.p., g.) 76–100°, 15.9; 100–115°, 3.1; 115–116°, 12.8; residue, 2 g. The last fraction was the acetic ester. Redistillation of the first fraction, after washing it with sodium hydroxide solution, yielded 11 g. of material boiling mostly at 83.5–85° (16 mm.); n_D^{20} 1.5175. For 2,2-dimethylcoumaran, these constants are recorded (13): b.p. 62° at 7 mm.; n_D^{20} 1.5190.

o-(*γ,γ-Dimethylallyl*)*phenol with ketene.* Ketene was passed into 31.7 g. of the above phenol to which had been added one drop of sulfuric acid. Distillation under reduced pressure gave approximately 21.8 g. of 2,2-dimethylchroman and 10.4 g. of *o*-(*γ,γ*-dimethylallyl)phenyl acetate, b.p. 134–135° (12 mm.), n_D^{20} 1.5105, d_4^{20} 1.019. M.R.: Calc'd, 59.82; Found, 60.00.

Anal. (By E. M. Washburn)

Calc'd for $C_{13}H_{16}O_2$: C, 76.44; H, 7.89. Found: C, 76.66; H, 8.13.

o-*Allylphenol and ascaridole.* Four grams of *o*-allylphenol and 0.5 g. of ascaridole were heated at 100° for two days. There was 0.5 cc. of alkali-insoluble material, b.p. 122–130° (33 mm.), n_D^{20} 1.5270, chiefly 2-methylcoumaran.

RING CLOSURE OF THE ACETIC ESTERS

o-Allylphenyl Acetate and Hydrogen Bromide

With hydroquinone. A mixture of 8 g. of *o*-allylphenyl acetate, 0.15 g. of hydroquinone, and 10 cc. of dry carbon tetrachloride gave a negative test (14) for peroxides with crystals of ferrous ammonium sulfate and 10% ammonium thiocyanate. The mixture was cooled in a 15-mm. tube to −78° and hydrogen bromide, prepared by the action of 3 cc. of liquid bromine on 15 cc. of boiling tetralin, was passed in. The tube was sealed and allowed to stand at room temperature for thirty-eight hours, after which it was opened, the solvent removed, and the reaction-mixture was taken up with dilute sodium hydroxide solution. The alkali-insoluble layer was separated, and refluxed for two hours with a solution of 5 g. of potassium hydroxide in 25 cc. of water and 50 cc. of 95% alcohol. The product was extracted with ether, dried over calcium chloride, and distilled at 15 mm. At 80–81°, 1.8 g. (30% yield) of 2-methylcoumaran was collected; n_D^{20} 1.5309. The residue weighed 0.5 g.

With air. Ten grams of *o*-allylphenyl acetate in 54 cc. of dry carbon tetrachloride was shaken with air at −8°. Then an excess of hydrogen bromide was passed in during forty-five minutes. The solvent was distilled off, and the mixture worked up as before. The chroman obtained weighed 2.3 g. (30% yield), b.p. 95–96° (13 mm.); n_D^{20} 1.5438. Acidification and extraction of the aqueous alkaline solution remaining after ether extraction gave 2.3 g. of *o*-allylphenol, b.p. 97–98° (12 mm.), n_D^{20} 1.5430.

With ascaridole. To 10 g. of *o*-allylphenyl acetate and 0.8 g. of ascaridole dissolved in 45 cc. of dry carbon tetrachloride at 0° was added an excess of hydrogen bromide during forty-five minutes. The mixture was treated as in the preceding run. The product was dried over calcium chloride and distilled at 15 mm. About 0.7 g. was

collected at 85–95°, then 4.4 g. (57%) of chroman was collected at 95–96°; n_D^{20} 1.5472. The residue weighed 2 g.

o-*Allyl*-p-*tolyl Acetate and Hydrogen Bromide*

With hydroquinone. Ten grams of *o*-allyl-*p*-tolyl acetate in 30 cc. of carbon tetrachloride was placed in a 20-mm. Pyrex tube. To this was added 0.2 g. of hydroquinone and five drops of thiophenol. The mixture was cooled to 0° and saturated with hydrogen bromide, after which the tube was sealed and left for three days. The contents were worked up as outlined above. Distillation at 13 mm. gave 2.5 g. of 2,5-dimethylcoumaran at 95–96°, n_D^{20} 1.5265. Also, 0.4 g. (n_D^{20} 1.5265) was collected at 96–97° and 0.2 g. (n_D^{20} 1.5265) at 97–103°. The total distillate corresponds to a yield of 40%. The reported values (1c) for 2,5-dimethylcoumaran are: b.p. 99–99.5° (14 mm.), n_D^{20} 1.5251, $n_D^{13.7}$ 1.528.

With ascaridole. To 10 g. of *o*-allyl-*p*-tolyl acetate, 0.5 g. of ascaridole and 30 cc. of carbon tetrachloride at 0° was added an excess of hydrogen bromide. The reaction-mixture was set aside for seven hours and again saturated with hydrogen bromide at 0°. After standing overnight at room temperature the product was worked up in the usual manner. The product was 3.0 g. of liquid, b.p. 110–111° at 15 mm., n_D^{14} 1.5355. Another 0.5 g. of distillate was collected at 111–112° (15 mm.), n_D^{14} 1.5382, and there was 2 g. of residue. The 3.5 g. of product make up a 44% yield. The physical constants suggest that the product was mainly 6-methylchroman with a small amount of 2,5-dimethylcoumaran. Reported physical constants (1c, 15) for 6-methylchroman are: $n_D^{14.3}$ 1.542; b.p. 107° (12 mm.). The low refractive index of the above material may be influenced a little by a trace of ascaridole, since this distils at 115° (15 mm.), n_D^{20} 1.4743.

o-*Allyl*-o-*tolyl Acetate and Hydrogen Bromide*

With hydroquinone. Ten grams of the above ester, 0.2 g. of hydroquinone, and 30 cc. of carbon tetrachloride were placed in a Pyrex tube, cooled to 0°, and saturated with hydrogen bromide during thirty minutes. The tube was sealed and allowed to stand at room temperature for forty-eight hours, and the product was worked up in the usual manner. Distillation at 15 mm. yielded 0.2 g. at 90–95° (n_D^{20} 1.5250), 1.6 g. at 90–96° (n_D^{20} 1.5288), 0.8 g. at 96–105° (n_D^{20} 1.5288), and 2.4 g. of residue. The distillate (31% yield) was chiefly 2,7-dimethylcoumaran, for which the reported constants (1c, 16) are: b.p. 92–92.5° (13 mm.), $n_D^{13.8}$ 1.530. A small amount of phenolic material (1.5 g.) remained after acidifying the alkaline solution and extracting with ether.

With benzoyl peroxide. This run was identical with the preceding, except that 0.2 g. of benzoyl peroxide was used in place of the hydroquinone. Distillation at 15 mm. produced 1.4 g. at 105–105.5° (n_D^{27} 1.5380), 1.4 g. at 106–108° (n_D^{27} 1.5420), and 3.2 g. of residue. The 2.8 g. represented 36.5% of the theory. The reported constants (1a) for 8-methylchroman are: b.p. 114–116° (20 mm.), n_D^{27} 1.542.

o-*Allyl*-p-*bromophenyl Acetate and Hydrogen Bromide*

With hydroquinone. In this experiment 16 g. of the above ester, 0.6 g. of hydroquinone, and 50 cc. of carbon tetrachloride in a Pyrex tube were treated at 0° with an excess of hydrogen bromide. The tube was sealed and allowed to stand at room temperature for twenty-four hours, then opened and the carbon tetrachloride distilled off. The brown oil which remained was refluxed for two hours with a mixture of 6 g. of potassium hydroxide and 100 cc. of 85% alcohol. The alcohol was evaporated on the water-bath, 150 cc. of water was added, and the product was extracted

with ether, dried, and distilled under diminished pressure. From the aqueous extract, 2 g. of *o*-allyl-*p*-bromophenol was recovered. The distillate became blue on standing, indicating the presence of some of the phenol. Hence, it was dissolved in ether and washed with two 20-cc. portions of Claisen's alkali. On drying and redistillation, 8.5 g. of material was collected between 142–144° (20 mm.), n_D^{22} 1.5725, d_4^{25} 1.430, compared with the literature values (1a, 1b) for 2-methyl-5-bromocoumaran: b.p. 139–140° (18 mm.); n_D^{22} 1.570; $d_4^{?}$ 1.434, 1.403.

With benzoyl peroxide. An excess of hydrogen bromide was passed into a mixture of 16 g. of *o*-allyl-*p*-bromophenyl acetate, 1.2 g. of benzoyl peroxide, and 50 cc. of carbon tetrachloride at 0°. The reaction-mixture was carried through the same procedure as in the preceding experiment, including treatment with Claisen's alkali and a second vacuum distillation. 6-Bromochroman was formed in 71% yield (9.5 g.); b.p. 149–150° (22 mm.), n_D^{22} 1.5850, d_4^{25} 1.467. M.R. (Calc'd) 47.37, M.R. (Obs.) 47.56. Values in the literature (1a, 1b) for 6-bromochroman are: b.p. 143–144° (18 mm.), n_D^{22}:1.580, d_{25}:1.465. About 0.5 g. of *o*-allyl-*p*-bromophenol was recovered.

o-*Crotylphenyl Acetate and Hydrogen Bromide*

With hydroquinone. Five grams of *o*-crotylphenyl acetate, 0.5 g. of hydroquinone, and 40 cc. of carbon tetrachloride were treated with an excess of hydrogen bromide at 0°. The tube was sealed, and after twenty-four hours the reaction-product was worked up as in the previous experiment. There was obtained 0.3 g. of liquid, b.p. 224° (micro method), n_D^{22} 1.5325. Harries (17) reported for 2-methylchroman, b.p. 224–225°. There was recovered 2.9 g. of crotylphenol arising from hydrolysis of unreacted *o*-crotylphenyl acetate.

With benzoyl peroxide. One gram of benzoyl peroxide was added to a solution of 5 g. of *o*-crotylphenyl acetate in 40 cc. of carbon tetrachloride. The mixture was treated with hydrogen bromide exactly as in the preceding experiment. Distillation gave 1.6 g. of 2-methylchroman, b.p. 92–94° (10 mm.), n_D^{20} 1.5335–1.5340. The slightly colored distillate was washed again with 10% sodium hydroxide solution and redistilled from a small molecular still. Constants: b.p. (micro method) 224°; n_D^{20} 1.5325; d_4^{20} 1.034; M.R. (Calc'd) 44.22, (Obs.) 44.34.

This product appeared to be identical with that obtained in the preceding experiment. Both liquids gave a red color with concentrated sulfuric acid as observed by Claisen (8). The boiling point is somewhat lower and the refractive index slightly higher than recorded by Baker and Walker (18), who gave b.p. 100–102° (11 mm.), $n_D^{13.6}$ 1.532. Stoermer and Schaffer (19) gave for the boiling point, 223°.

o-(*β-Methylallyl*)*phenyl Acetate and Hydrogen Bromide*

With hydroquinone. Ten grams of the above ester, 1 g. of hydroquinone, and 50 cc. of dry carbon tetrachloride were saturated at −5° with hydrogen bromide. After standing at room temperature in a sealed tube for twenty-four hours the products were worked up as before by hydrolysis with hot alcoholic potash, removing the alcohol, ether extracting, washing the ether extract with Claisen's alkali, and distilling. There was obtained 2.7 g. of liquid, b.p. 102–104° (15 mm.), n_D^{20} 1.5335, d_{20}^{20} 1.004. This was presumably 3-methylchroman rather than 2,2-dimethylcoumaran: b.p. 83–83.5° (16 mm.); n_D^{20} 1.5190; d_{20}^{20} 0.996. Two grams of *o*-(β-methylallyl)phenol was recovered. The 3-methylchroman was analyzed.

Anal. Calc'd for $C_{10}H_{12}O$: C, 81.04; H. 8.16.
Found: C, 81.00; H, 8.18.

With benzoyl peroxide. Ten grams of the above ester, 1 g. of benzoyl peroxide,

and 50 cc. of carbon tetrachloride were treated with hydrogen bromide as in the preceding experiment. The distillate weighed 2.8 g., b.p. 102–104° (16 mm.), n_D^{20} 1.5335, d_{20}^{20} 1.013. This material is evidently the same as that obtained when the reaction was carried out in the presence of hydroquinone. The yield was 36% of the theoretical; 2.2 g. of the original phenol was recovered.

o-(γ,γ-Dimethylallyl)phenyl Acetate and Hydrogen Bromide

With benzoyl peroxide. Five grams of this ester, 0.5 g. of benzoyl peroxide and 30 cc. of carbon tetrachloride were placed in a Pyrex tube through which was passed a stream of oxygen for five minutes, followed by saturation with hydrogen bromide at 0°. The tube was sealed and allowed to stand overnight at room temperature. The reaction-mixture was worked up in the usual manner. Upon distillation, 1.8 g. (46%) of a clear liquid was obtained: b.p. 102–102.5° (15 mm.); n_D^{20} 1.5270–1.5275; d_4 1.007. This material appears to be 2,2-dimethylchroman for which Claisen (20) has reported the following physical constants: b.p. 98–98.5° (11.5 mm.), d_{15}^{15} 1.009.

With hydroquinone. Excess hydrogen bromide was passed into an ice-cold mixture of 5 g. of *o*-(γ,γ-dimethylallyl)phenyl acetate, 0.7 g. of hydroquinone, and 30 cc. of carbon tetrachloride. The treatment was as in the preceding experiment. The product weighed 2.1 g. and possessed these constants: b.p. 102–103° (16 mm.); n_D^{20} 1.5275–1.5285; d_4^{20} 1.009. This liquid appeared to be essentially the same as that obtained in the other experiment where benzoyl peroxide was present.

SUMMARY

Directed ring closure of *o*-allylphenols to 5-membered or 6-membered heterocyclic rings has been achieved with *o*-allylphenol, *o*-allyl-*p*-cresol, *o*-allyl-*o*-cresol, and *o*-allyl-*p*-bromophenol. For this purpose, the phenolic hydroxyl was protected by acetylation. Then a little hydroquinone was added, to maintain peroxide-free conditions, if coumarans were desired. If chromans were desired, oxygen or some peroxide was introduced. In both reactions, hydrogen bromide effected the ring closure.

Acetylation of these phenols and also of *o*-crotylphenol was performed in 90–96% yields by ketene in the presence of a trace of sulfuric acid.

o-Crotylphenyl acetate, *o*-(β-methylallyl)phenyl acetate, and *o*-(γ,γ-dimethylallyl)phenyl acetate reacted with hydrogen bromide to give chromans regardless of whether peroxide conditions or peroxide-free conditions were maintained.

Acetylation of *o*-(β-methylallyl)phenol by acetic anhydride proceeded smoothly, but acetylation by ketene and a trace of sulfuric acid promoted a concurrent isomerization to 2,2-dimethylcoumaran.

Acetylation of *o*-(γ,γ-dimethylallyl)phenol by ketene and a trace of sulfuric acid yielded 2,2-dimethylchroman and *o*-(γ,γ-dimethylallyl)-phenyl acetate, the former predominating.

o-Allyl-*p*-bromophenyl acetate, *o*-crotylphenyl acetate, *o*-(γ,γ-dimethylallyl)phenyl acetate, and 3-methylchroman are new compounds.

EVANSTON, ILL.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF YENCHING UNIVERSITY]

FRIEDEL AND CRAFTS REACTION. II.

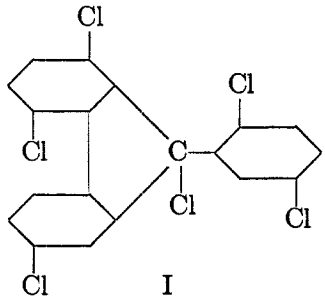
THE CONDENSATION OF *ortho-* AND *meta-* DICHLOROBENZENE WITH CHLOROFORM AND CARBON TETRACHLORIDE

STANLEY D. WILSON AND YUAN-YING CHENG

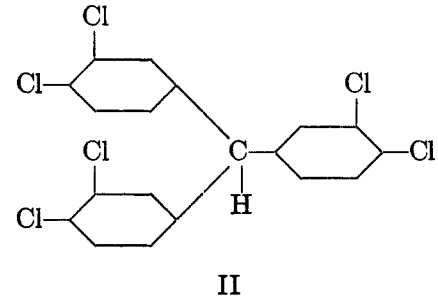
Received July 10, 1939

Triphenylmethane derivatives with two or more halogen atoms on each of the three benzene rings were needed in one of our studies. A search of the literature indicated that while numerous triphenylmethane compounds with two or more halogens on one or two of the three rings have been prepared, there was no report of any with two or more on each of the three rings. Norris and Green (1) attempted to prepare this type of compound by condensing *p*-dichlorobenzene with carbon tetrachloride in the presence of aluminum chloride with carbon disulfide as a solvent. They obtained only tetrachlorobenzophenone chloride.

In a previous paper from this laboratory (2), we have shown that in the absence of solvents *p*-dichlorobenzene will condense with chloroform to give the expected hexachlorotriphenylmethane. But with carbon tetrachloride the product of the reaction is 1,4,7,9-tetrachloro-9-(2,5-dichlorophenyl)fluorene (I) if the reaction is carried out at 55°, while if the reaction is carried out at room temperature the product is the tetrachlorobenzophenone chloride.



I



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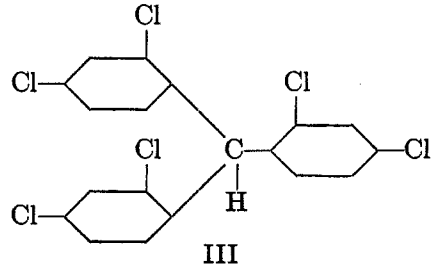

III

We have recently extended this study to include the condensation of the *o*- and *m*-dichlorobenzenes with chloroform and carbon tetrachloride. Further study of these compounds is planned, but the disturbed conditions in China, together with the approaching furlough of the senior author leads us to make a record of our present results.

o-Dichlorobenzene condenses with chloroform in the absence of solvents and in the presence of aluminum chloride to give a product which is probably 3,4,3′,4′,3″,4″-hexachlorotriphenylmethane (II), though the structure 2,3,2′,3′,2″,3″- has not been definitely ruled out for this compound.

m-Dichlorobenzene under similar conditions gives a product which is most probably 2,4,2′,4′,2″,4″-hexachlorotriphenylmethane (III), since, when carbon tetrachloride condenses with this dichlorobenzene under the same conditions, it gives a known tetrachlorobenzophenone with the chlorines in the 2,4,2′,4′ positions.

When these dichlorobenzenes are treated with carbon tetrachloride in the absence of solvents and in the presence of aluminum chloride we have so far obtained only derivatives with two benzene rings rather than those with three rings attached to the central carbon atom. With the ortho compound the product first formed was probably 3,4,3′,4′-tetrachlorobenzophenone chloride, but the purification of this product proved somewhat difficult, and in this process it was hydrolyzed to give the corresponding tetrachlorobenzophenone. However, it is possible that the chlorine atoms in these two compounds occupy positions 2,3,2′,3′.

On the other hand, the product from *m*-dichlorobenzene was purified without hydrolysis, and proved to be 2,4,2′,4′-tetrachlorobenzophenone chloride.

We have thus found it possible to obtain triphenylmethane derivatives with each of the three dichlorobenzenes when we condense them with chloroform in the presence of aluminum chloride and in the absence of solvents. But when carbon tetrachloride is used, it has been proved possible only with *p*-dichlorobenzene to obtain a compound with three benzene rings joined to the central carbon atom. However, one molecule of hydrogen chloride splits off between two of these rings to give a fluorene compound. With the *o*- and *m*-dichlorobenzenes, only two rings have been joined to the central atom. We are carrying on further work to enable us to determine the conditions under which the triphenyl compounds can be obtained, and to determine why these condensations with carbon tetrachloride take a course different from that taken when chloroform is used.

EXPERIMENTAL

The chloroform, carbon tetrachloride, and aluminum chloride employed were obtained from E. Merck, Darmstadt. The dichlorobenzenes were from the Eastman Kodak Company and were employed without further purification.

Condensation product with o-dichlorobenzene and chloroform (III). Our best yields were obtained as follows. To a mixture of 7 g. of chloroform and 26 g. of *o*-dichlorobenzene was added 10 g. of powdered anhydrous aluminum chloride. This was heated at 55–60° for eight hours. Condensation at higher temperatures gave chiefly tarry products while at lower temperatures the reaction was slow. On cooling, the reaction-product solidified. This was broken up and poured into cold water. The mixture of water and solid was extracted three times with ether. The ether solution was washed with dilute hydrochloric acid to remove aluminum compounds, and finally with water. On evaporation of the ether, a reddish-yellow liquid remained. On standing two weeks, abundant crystals separated from this oil. These were washed with small portions of acetone and finally recrystallized from hot acetone. The final product consisted of white crystals in the form of elongated microscopic plates with beveled sides and square ends, m.p. 160.5–162°. The yield was 15% of that calculated from the chloroform used. These crystals were soluble in hot benzene, ether, and acetone.

Anal. Calc'd for $C_{19}H_{10}Cl_6$: C, 50.57; H, 2.24; Cl, 47.19.

Found: C, 50.82; H, 2.25 (semi-micro); Cl, 47.04 (semi-micro bomb).

2,4,2′,4′,2″,4″-Hexachlorotriphenylmethane (III). This was prepared from chloroform and *m*-dichlorobenzene, as above, except that the best yields were obtained by heating at 60–65° for 12–14 hours. The condensed mass was a dark red, viscous liquid. This was poured into cold water, the mixture was then extracted with ether, and the ether solution washed first with dilute hydrochloric acid and finally with water. On evaporation of the ether a red liquid was obtained. This was purified in two different ways. On treatment with alcohol, one fraction of the oil dissolved. The alcohol solution was then diluted with water, when white crystals separated. The second method consisted in washing the original oil with acetone. The colored portion dissolved in the acetone and a white residue remained. The two white products proved to be the same substance, which was further purified by recrystallization from hot acetone, to give characteristic white crystals that melted at 227–228.5°. The yield was 18% of the calculated. These crystals are soluble in benzene, toluene, ether, acetone, and alcohol.

Anal. Calc'd for $C_{19}H_{10}Cl_6$: C, 50.57; H, 2.24; Cl, 47.19.

Found: C, 50.88; H, 2.28 (semi-micro); Cl, 46.90 (semi-micro bomb).

Condensation product of o-dichlorobenzene and carbon tetrachloride. In this reaction, the condensation was carried out between carbon tetrachloride and somewhat more than three equivalents of *o*-dichlorobenzene in the presence of powdered anhydrous aluminum chloride. Many runs were made, with the time varying from 2 to 24 hours and temperature varying from 20° to 100°, in efforts to obtain products with three rings on the methane carbon, but only products with two rings resulted. These products were gummy and proved difficult to purify except by treating with hot 95% alcohol, which caused hydrolysis of the chlorine on the methane carbon, and gave the ketone as the final product. This ketone was isolated by treating the gummy products with hot alcohol and diluting the alcohol solution with water, when white crystals separated. By recrystallization from hot alcohol or hot acetone, the pure white, flat, rod-shaped crystals were obtained, m.p. 141–142°. The yield was 40% of the theory, based on carbon tetrachloride used.

Anal. Calc'd for $C_{13}H_6Cl_4O$: C, 48.77; H, 1.89; Cl, 44.33.
Found: C, 49.04; H, 1.88 (semi-micro); Cl, 44.44 (semi-micro bomb).

2,4,2′,4′-*Tetrachlorobenzophenone chloride.* Attempts here were again made to obtain products with three rings on the methane carbon, but without success, even though the temperature was varied from 60-140° in various runs, and the time of heating extended from 2 to 24 hours. In all experiments, carbon tetrachloride was treated with somewhat more than 3 equivalents of *m*-dichlorobenzene in the presence of powdered anhydrous aluminum chloride. The product of the condensation was poured into cold dilute hydrochloric acid. The aluminum compounds dissolved, leaving slightly pinkish crystals, which were washed with cold water followed by small amounts of cold alcohol, and were finally recrystallized from hot acetone, giving crystals in the form of white plates, m.p. 139-140.5°. Here the yield was 60% of the theory, based on carbon tetrachloride used. Jaeger (3) reports that this compound melts at 140°.

Anal. Calc'd for $C_{13}H_6Cl_6$: C, 41.62; H, 1.61; Cl, 56.78.
Found: C, 41.73; H, 1.69; Cl, 56.50.

All these compounds proved to be difficult to decompose in the sodium peroxide bomb.

SUMMARY

1. *o*- and *m*-Dichlorobenzene have been condensed with chloroform in the presence of aluminum chloride and in the absence of solvent to give the corresponding hexachlorotriphenylmethane. These compounds are new.

2. *o*-Dichlorobenzene, when condensed with carbon tetrachloride in the presence of aluminum chloride as above, gave a tetrachlorobenzophenone chloride which most probably has the chlorine in the 3,4,3′,4′ positions. During purification this was hydrolyzed to tetrachlorobenzophenone. This is also a new compound.

3. *m*-Dichlorobenzene with carbon tetrachloride gave 2,4,2′,4′-tetrachlorobenzophenone chloride.

PEIPING, CHINA

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

SYNTHESIS OF IODOHIPPURIC ACIDS. I. 2,5-, 3,5- AND 3,4-DIIODOHIPPURIC ACIDS[1]

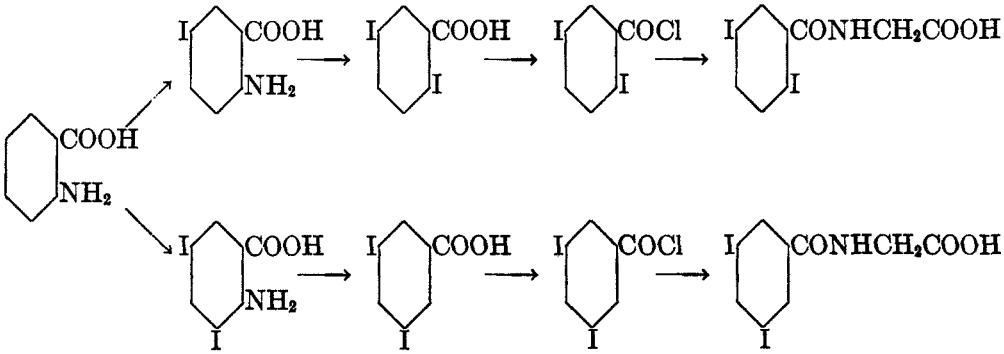
CARL J. KLEMME AND JAMES H. HUNTER

Received November 16, 1939

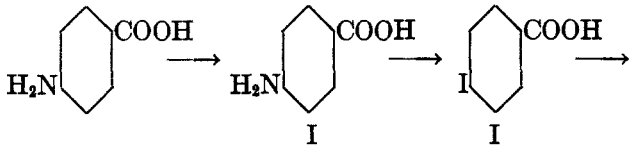
Coincident with the recent developments in the field of clinical radiography, a demand has arisen for suitable contrast agents. Various organic iodine derivatives have attained a prominent position in this capacity. The success attending the use of sodium *o*-iodohippurate (Hippuran) suggested a study of other iodinated hippuric acids.

The first phase of this study, *i.e.*, the synthesis of the desired iodohippuric acids, is the subject of this and other reports to be published later. The pharmacological and radiological investigations of these derivatives are problems for subsequent studies.

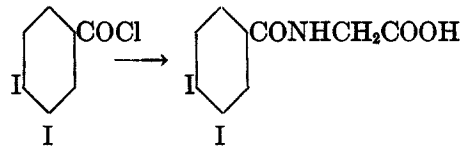
With *o*-aminobenzoic acid as the starting point, 2,5- and 3,5- diiodohippuric acids were synthesized as indicated below:



while 3,4-diiodohippuric acid was obtained from *p*-aminobenzoic acid through the following steps:



[1] From a portion of a thesis submitted by James H. Hunter in partial fulfilment for the degree of Doctor of Philosophy, August, 1938.



The preparation of 2-amino-5-iodobenzoic acid has been effected by a number of different methods. Grothe (1) prepared it as early as 1878 by reduction of the corresponding nitro-iodo acid; Wheeler and Liddle (2) by acid hydrolysis of 2-acetamino-5-iodobenzoic acid; Wheeler and Johns (3) by the action of finely powdered iodine on a solution of anthranilic acid in potassium hydroxide; Schoeller and Hueter (4) by treating the anhydride of 5-hydroxymercuri-anthranilic acid with iodine in potassium hydroxide; and Borsche, Weussmann, and Fritzsche (5) by the action of iodine monochloride on an acetic acid solution of anthranilic acid[2].

The method of Wheeler and Johns (3) appeared to afford a convenient means of preparing 2-amino-5-iodobenzoic acid for our study. However, in our experience, this method proved unsatisfactory owing to an extremely contaminated crude product and low yields. By chance, our attention was attracted to a reaction between anthranilic acid and nascent iodine[3]. Based on this reaction, we have developed a satisfactory method for the preparation of this amino-iodobenzoic acid. It is not without interest to mention that 2-amino-5-iodobenzoic acid can also be prepared by application of the iodination method of Datta and Prosad (6). This procedure was not critically studied; however, in our preliminary experiments, the yields were found to be low.

2-Amino-5-iodobenzoic acid was converted into the 2,5-diiodo acid by diazotization and treatment of the diazonium compound with aqueous potassium iodide according to the directions of Wheeler and Johns (3). This acid, upon treatment with thionyl chloride, readily yielded the corresponding acid chloride, and the latter, when shaken with glycine in the presence of dilute sodium hydroxide, gave the sodium salt of 2,5-diiodohippuric acid. The free acid was liberated from the sodium salt by treatment with dilute mineral acid.

2-Amino-3,5-diiodobenzoic acid, the essential intermediate for the synthesis of 3,5-diiodohippuric acid, has been prepared by iodinating 2-amino-5-iodobenzoic acid with iodine monochloride (3), and by the

[2] Since the completion of this work, a detailed procedure for the preparation of 2-amino-5-iodobenzoic acid has appeared in *Organic Syntheses*, John Wiley and Sons, New York City, **1939**, Vol. XIX, p. 52.

[3] A brief description of this method of iodination is given by Kempf in Houben's "Die Methoden der organischen Chemie," Georg Thieme, Leipzig, **1923**, Zweite Auflage, Vol. III, p. 877.

action of two moles of this reagent on *o*-aminobenzoic acid in dilute hydrochloric acid (3). Preparation of this acid for our purpose was based on the latter method.

Wheeler and Liddle (2) originally obtained 3,5-diiodobenzoic acid by diazotizing 4-amino-3,5-diiodobenzoic acid and decomposing the resulting diazonium compound with boiling alcohol. Later (7) they reported the preparation of this acid from 3-iodo-5-aminobenzoic acid. We have used a procedure of Wheeler and Johns (3), based on the deamination of 2-amino-3,5-diiodobenzoic acid. From 3,5-diiodobenzoic acid, 3,5-diiodohippuric acid was obtained by the aforementioned procedure for the isomeric 2,5-diiodohippuric acid.

3-Iodo-4-aminobenzoic acid was first prepared by hydrolysis of 3-iodo-4-acetaminobenzoic acid (2). In 1909, Wheeler and Liddle (2) reported that 3-iodo-4-aminobenzoic acid could be prepared by passing the vapors of iodine monochloride into a solution of *p*-aminobenzoic acid in cold, concentrated hydrochloric acid. We sought to employ the latter method for producing this acid. In spite of repeated attempts, we were unable to repeat their preparatory directions, and it was necessary to modify their procedure by using glacial acetic acid rather than concentrated hydrochloric acid. With this modification, 3-iodo-4-aminobenzoic acid was prepared, although in poor yields.

An attempt to apply the method developed for the preparation of 2-amino-5-iodobenzoic acid, *i.e.*, iodination with nascent iodine[3], to the preparation of the isomeric 3-iodo-4-aminobenzoic acid naturally suggested itself. While a small amount of the latter compound was obtained by adapting this method to *p*-aminobenzoic acid, the principal product formed was 2,4-diiodoaniline. Preliminary experiments on the iodination of *p*-aminobenzoic acid with elementary iodine in the presence of ammonia (6) gave no promise of being satisfactory. Efforts to iodinate *p*-aminobenzoic acid by treatment with the calculated quantities of potassium iodide and potassium iodate in dilute sulfuric acid were likewise unsuccessful. For use in the present investigation, 3-iodo-4-aminobenzoic acid was prepared both by the action of gaseous iodine monochloride on an acetic acid solution of *p*-aminobenzoic acid, and by the action of nascent iodine on aqueous potassium *p*-aminobenzoate. Neither of these methods may be regarded as practical.

3-Iodo-4-aminobenzoic acid gave, upon diazotization and treatment with aqueous potassium iodide, the corresponding diiodo acid (2). This acid has also been prepared by Wheeler and Johns (8) from 2-amino-4,5-diiodobenzoic acid. Conversion of 3,4-diiodobenzoic acid into its chloride and the latter into 3,4-diiodohippuric acid was effected in a manner similar to that mentioned above for the 2,5-diiodo derivative.

Iodine was estimated, in most cases, by slight modifications of the official method described for tetraiodophenolphthalein (9). A potentiometric method was used for analysis of the iodo acid chlorides. In brief: A sample of the compound was decomposed by fusing with anhydrous sodium carbonate and the fusion filtrate, in excess dilute sulfuric acid, titrated with $N/10$ silver nitrate using a silver-silver chloride indicator electrode and a reference electrode of mercurous sulfate. Molecular weight determinations were made by titration of an alcoholic solution of the appropriate compound in accordance with a recognized procedure for neutral equivalent determinations (10).

EXPERIMENTAL

2-Amino-5-iodobenzoic acid. With mechanical stirring, 25 g. (0.184 mole) of recrystallized anthranilic acid (m.p. 145°)[4] was dissolved in a solution of 16.9 g. of stick potassium hydroxide in 500 cc. of water contained in a 2-liter beaker. A solution of 46.5 g. (0.184 mole) of iodine in 250 cc. of water containing 24.75 g. of stick potassium hydroxide was slowly run into the well-stirred potassium anthranilate solution. After one minute, 100 cc. of glacial acetic acid was quickly added and the reaction-mixture immediately diluted with 500 cc. of water. A dark precipitate began to appear almost at once; stirring was continued for one hour, during which time this precipitate assumed a light brown color. After standing undisturbed for two hours, excess iodine was removed by adding 25 cc. of 15% sodium bisulfite and thoroughly agitating. The mixture was allowed to stand a short while. The precipitate was collected, repeatedly washed with water and air-dried. Yield of crude product, 41.69 g. (86.8%). One crystallization from dilute alcohol gave, after working up the mother liquor, 34.84 g. (72.2%) of a pure product melting at 210–211.5°. A portion of this product, when mixed with an authentic specimen of 2-amino-5-iodobenzoic acid, caused no depression of the melting point of the latter. Identity of our product was further confirmed by converting it into 2,5-diiodobenzoic acid, and identifying the latter by a mixed melting point with a known sample of this diiodobenzoic acid. Several repetitions of this preparatory procedure with different amounts of starting materials gave equally good yields.

2,5-Diiodobenzoic acid. This compound was prepared in good yields according to the directions reported by Wheeler and Johns (3). The alkali-acid purification step described by these investigators was omitted. The crude product was directly crystallized from dilute alcohol. Thus, from 15.0 g. (0.0593 mole) of 2-amino-5-iodobenzoic acid, 17.8 g. (83.6%) of crude 2,5-diiodobenzoic acid was obtained. Crystallization from dilute alcohol gave 14.6 g. (68%) of the pure compound, m.p. 180.5–181.5°[5].

2,5-Diiodobenzoyl chloride. Fifty grams (0.134 mole) of pure 2,5-diiodobenzoic acid was treated with 50 cc. of thionyl chloride (Eastman's "Practical") and the mixture gently refluxed on a steam-bath for two hours. Excess thionyl chloride was distilled from a steam-bath and the residue crystallized from carbon tetrachloride.

[4] All melting points are uncorrected.

[5] Wheeler and Johns (3) reported a quantitative yield for the crude diiodo acid; the yield of purified acid, m.p. 183°, is not reported. Following their procedure, we have obtained, after purification, an acid melting at 181° instead of 183°.

After washing once with petroleum ether, the pale yellow crystals melted at 93–95°. Yield: 45 g. (85.8%). For analysis, the compound was recrystallized from carbon tetrachloride. This gave pale, yellowish-green needles, melting at 93–94.5°.

Anal. Calc'd for $C_7H_3ClI_2O$: I, 64.70; Cl, 9.03.
Found: I, 64.56; Cl, 8.79.

Alkaline hydrolysis of the above compound gave, after acidifying and crystallizing from dilute alcohol, an acid melting at 182.5–183°. When this acid was mixed with pure 2,5-diiodobenzoic acid no depression of the melting point was observed.

2,5-Diiodohippuric acid. Sixteen grams of glycocoll (Eastman) was dissolved in 100 cc. of 5% sodium hydroxide and 20 g. (0.051 mole) of 2,5-diiodobenzoyl chloride was added. The mixture was vigorously shaken, whereupon most of the acid chloride went into solution. The reaction-mixture was diluted with 50 cc. of water and filtered. The clear, yellow filtrate was poured, with efficient stirring, into a mixture of 25 cc. of concentrated hydrochloric acid and 150 g. of crushed ice. The white, gelatinous precipitate was collected, washed, and air-dried. The dry product was pulverized and extracted with hot ether to remove any 2,5-diiodobenzoic acid present. Yield: 20.3 g. (92.6%). Crystallization from dilute alcohol gave white burrs melting at 210.5–211°.

Anal. Calc'd for $C_9H_7I_2NO_3$: N, 3.25; I, 58.67; M.W. 430.9.
Found: N, 3.36; I, 57.53; M.W. 435.9.

3-Iodo-4-aminobenzoic acid. (A) A solution of 3 g. (0.022 mole) of *p*-aminobenzoic acid in 30 cc. of glacial acetic acid was placed in a small suction-flask fitted with an inlet tube, the lower end of which dipped below the surface of the solution. The flask was connected to a second small suction-flask containing 3.5 g. (0.0197 mole) of iodine monochloride (11) and also fitted with an inlet tube reaching almost to the bottom. While a current of air was drawn through the system, the iodine monochloride was vaporized by warming on a steam-bath. After all the iodine monochloride had passed over, the reaction-mixture was poured into 150 cc. of water and allowed to stand for two hours. The brown, flocculent precipitate was collected, washed with water and air-dried. Yield: 2.1 g. (36.5 per cent) of a substance melting at 202°. Crystallization from water gave a small amount of a compound melting at 204°. A mixture of this compound and 3-iodo-4-aminobenzoic acid melted at 203–204°. Repetition of this procedure, using 10 g. of *p*-aminobenzoic acid and proportional quantities of other reagents, gave a much lower yield (15.6%).

(B) Ten grams (0.073 mole) of *p*-aminobenzoic acid was dissolved in 200 cc. of water containing 8 g. of potassium hydroxide. To this was added a solution of 18.6 g. (0.073 mole) of iodine dissolved in 100 cc. of water containing 9 g. of potassium hydroxide. With stirring, 40 cc. of glacial acetic acid was run into the combined solutions and the whole immediately diluted with 190 cc. of water. The mixture was stirred vigorously and allowed to stand overnight. After treating with a small amount of 15% sodium bisulfite, the brown precipitate was filtered off, washed with water and air-dried. Yield: 8.35 g. (43.4%).

The crude product was extracted with 40 cc. of 10% ammonia water and the residue washed with water. The dry, ammonia-insoluble residue weighed 5.04 g. (26.3%). Acidification of the ammoniacal extract with acetic acid gave, after long standing, 2.15 g. (11.2%) of dark crystals melting at 200–201°. Crystallization from dilute alcohol yielded 1.7 g. (8.85%) of faintly colored crystals, m.p. 203–204°. Identity of this product was supported by diazotizing and treating with aqueous potassium iodide; this yielded a product which, after purification, melted at 257–258°.

Wheeler and Liddle (2) have reported the melting point of 3,4-diiodobenzoic acid as 257°.

The ammonia-insoluble product, after crystallizing from dilute alcohol, melted at 94–96°. It was soluble in dilute sulfuric acid; insoluble in water and alkali. From these properties, 2,4-diiodoaniline was suspected. Two more crystallizations from dilute alcohol gave a product which melted at 95.5–96°.

Anal. Calc'd for $C_6H_5I_2N$: N, 4.06; I, 73.6.
Found: N, 4.05; I, 70.22.

Method (B) was carried out under various conditions, particularly of temperature, but no improvement was observed. Indeed, at temperatures of 0° to 10°, elementary iodine was deposited.

3,4-Diiodobenzoic acid was prepared from 3-iodo-4-aminobenzoic acid according to the procedure of Wheeler and Liddle (8).

3,4-Diiodobenzoyl chloride. A mixture of 4 g. (0.0106 mole) of 3,4-diiodobenzoic acid and 10 cc. of thionyl chloride (Eastman's "Practical") was gently refluxed for three-fourths of an hour on a steam-bath. Excess thionyl chloride was distilled from a steam-bath and the residue extracted with four small portions of carbon tetrachloride. The combined extracts were evaporated to about 3 cc. and chilled. Separation of the yellow solid was completed by the addition of a small volume of petroleum ether. The product, after decanting the petroleum ether and drying, weighed 2.6 g. (62.4%) and melted at 74–76°.

Anal. Calc'd for $C_7H_3ClI_2O$: I, 64.70; Cl, 9.03.
Found: I, 64.35; Cl, 9.16.

Hydrolysis of this product gave an acid melting at 258–259°. No depression of the melting point was observed when this acid was mixed with 3,4-diiodobenzoic acid.

3,4-Diiodohippuric acid. One and nine-tenths grams (0.0048 mole) of 3,4-diiodobenzoyl chloride was added to a hot solution of 2 g. of glycocoll (Eastman) in about 40 cc. of approximately 1% sodium hydroxide. The temperature was held between 85° and 100° for thirty-five minutes. The reaction-mixture was then filtered and washed. After acidifying the filtrate with concentrated hydrochloric acid, the white precipitate was collected, washed with water and air-dried. The crude, dry product was repeatedly extracted with hot ether to remove 3,4-diiodobenzoic acid. The dry, ether-insoluble residue weighed 1.32 g. (64.0%). Crystallization from dilute alcohol gave pure white crystals melting at 150–154° after beginning to soften at 148°.

Anal. Calc'd for $C_9H_7I_2NO_3$: N, 3.25; I, 58.67; M.W. 430.9.
Found: N, 3.02; I, 57.61; M.W. 436.8.

2-Amino-3,5-diiodobenzoic acid. The preparation of this compound was based on the procedure of Wheeler and Johns (3), who treated anthranilic acid in 5% hydrochloric acid with aqueous iodine monochloride. In our experience, attempts to prepare an aqueous solution of iodine monochloride resulted in its prompt decomposition. The following modification was found to be satisfactory. Two hundred and fifty cubic centimeters of 25% hydrochloric acid contained in a 2-liter beaker was heated to 80° and stirred mechanically. Twelve and one-half grams (0.091 mole) of recrystallized anthranilic acid was dissolved in this warm solution and a solution of 29.5 g. (0.183 mole) of iodine monochloride (11) in 30 cc. of 25% hydrochloric acid was added. After stirring for one minute, the reaction-mixture was diluted with 1 l. of water, whereupon a yellow precipitate began to appear almost at once. With continued stirring, the mixture was heated at 80–90° for fifteen minutes and then cooled to 28°. The flesh-colored precipitate was filtered off, washed thoroughly with water, and dried in air. The crude product was dissolved in 300 cc. of

warm (45°) sodium hydroxide and filtered into dilute hydrochloric acid. The flocculent precipitate was collected, washed with water, and air-dried. Yield: 17.5 g. (49.3%), m.p. 226–229°. One crystallization from dilute alcohol, using a little decolorizing charcoal, gave 14.0 g. (39.4%) of the crystalline acid melting at 231°. Wheeler and Johns (3) report yields of 85–90% of crude product. They gave no yield for the pure compound, m.p. 230–232°.

3,5-Diiodobenzoic acid. This compound was prepared from the foregoing 2-amino-3,5-diiodobenzoic acid according to the procedure of Wheeler and Johns (3).

3,5-Diiodobenzoyl chloride[6]. A mixture of 2.5 g. (0.0067 mole) of 3,5-diiodobenzoic acid and 5 cc. of thionyl chloride (Eastman's "Practical") was gently refluxed on a steam-bath for three-fourths of an hour, and the excess thionyl chloride distilled. The residue was crystallized from a small volume of carbon tetrachloride using a little decolorizing charcoal. Yield: 2.07 g. (79%) of yellow crystals, m.p. 66–67°. Recrystallization from carbon tetrachloride gave 1.6 g. (60.8%) of crystals melting at 67–68°.

Anal. Calc'd for $C_7H_3ClI_2O$: I, 64.70; Cl, 9.03.
Found: I, 64.25; Cl, 8.66.

Hydrolysis of the above compound gave an acid melting at 237.5–238°. When mixed with a known specimen of 3,5-diiodobenzoic acid (m.p. 233–234°), the mixture melted at 236.5–237.5°.

3,5-Diiodohippuric acid[6]. Five grams of glycocoll (Eastman) was dissolved in about 100 cc. of approximately 1% sodium hydroxide and the solution warmed to 90°. Four and eight-tenths grams (0.0122 mole) of 3,5-diiodobenzoyl chloride was added and the mixture shaken vigorously for ten minutes. During this time, the temperature was kept between 80° and 90°. After cooling slightly, the supernatant liquid was filtered off. The filtrate was cooled to room temperature, acidified with concentrated hydrochloric acid, and cooled to 16°. The white precipitate was collected, washed with water and air-dried. Yield: 1.7 g.[7]. The crude product was extracted with hot ether and the ether-insoluble residue crystallized from dilute alcohol. Yield: 0.95 g. (39.9%) of white crystals melting at 208–209°.

Anal. Calc'd for $C_9H_7I_2NO_3$: N, 3.25; I, 58.67, M.W. 430.9.
Found: N, 3.11; I, 57.88; M.W. 430.9.

SUMMARY

1. A new and practical method has been developed for the preparation of 2-amino-5-iodobenzoic acid. It was further found that this acid could be prepared by adapting the iodination method of Datta and Prosad (6) to anthranilic acid.

2. A new method for the preparation of 3-iodo-4-aminobenzoic acid by the iodination of *p*-aminobenzoic acid with nascent iodine[3] is reported. The method can not be recommended as practical; the principal product formed in this reaction was found to be 2,4-diiodoaniline.

[6] This compound is mentioned in English patent 465,994; *Chem. Abstr.*, **31**, 7446 (1937).

[7] Two and one-half grams of impure 3,5-diiodobenzoyl chloride was recovered after filtering off the supernatant liquid, hence only 2.3 g. (0.00586 mole) of the acid chloride actually was used in this reaction.

3. The preparation of 2,5-, 3,4- and 3,5- diiodobenzoyl chlorides, and conversion of these into the corresponding diiodohippuric acids is described in detail.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE INSTITUTO BACTERIOLOGICO D. N. H.]

THE OCCURRENCE OF α-AMYRIN AND URSOLIC ACID IN THE LEAVES OF *Ilex paraguariensis*

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In Argentina, Uruguay, and Brazil, a beverage called maté, an infusion of the leaves of *Ilex paraguariensis*, is extensively used as tea. This has created special interest in this plant material, and as a result, chemical investigation of its constituents has been undertaken. The writer, working in this field, has isolated two constituents, namely, α-amyrin and ursolic acid. From a phytochemical standpoint, the discovery that α-amyrin occurs in *Ilex paraguariensis* is significant, as it is the first report of its occurrence in a plant of the Aquifoliaceae family, to which *Ilex paraguariensis* belongs. The fact that α-amyrin and ursolic acid occur together in this plant leads to the belief that the plant converts α-amyrin to ursolic acid. This is in harmony with the findings of Goodson (1), who has shown that ursolic acid is an oxidation product of α-amyrin.

While this is the first time ursolic acid has been reported as a constituent of the leaves of *Ilex paraguariensis*, attention is directed to a paper by Hauschild (2) in which he reports that he isolated from the leaves of *Ilex paraguariensis* a substance that he thought was a sterol, and consequently named matésterol. However, from a comparison of the analysis and other descriptive data of Hauschild's compound with those of ursolic acid, it appears that the two materials are identical. This is further confirmed by the fact that in the present work no indications of a typical sterol were found in the extractives studied.

EXPERIMENTAL

alpha-Amyrin. Chloroform treatment of finely-ground leaves of *Ilex paraguariensis* yielded 10% of extractives. A solution of 10 g. of these extractives in 200 cc. of 5% ethanolic potassium hydroxide solution was refluxed for 3 hours. Water was then added to the solution, and the mixture was extracted with petroleum ether. The material obtained after the petroleum ether was removed was a yellow, semicrystalline mass. Its solution in acetone was decolorized with carbon, and evaporated until crystallization began. The crude crystals melted at 175–178°. These were recrystallized from acetone (yield 0.43 g.), and then melted at 183–185°. The purified material had a specific rotation of $[\alpha]_D^{20} + 90.9°$ ($c = 0.958$ in benzene),

and when it was mixed with an authentic sample of α-amyrin,[1] there was no depression of the melting point.

Anal. Calc'd for $C_{30}H_{50}O$: C, 84.50; H, 11.73.
Found: C, 84.33; H, 11.91.

alpha-Amyrin acetate. A solution of 0.25 g. of the above α-amyrin in 2.5 cc. of acetic anhydride was boiled for 30 minutes. As the solution cooled, crystallization took place, and 0.25 g. of material was obtained. When this was recrystallized from acetic acid it melted at 217–219° and had a specific rotation of $[\alpha]_D^{20}$ +76.1° (c = 1.316 in benzene). When the purified substance was mixed with an authentic sample of α-amyrin acetate, no depression of the melting point occurred.

alpha-Amyrin benzoate. This compound was made by boiling for 30 minutes a solution of 0.1 g. of α-amyrin and 0.6 cc. of benzoyl chloride in 2.5 cc. of pyridine. After the reaction-mixture was cooled, it was poured into water, and the mixture was extracted with ether. The ethereal extract was dissolved in methanol, from which the benzoate crystallized. It melted at 193–195°, and it did not depress the melting point of an authentic sample of α-amyrin benzoate.

alpha-Amyrone. This product was prepared from the *Ilex* α-amyrin according to the directions of Ruzicka, Muller, and Schellenberg (3). It melted at 123–125°, and it did not depress the melting point of an authentic sample of amyrone.

The following is a comparison of certain properties of authentic α-amyrin and some of its derivatives as reported by Professor Ruzicka and the corresponding data concerning α-amyrin obtained from the leaves of *Ilex paraguariensis*.

MATERIAL	M.P., °C.	C, %	H, %	$[\alpha]_D$	ACETATE M.P., °C.	$[\alpha]_D$	BENZOATE M.P., °C.	AMYRONE M.P., °C.
α-amyrin Ruzicka	176–179	84.50	11.73	+89°	224–225	+77.°	195	125
α-amyrin from *Ilex par.*	183–185	84.33	11.91	+90.9°	221–222	+76.1°	193	125

Ursolic acid. After storage at 0° for some days, an ethereal extract of ground leaves of *Ilex paraguariensis* yielded a deposit of crude ursolic acid. An ethanolic solution of this material was decolorized with carbon and evaporated until it crystallized. Crystals melting at 279–282° were obtained. Upon recrystallization, this gave a product which melted at 283.5–285°. $[\alpha]_D^{20}$ (c = 1.363 in pyridine) was +65.9°.

Ursolic acid diacetate. This compound was prepared by boiling a solution of 50 mg. of the above ursolic acid in 0.9 cc. of acetic anhydride. Upon cooling the solution, the diacetate crystallized. The product melted at 200–201°, became solid at 204–205°, and remelted above 300°. Van der Haar (4) reports the first melting point of ursolic acid as 200–201° and the second melting point as 320–322°.

Monoacetylursolic acid. This substance was prepared by boiling one-half hour an ethanolic solution of the above diacetylursolic acid. After recrystallization from ethanol it melted at 283–285°. $[\alpha]_D^{20}$ (c = 0.468 in chloroform) was +61°.

Some of the properties of ursolic acid and derivatives as reported in the literature,

[1] The authentic samples of α-amyrin and its derivatives were kindly furnished by Professor Ruzicka of Zurich.

the same data obtained with ursolic acid from *Ilex paraguariensis*, and the recorded properties of Hauschild's matésterol follow:

SUBSTANCE	M.P., °C.	C, %	H, %	$[\alpha]_D$	DIACETATE M.P., °C.	MONOACETATE	
						M.p., °C.	$[\alpha]_D$
Ursolic acid.....	284–285	78.88	10.6	+67.5°[a]	200–201	289–290	+62.4°
Ursolic acid from *Ilex par*.....	283.5–285			65.9°	200–201	283–285	+61.°
Matésterol Hauschild.....	276–278	78.14	10.7	+65.0°[b]	—	274–276	—

a In ethanolic potassium hydroxide.
b In pyridine.

SUMMARY

Ursolic acid and α-amyrin have been isolated from the leaves of *Ilex paraguariensis*.

Matésterol described by Hauschild appears to be somewhat impure ursolic acid.

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[CONTRIBUTION FROM THE MEDICAL RESEARCH DIVISION, SHARP AND DOHME, INC.]

THIOBARBITURATES. III. SOME N-SUBSTITUTED DERIVATIVES

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Received November 30, 1939

The synthesis of a number of 5,5-dialkyl-2-thiobarbituric acids has been described, and pharmacological and clinical evidence indicates that some of these compounds may have therapeutic value (1, 2, 3). Since the N-alkyl substituted barbituric acids, 1-methyl-5-ethyl-5-phenylbarbituric acid (Prominal) and 1,5-dimethyl-5-(1-cyclohexenyl)barbituric acid (Evipal), exhibited physiological properties that encouraged their use in medicine, it appeared worth while to prepare a series of analogous 1,5,5-trialkyl-2-thiobarbituric acids. The preparation, properties, and a preliminary study of their pharmacodynamic behavior are described in this report.

A search of the literature revealed that the following related compounds have been prepared, namely, 1-methyl-6-imino-2-thiobarbituric acid (4-oxy-6-imino-2-thio-1-methylhexahydropyrimidine)(4); 1,3-diphenyl-2-thiobarbituric acid (5), 1-allyl-5-phenylamino-2-thiobarbituric acid (1-allyl-2-thio-7-phenyluramil)(6), 1-methyl-3-phenyl-5,5-diethyl-2-thiobarbituric acid (7), and 1,3-di-*o*-tolyl-2-thiobarbituric acid (8).

Among the 5,5-disubstituted barbituric acids, certain alkyl groups may be introduced on the nitrogen by allowing the sodium salt of the acid to react with an alkyl halide. A similar procedure with analogous thiobarbituric acids, according to Tabern and Volwiler (2), forms compounds in which the third alkyl becomes attached to the sulfur, the products being semi-solids from which mercaptans are slowly evolved[2]. Consequently, the best available method for obtaining the desired products seemed to be the condensation of an appropriate dialkylmalonic or cyanoacetic ester with an N-alkylthiourea. Thus far we have examined various compounds obtained by the condensation of nine dialkyl substituted malonic or cyanoacetic esters with allyl-, methyl-, or ethyl- thiourea.

The reaction between the dialkylmalonic ester and allylthiourea proceeded quite normally when the customary ratio of reagents was used, *i.e.*, 1 mole of the malonic ester, 1.6 moles of allylthiourea, and 3 moles of metallic sodium dissolved in the required quantity of anhydrous ethanol.

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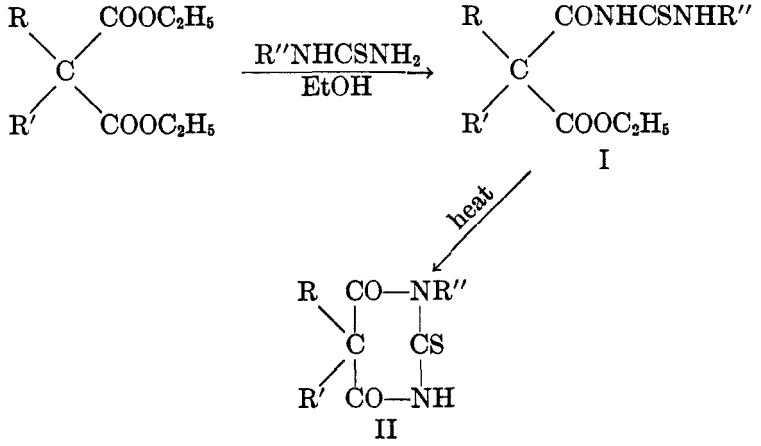
[2] These reactions were independently observed in our laboratories also. Lee, *J. Am. Chem. Soc.*, **60**, 993 (1938) observed similar reactions with 5-monoalkylthiobarbituric acids.

Satisfactory yields of 1-allyl-5,5-dialkylthiobarbituric acids were obtained. However, when methyl-, ethyl-, or phenyl- thiourea was used, a product was obtained, but it was not the desired trisubstituted thiobarbituric acid. The present evidence indicates that this product may be a dialkyl-N,N′-bis(alkylthiocarbamyl)malonamide, $R_2C(CONHCS\cdot NHR'')_2$ or, for certain derivatives, a compound derived from it by ring closure. The preparation, properties, and identification of these compounds are under investigation.

By varying the relative amounts of reagents used and the conditions of the reaction, 1,5,5-trialkyl-2-thiobarbituric acids (II), together with some of the corresponding α,α-dialkyl-N-alkylthiocarbamylmalonamic acids (I), have been obtained in the condensation of dialkylmalonic esters with N-methyl- and N-ethyl- thiourea. It was found that when the proportion of malonic ester was increased, the proportion of metallic sodium decreased, and the refluxing prolonged, the yield of desired 1,5,5-trialkyl-2-thiobarbituric acid became larger. By employing 1.1 moles of ester, 1 mole of alkylthiourea, and 1.1 moles of metallic sodium (dissolved in ethanol), significant quantities of the thiobarbituric acid derivative can be obtained. Even under these conditions, however, the main product is accompanied by appreciable amounts of the other two by-products. For example, when diethylmalonic ester was condensed with methylthiourea, the following compounds were isolated: α,α-diethyl-N-methylthiocarbamylmalonamic acid,[3] and 1-methyl-5,5-diethyl-2-thiobarbituric acid. The isolation of the above products in varying amounts, as conditions were altered, indicates that the reaction parallels that suggested by Fischer and Dilthy (9) in the urea series and may be represented as follows:



[3] A similar compound, α-butyl-α-ethyl-N-*p*-ethoxyphenylcarbamylmalonamic acid, was obtained by Hjort and Dox, *J. Pharmacol.*, **35**, 155 (1929) from ethyl-*n*-

EXPERIMENTAL

The malonic and cyanoacetic esters used in this work are all described in the literature and were purchased when possible, or synthesized by well-known procedures. Allylthiourea was purchased, and the methyl- and ethyl- thioureas were prepared by a modification of the method described by Slotta and Dressler (10).

1-Allyl-5,5-dialkyl-2-thiobarbituric acids. Diethylmalonic ester was condensed with allylthiourea according to the usual procedure for barbituric acid synthesis. The desired 1-allyl-5,5-diethyl-2-thiobarbituric acid was obtained as an oil which solidified after vacuum distillation and was purified by crystallization from dilute ethanol, m.p. 97.5–98°. 1-Allyl-5-ethyl-5-isoamyl-2-thiobarbituric acid was obtained in the same manner. The physical properties of these compounds are given in Table I.

TABLE I

TRIALKYLTHIOBARBITURIC ACIDS

2-THIOBARBITURIC ACIDS			FORMULA	M.P., °C.	N ANALYSIS, %	
5-Alkyl	5-Alkyl	1-Alkyl			Calc'd	Found
Methyl	Isopropyl	Methyl	$C_9H_{14}N_2O_2S$	107–107.5	13.08	13.02
Methyl	1-Methylbutyl	Methyl	$C_{11}H_{18}N_2O_2S$	b.p. 148–150/1 mm.	11.57	11.00
Methyl	1-Cyclohexenyl	Methyl	$C_{12}H_{16}N_2O_2S$	140–141	11.11	11.19
Ethyl	Ethyl	Methyl	$C_9H_{14}N_2O_2S$	123–124	13.09	13.08
Ethyl	*n*-Propyl	Methyl	$C_{10}H_{16}N_2O_2S$	79–80	12.28	12.30
Ethyl	Isopropyl	Methyl	$C_{10}H_{16}N_2O_2S$	104–104.5	12.28	12.12
Ethyl	Isopropenyl	Methyl	$C_{10}H_{14}N_2O_2S$	94.5–95	12.38	12.64
Ethyl	Isoamyl	Methyl	$C_{12}H_{20}N_2O_2S$	84.5–85	10.94	10.98
Ethyl	Phenyl	Methyl	$C_{13}H_{14}N_2O_2S$	120–121	10.69	10.67
Ethyl	Benzyl	Methyl	$C_{14}H_{16}N_2O_2S$	119–119.5	10.15	10.11
Ethyl	Benzyl	Ethyl	$C_{15}H_{18}N_2O_2S$	b.p. 170–175/1 mm.	9.65	9.89
Ethyl	Ethyl	Allyl	$C_{11}H_{16}N_2O_2S$	97.5–98	11.66	11.75
Ethyl	Isoamyl	Allyl	$C_{14}H_{22}N_2O_2S$	b.p. 175–180/1 mm.	9.93	9.85

1,5,5-Trialkyl-2-thiobarbituric acids. The reaction of ethylisopropenylmalonic ester with N-methylthiourea will serve as an example of the best conditions employed in preparing the trialkylthiobarbituric acids described in Table I from malonic esters and methyl- or ethyl- thiourea. While the procedure still leaves much to be desired, it served to provide sufficient amounts of the thiobarbituric acids for identification and pharmacological examination. Least satisfactory was the condensation with diethylmalonic ester, because of the difficulty encountered in separating the thiobarbituric acid from its by-products.

In 102 ml. of anhydrous ethanol was dissolved 5.06 g. of sodium (0.22 mole); the solution was cooled to room temperature and 50.2 g. of ethylisopropenylmalonic ester (0.22 mole) and 18 g. of methylthiourea (0.2 mole) were added. The mixture

butylmalonic ester and *p*-ethoxyphenylurea. This compound is erroneously listed in *Chem. Abstr.*, **23**, 3024 (1929) as α-butyl-α-ethyl-N-*p*-phenethylcarbamylmalonamic acid.

was stirred at room temperature for one hour and then refluxed from twelve to fifteen hours. It was then diluted to 500 ml. with water and extracted with benzene to remove alkali-insoluble matter. Acidification of the aqueous solution gave an oil which was extracted from the mixture with benzene. The benzene solution was washed twice with water and extracted with sodium bicarbonate solution to remove any α,α-ethyl-α-isopropenyl-N-methylthiocarbamylmalonamic acid present. The sodium bicarbonate extract yielded 2 g. of an oily product on acidification.

The residual benzene solution was then extracted with 2% sodium hydroxide solution. Acidification of the sodium hydroxide extract gave 22 g. of an oil which solidified upon long standing. 1-Methyl-5-ethyl-5-isopropenyl-2-thiobarbituric acid, 10 g., melting at 94.5–95°, was separated from an unidentified by-product contained in the crude material, by four recrystallizations from dilute ethanol.

Condensation of (1-cyclohexenyl)methylcyanoacetic ester with N-methylthiourea. (1-Cyclohexenyl)methylcyanoacetic ester (42 g.) was condensed with methylthiourea under the same experimental conditions as above, to give 18 g. of the iminothio-

TABLE II

DIALKYL-N-METHYLTHIOCARBAMYLMALONAMIC ACIDS

N-METHYLTHIOCARBAMYL-MALONAMIC ACIDS		FORMULA	M.P., °C. (DECOMP. WITH EVOLUTION OF GAS)	N ANALYSIS, %	
α-Alkyl	α-Alkyl			Calc'd	Found
Methyl	*n*-Propyl	$C_9H_{16}N_2O_3S$	109–109.5	12.07	12.28
Ethyl	Ethyl	$C_9H_{16}N_2O_3S$	132.5–133	12.07	12.09
Ethyl	*n*-Propyl	$C_{10}H_{18}N_2O_3S$	120.5–121	11.38	11.48
Ethyl	Phenyl	$C_{13}H_{16}N_2O_3S$	131–132[a]	10.00	10.36
n-Propyl	Allyl	$C_{11}H_{16}N_2O_3S$	97–98	10.85	10.99

[a] After standing for approximately two years, this sample was found to melt at 107.5°, without effervescence, and the nitrogen content had risen to 12.09%, which corresponds closely to the theory for phenylethylacetylmethylthiourea, 11.86%. The identity was established by synthesis of phenylethylacetylmethylthiourea, m.p. 107–107.5°. *Anal.* Found: N, 11.85%.

barbituric acid, which upon hydrolysis with dilute hydrochloric acid (1:2) gave 15 g. of 1,5-dimethyl-5-(1-cyclohexenyl)-2-thiobarbituric acid, melting at 140–141° after recrystallization from anhydrous ethanol.

α,α-Dialkyl-N-methylthiocarbamylmalonamic acids. An increase in the molecular proportion of sodium and dialkylmalonic ester in the above procedure for the preparation of 1-methyl-5,5-dialkyl-2-thiobarbituric acids led to the production of a significant quantity of α,α-dialkyl-N-methylthiocarbamylmalonamic acids.

In a typical reaction, 18.4 g. of sodium in 370 ml. of anhydrous ethanol, 69.1 g. of diethylmalonic ester, and 18 g. of methylthiourea (molar ratio—Na:ester:thiourea:: 4:1. 6:1) were refluxed for seven and one-half hours. The solution was concentrated to one-third its volume on the steam-bath and then acidified with concentrated hydrochloric acid, whereupon an oil separated. This oil was dissolved in benzene and the solution extracted with sodium bicarbonate. The bicarbonate extract was acidified and an oil, which slowly crystallized, was obtained. Yield, 9 g. The product melted with effervescence at 132.5–133° after several recrystallizations from a mixture of solvent naptha and benzene. These crystals were identified as α,α-

diethyl-N-methylthiocarbamylmalonamic acid. Its properties, with those of its homologs, are summarized in Table II.

A sodium hydroxide extract of the residual benzene solution, on acidification with hydrochloric acid, gave 8 g. of an oil which crystallized rapidly on stirring, and upon recrystallization from benzene melted at 142.5–143°. The identity and reactions of this compound are being investigated.

Synthesis of phenylethylacetylmethylthiourea. In a one-liter three-necked flask, equipped with reflux condenser and mechanical stirrer, were placed 22.5 g. (0.25 mole) of methylthiourea, 45.6 g. (0.25 mole) of phenylethylacetyl chloride, and 250 ml. of toluene. This mixture was refluxed with stirring for fifteen hours. The toluene was removed by evaporation on a steam-bath and the residue purified by

TABLE III

TRIALKYLTHIOBARBITURIC ACIDS

Results of Pharmacological Tests in White Mice[a, b]

2-THIOBARBITURIC ACIDS			AD 50 MG/KG	AD 100 MG/KG	LD 50 MG/KG	RATIO LD 50/AD 50	DURATION AT AD 100	
5-Alkyl	5-Alkyl	1-Alkyl					Induction Minutes	Anesthesia Hours
Methyl	1-Methylbutyl	Methyl	45	60	190	4.2	1	0.3
Methyl	1-Cyclohexenyl	Methyl	100	125	600	6.0	4	1.3
Ethyl	Isopropyl	Methyl	85	100	270	3.2	2	0.5
Ethyl	Isopropenyl	Methyl	85	90	320	3.7	3	2.0
Ethyl	Isoamyl	Methyl	125	150	290	2.3	5	0.3
Ethyl	Benzyl	Methyl	Convulsions		15			
Ethyl	Benzyl	Ethyl	Convulsions		100			
Ethyl	Ethyl	Allyl	250	300	700	2.8	4	0.2
Ethyl	Isoamyl	Allyl	300		500	1.7	11	0.3–1.0

[a] We are indebted to Mr. H. J. Pratt for technical assistance in the pharmacological testing of these compounds.

[b] We have followed the method of testing described by Cope and Hancock, *J. Am. Chem. Soc.*, **61**, 96 (1939), and the terms and symbols used herein have the meaning defined by them.

crystallization from boiling anhydrous alcohol, yield 38 g. (65% of the theoretical), m.p. 107–107.5°.

Anal. Calc'd for $C_{13}H_{16}N_2OS$: N, 11.86. Found: N, 11.85.

Pharmacological data. Pharmacological data obtained by the intraperitoneal injection into white mice of the sodium salt of the thiobarbituric acids are summarized in Table III. In general, it can be said that all of the compounds are active as hypnotics, having short induction periods and producing anesthesia of short duration, except the two containing a benzyl group, which were convulsant, rather than hypnotic in action. The effective and lethal doses, as well as the therapeutic ratios, varied widely within the group.

SUMMARY

The preparation, properties, and preliminary pharmacological data of several new 1,5,5-trialkyl-2-thiobarbituric acids are described.

The condensation of dialkylmalonic esters with N-methyl- and N-ethylthiourea gives rise to a series of α,α-dialkyl-N-alkylthiocarbamylmalonamic acids, and products as yet unidentified, as well as of thiobarbituric acids.

GLENOLDEN, PA.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, THE UNIVERSITY OF BUFFALO]

THE REACTION OF CERTAIN ORTHOESTERS WITH ALDEHYDES

HOWARD W. POST

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The reaction of an aliphatic orthoester with an aldehyde to form an acetal has been given considerable attention in the past, but generally in an attempt to develop a method for the preparation of the acetal. A detailed study of this type of reaction from the standpoint of the rôle of the orthoester has not been undertaken. Claisen (1) reported the preparation of acetals and ketals by the interaction of carbonyl compounds and imidoesters in alcohol.

Later, Harries and Schauwecker prepared the acetal of citronellal by the action of ethyl orthoformate on the aldehyde (2), and Claisen treated benzaldehyde in the same manner (3), using ammonium chloride as a catalyst and obtaining the diethyl acetal.

Pauly and von Beuttler found concentrated hydrochloric acid a suitable catalyst in the preparation of the diethyl acetal of salicylaldehyde from ethyl orthoformate and salicylaldehyde (4). Similarly, acetals of meta and para hydroxybenzaldehydes were also formed. Ammonium chloride served as the catalyst for the action of ethyl orthoformate on α-ethoxyfurfural producing the diethyl acetal (5). Wislicenus and Bilhuber studied the reaction of ethyl orthoformate on ethyl formylphenylacetate (6). A compound known as "paraldol" was treated with methyl orthoformate by Bergmann and Kamm (7) to yield a product whose formula was given as CH_3—$CHOH$—CH_2—$CH(OCH_3)_2$. The catalyst was ammonium chloride. Bergmann continued the work with certain sugar aldehydes (8), and salicylaldehyde (9). Ewlampieff (10) has also contributed to this field. Fleischer and Baer prepared the diethyl acetal of acrolein, and from this compound that of glyoxal by careful oxidation and retreatment with ethyl orthoformate (11). Ammonium nitrate and ammonium chloride were both used as catalysts.

The action of ethyl orthoformate on diphenylketene affords a novel instance wherein a ketone reacts to give a true acetal (12).

(I) $$(C_6H_5)_2C{=}CO + HC(OC_2H_5)_3 = (C_6H_5)_2C\begin{matrix}\diagup\ COOC_2H_5\\ \diagdown\ CH(OC_2H_5)_2\end{matrix}$$

It was the purpose of the work here presented, first, to attempt to place upon a broader comparative basis the reaction between an aldehyde and an alkyl orthoformate in the presence of an inorganic acidic catalyst, to the end that something might be determined with regard to comparative yields and reactivities, and second, that a possible mechanism might be set up.

The reaction of an alkyl orthoformate with acetaldehyde proceeds with the formation of the acetal and the alkyl formate when catalyzed by concentrated sulfuric acid.

(II) $CH_3CHO + HC(OC_3H_7)_3 = HCOOC_3H_7 + CH_3CH(OC_3H_7)_2$

In the work reported in Table I no product was isolated and determined save the major product, the acetal itself. In each case an impure alkyl formate was isolated, which had a slowly rising boiling point and showed physical properties almost identical with those of the expected ester. In addition, a small amount of intermediate-boiling material was obtained. It seems safe to say that formate and acetal are the major products. No unconverted orthoformate was ever found.

The dimethyl acetals of all three monohydroxybenzaldehydes have already been prepared (4, 9), but on repeating these preparations using ethyl orthoformate with sulfuric acid as the catalyst, we found the yields to be very small. In fact no acetal at all was found when the meta or para isomer was used. The diethyl acetal of salicylaldehyde was prepared by the method of Pauly and von Beuttler (4) with a yield of only 5 cc. of impure product from 10 cc. of aldehyde.

Attempts to prepare the diethyl acetals of the isomeric toluic aldehydes yielded little more than a trace of acetal from the ortho isomer and yields of 58% and 16% from meta and para respectively.

The proposed mechanism for the action of an alkyl orthoformate on an aldehyde was suggested by the reaction between acetaldehyde and ethyl thioorthoformate.

(III) $CH_3CHO + HC(SC_2H_5)_3 = HCOSC_2H_5 + CH_3CH(SC_2H_5)_2$

Dithioacetal was isolated and its physical properties determined (see experimental part), then synthesized by the action of mercaptan on aldehyde in the presence of dry hydrogen chloride gas (13).

When acetaldehyde and ethyl mercaptan were mixed, considerable heat was evolved, this heat corresponding, according to the discoverers of this reaction (13), to the formation of the hemiacetal. When dry hydrogen chloride was pumped into the mixture, the acetal was formed and water set free. This would involve an attachment of acidic mercaptan hydrogen to the carbonyl oxygen and of mercaptan sulfur to carbonyl carbon.

TABLE I

PREPARATION OF ACETALS

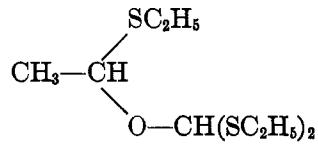
(Catalyst, one drop concd. H_2SO_4)

ALDEHYDE	ORTHOESTER	PRODUCT	YIELD, %	COMMENT
CH_3CHO	$HC(OC_2H_5)_3$	$CH_3CH(OC_2H_5)_2$	58	
CH_3CHO	$HC(OC_3H_7)_3$	$CH_3CH(OC_3H_7)_2$	43	
CH_3CHO	$HC(OC_4H_9)_3$	$CH_3CH(OC_4H_9)_2$	34	
C_6H_5CHO	$HC(OC_2H_5)_3$	$C_6H_5CH(OC_2H_5)_2$	66	
$(HCHO)_x$	$HC(OC_2H_5)_3$	none	0	"Paraform" used
$(C_2H_4O)_3$	$HC(OC_2H_5)_3$	none	0	"Paraldehyde" used
$(C_2H_4O)_3$	$HC(OC_2H_5)_3$	none	0	Paraldehyde, much polymerization
$CH_3CH{=}CHCHO$	$HC(OC_2H_5)_3$	none	0	Much polymerization
C_6H_5CHO	$HC(OC_3H_7)_3$	$C_6H_5CH(OC_3H_7)_2$	40	
C_2H_5CHO	$HC(OC_2H_5)_3$	$C_2H_5CH(OC_2H_5)_2$	40	
C_2H_5CHO	$HC(OC_4H_9)_3$	none	0	
C_2H_5CHO	$HC(OC_3H_7)_3$	$C_2H_5CH(OC_3H_7)_2$	13	
$C_6H_5CH{=}CHCHO$	$HC(OC_2H_5)_3$	none	0	Polymerization
CH_3CHO	$CH_3C(OC_2H_5)_3$	$CH_3CH(OC_2H_5)_2$	trace	
CH_3CHO	$CH_3C(OC_2H_5)_3$	$CH_3CH(OC_2H_5)_2$	trace	
$C_6H_4(CH_3)CHO$-*o*	$HC(OC_2H_5)_3$	$C_6H_4(CH_3)CH(C_2H_5)_2$-*o*	trace	
$C_6H_4(CH_3)CHO$-*m*	$HC(OC_2H_5)_3$	$C_6H_4(CH_3)CH(OC_2H_5)_2$-*m*	58	
$C_6H_4(CH_3)CHO$-*p*	$HC(OC_2H_5)_3$	$C_6H_4(CH_3)CH(OC_2H_5)_2$-*p*	16	

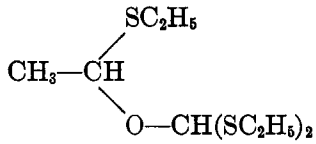
Making use of this mechanism, the action of the orthoester on the aldehyde could be formulated in accordance with equations IV and V.

$$CH_3—CH—O + (HC(SC_2H_5)_2)^+ + (SC_2H_5)^- =$$

(IV)



(V)



$$= CH_3CH(SC_2H_5)_2 + HCOSC_2H_5$$

TABLE II

PREPARATION OF THIOACETALS

REACTANTS	PRODUCT	YIELD, %
0.15 mole $HC(SC_2H_5)_3$ + 0.31 mole CH_3CHO	$CH_3CH(SC_2H_5)_2$	33⅓
0.30 mole $HC(SC_2H_5)_3$ + 0.60 mole CH_3CHO	$CH_3CH(SC_2H_5)_2$	9[a]
2.0 mole C_2H_5SH + 1.0 mole CH_3CHO	$CH_3CH(SC_2H_5)_2$	6[a]
0.06 mole $HC(SC_3H_7)_3$ + 0.12 mole CH_3CHO	$CH_3CH(SC_3H_7)_2$	10

a Very small fraction taken for analysis.

The type of reaction expressed in equation V has already been presented by Erickson (14) in connection with the decomposition of diethoxymethyl acetate to ethyl acetate and ethyl formate.

EXPERIMENTAL PART

Materials purchased were purified. Their physical properties were found to agree with values obtained from the literature.

Ethyl thioorthoformate, $HC(SC_2H_5)_3$, was prepared by the interaction of anhydrous formic acid and ethyl mercaptan in the presence of dry hydrogen chloride (15), b.p. 174° (760 mm.).

Propyl thioorthoformate, $HC(SC_3H_7)_3$, was prepared in the same manner as the corresponding ethyl compound. The reaction was much slower.

Acetal, $CH_3CH(OC_2H_5)_2$, was prepared as indicated above, by the interaction of acetaldehyde and ethyl orthoformate. The materials were mixed and two drops of concentrated sulfuric acid added, then the whole shaken to ensure complete mixing. A rise in temperature was always noted at this point. After twenty-four hours the mixture was neutralized with sodium carbonate, filtered, and distilled.

Propyl acetal, $CH_3CH(OC_3H_7)_2$, was prepared as was acetal, also by the interaction of propyl alcohol and acetaldehyde in the presence of calcium chloride after the manner of Adkins and Nissen (16).

Butyl acetal, $CH_3CH(OC_4H_9)_2$, was prepared in two ways, like the propyl compound. The preparation based on Adkins and Nissen was carried out by Mr. Henry Wolanczyk, formerly of the University of Buffalo (16).

All other acetals were prepared by the interaction of aldehyde and orthoformate as was acetal.

Ethyl and propyl thiolformates, $HCOSC_2H_5$ and $HCOSC_3H_7$, were isolated in the preparation of thioacetal and propyl thioacetal respectively.

TABLE III

PHYSICAL CONSTANTS OF PRODUCTS

SUBSTANCE	B.P., °C/MM.	n_D	d
$CH_3CH(OC_2H_5)_2$	102/760	1.3797, 23°	
	102.2/760[a]	1.38193, 20°[a]	
$CH_3CH(OC_3H_7)_2$	62–63/42[b]	1.3939, 26°[b]	0.8239, 27°/4°[b]
	144/760[b,d]	1.3949, 26°[d]	0.824[c]
$CH_3CH(OC_4H_9)_2$	95–96/30	1.4045, 25°	0.8293, 25°/4°
	188/760	1.4094[e]	0.8313[b,e]
	185/760[d]		
$C_2H_5CH(OC_2H_5)_2$	123/740	1.3872, 25.5°	0.833, 25°/4°
	122.8/744[f]		0.8825, 0°[f]
$C_2H_5CH(OC_3H_7)_2$	157–160/760	1.4038, 24°	0.8223, 22°/4°
	165.6/747[f]		
$C_6H_5CH(OC_2H_5)_2$	222 (corr.)/760	1.4721, 24.5°	0.906, 22°/4°
	222 (corr.)[g]		
$C_6H_5CH(OC_3H_7)_2$	242/760	1.4761, 25.5°	0.949, 25.5°/4°
$CH_3C_6H_4CH(OC_2H_5)_2$-*o*	125/37	1.4949, 23°	
$CH_3C_6H_4CH(OC_2H_5)_2$-*m*	190 (corr.)/750.5	1.4841, 25°	0.9618, 23°/4°
	125/41	1.4890, 23.5°	0.9642, 23.5°/4°
	116–117/30		
$CH_3C_6H_4CH(OC_2H_5)_2$-*p*	105–106/22	1.4845, 22°	0.9583, 20°/4°
		1.47603, 22°[h]	
$CH_3CH(SC_2H_5)_2$	186–189/753[i]	1.4985, 28°[i]	0.9425, 26°/4°[i]
	185–187[i]	1.4984, 26°[i]	0.9550, 27°/4°[i]
	183–185/760[i]	1.5005, 27°[i]	
$CH_3CH(SC_3H_7)_2$	116/13	1.4950, 23.5°	0.9539, 23.5°/4°
$HCOSC_2H_5$	103–106/760	1.4500, 26°	1.019, 25°/4°
$HCOSC_3H_7$	108.5/753	1.4580, 23.5°	0.9323, 23.5°/4°

a Pinner, *Ber.*, **16**, 356 (1883).

b Prepared from orthoformate and aldehyde.

c Beilstein, Prager, and Jacobson, **1**, 604 (4th Ed.).

d Unpublished, prepared by Mr. Henry Wolanczyk, formerly of the University of Buffalo, according to the method of Adkins and Nissen (16).

e Hinton and Nieuwland, *J. Am. Chem. Soc.*, **52**, 2893 (1930).

f Beilstein, Prager, and Jacobson, **1**, 629 (4th Ed.).

g Beilstein, Prager, and Jacobson, **7**, 209 (4th Ed.).

h *J. Pharm. Soc. Japan*, **500**, 746 (1923); *Chem. Abstr.*, **18**, 386 (1924).

i Prepared according to Ref. 13.

j Prepared from aldehyde and thioorthoformate

SUMMARY

1. Comparative data are presented on the yields of acetals from the interaction of an aldehyde with an aliphatic orthoester in the presence of a little sulfuric acid as catalyst, to show (a) that polymerized aldehydes do not so react, (b) that the highest yields are obtained from benzaldehyde, second from acetaldehyde, and third from propionaldehyde, (c) that ethyl orthoformate reacts to the best advantage, propyl second, and butyl third, of those tried, (d) that ethyl orthoacetate does not so react, and (e) that certain aldehydes, namely cinnamaldehyde and crotonaldehyde polymerize under these conditions without further reaction which could be detected.

2. Using acetaldehyde with ethyl or propyl thioorthoformate, the dithioacetals are obtained. A mechanism is suggested for this reaction.

BUFFALO, N. Y.

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

QUINONES BY THE PEROXIDE OXIDATION OF AROMATIC COMPOUNDS

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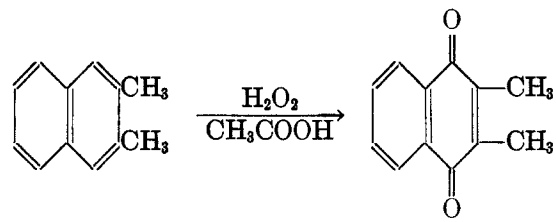
An attempt to prepare 1-naphthoic acid from the aldehyde using perhydrol in glacial acetic acid gave only a small quantity of the carboxylic acid and workable amounts of 1,4-naphthoquinone. If the acid was not isolated the quinone could be obtained in a yield of twenty-seven per cent.

In contrast to the work of Charrier (1) it has been shown that naphthalene can be oxidized under similar conditions to give a twenty per cent yield of 1,4-naphthoquinone. The conditions of the reaction cannot be changed materially without seriously affecting the yield of quinone. It has been reported (2) that anthracene yields anthraquinone and 9,9′-dianthrone, and that phenanthrene gives diphenic acid. These results have been confirmed.

Because of the present interest in quinones, due primarily to the investigations with vitamins E, K_1, and K_2, the products of bacterial metabolism, and carcinogenic substances, we have extended the reaction to include 1,2-benzanthracene, pyrene, and alkyl derivatives of benzene and naphthalene. All of these hydrocarbons form the expected quinones. A typical reaction is shown in formula I.

I.



The yields vary over a wide range depending on, and increasing with, the reactivity of the aromatic nucleus toward oxidation. It should be pointed out that 1,2-benzanthracene differs from anthracene in that the quinone is formed as the chief product.

Boeseken (3) has shown that certain aromatic aldehydes react with peracetic acid to replace the formyl group with acetoxy in good yields. This reagent, however, when tried on hydrocarbons gave practically no quinone.

The authors are indebted to Professors L. I. Smith, W. E. Bachmann, and L. F. Fieser for many compounds used in this study.

EXPERIMENTAL

Oxidation of 1-naphthaldehyde. A solution containing 4.03 g. of 1-naphthaldehyde in 80 cc. of glacial acetic acid was treated with 25 cc. of perhydrol and heated on a steam-bath. Within fifteen minutes the solution turned yellow, and in time, to cherry red. The solution was concentrated by removal of half the solvent, and water was added dropwise until precipitation began. Two crops of crystals were collected; m.p. 124–125°; yield 1.1 g. A mixed melting point determination with an authentic sample of 1,4-naphthoquinone proved the identity of the material.

Oxidation of naphthalene. Several attempts failed, but the following directions proved satisfactory. Ten grams of naphthalene, 25 cc. of perhydrol, and 50 cc. of acetic acid were heated together just above 80° for forty-five minutes. The volume of the solution was reduced to half by direct distillation at atmospheric pressure. Water was added slowly until crystallization started. The first crop melted at 121–125°, and the second began to melt at 115°. The odor of naphthalene was evident in the second crop. After recrystallization, a twenty per cent yield of the quinone was obtained.

Duroquinone. Five grams of durene in 50 cc. of glacial acetic acid containing 25 cc. of perhydrol was heated on a steam-bath for fifteen hours. After the bulk of the solvent was removed at diminished pressure, the material was steam distilled. The substance weighed 2.1 g. and melted at 110–111°. A mixed melting point determination with pure duroquinone gave no depression.

o-*Xyloquinone.* The procedure for duroquinone was followed, except that the temperature was held at 120° for twenty hours; only a trace of the yellow quinone was obtained. Practically all of the hydrocarbon was recovered in the steam distillation.

2-Methyl-1,4-naphthoquinone. Five grams of the hydrocarbon was dissolved in 75 cc. of glacial acetic acid and warmed to 50°. To this was added 15 cc. of perhydrol, and the mixture was allowed to stand at 80° for ten hours. An inductive period of ten minutes was followed by the usual color changes. After evaporation of the solvent and steam distillation, 1.8 g. (30%) of the quinone was obtained. The melting point was 104–105° and the identity was shown by mixed melting point with an authentic sample from Dr. Fieser.

2,3-Dimethyl-1,4-naphthoquinone. Following the above directions for the monomethyl derivative we obtained without steam distillation a seventy-eight per cent yield of product; m.p. 127°.

1,2-Benzanthraquinone-9,10. One gram of pure 1,2-benzanthracene was dissolved in 30 cc. of glacial acetic acid, and 5 cc. of perhydrol was added. The solution was heated to boiling and the flame removed. The exothermic reaction caused the mixture to continue refluxing for an additional 10 minutes. The heating was continued for twenty minutes, and the entire solution then poured into cold water. The finely divided precipitate was collected by centrifuging. The solid was recrystallized twice from acetic acid and melted at 158–160°. A red impurity was removed by sublimation. The sublimate, after recrystallization, weighed 0.52 g. (46%) and melted at 166–167°.

Oxidation of pyrene. To 5 g. of pyrene in 80 cc. of boiling glacial acetic acid, 25 cc. of perhydrol was added. After refluxing for twenty minutes, the reaction-mixture was poured into cold water. The reddish precipitate was collected and

dried; it weighed 5.1 g. This material is a mixture of the 3,8- and 3,10-pyrene quinones as shown by our inability to obtain a pure quinone by crystallization. The product was completely reduced by sodium hydrosulfite in the usual manner. Because of the difficulty involved (4), separation of these two compounds was not attempted.

SUMMARY

1. It has been shown that many aromatic hydrocarbons and their simple derivatives can be oxidized by thirty per cent hydrogen peroxide in glacial acetic acid to give quinones.

2. The yields are comparable to those obtained by dichromate oxidation.

3. It seems that the greatest value of the reaction lies in the selective oxidation of alkyl polycyclic derivatives.

MINNEAPOLIS, MINN.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE UNIVERSAL OIL PRODUCTS COMPANY]

ISOMERIZATION ACCOMPANYING ALKYLATION. II. THE ALKYLATION OF BENZENE WITH OLEFINS, NAPHTHENES, ALCOHOLS AND ALKYL HALIDES[1]

V. N. IPATIEFF, HERMAN PINES, AND LOUIS SCHMERLING

Received December 12, 1939

It is well known that alkylbenzenes may be prepared by the reaction of benzene with olefins (1), naphthenes (2), alcohols (3), alkyl halides (4), ethers (5), and esters (6) in the presence of suitable catalysts such as acids and metal halides. However, because isomerization of the alkyl group in some cases does and in others does not accompany the alkylation, there is much confusion in the literature with regard to both the structure of the alkylation product and the mechanism of the reaction. In this paper, the results of a study that was undertaken for the purpose of gaining an insight into the true nature of the alkylation are given.

Both important types of catalyst will be discussed. Since sulfuric acid and aluminum chloride have been most widely used, they have been chosen as representatives of the two types.

A consideration of the experimental facts as summarized in Table I leads to some important conclusions concerning the mechanism of the alkylation. It is seen at once that the results obtained with aluminum chloride are different from those with sulfuric acid. It is seen further that, contrary to the general belief, it is sulfuric acid which is the stronger isomerizing catalyst insofar as the apparent shifting of a double bond is concerned, and that in many cases aluminum chloride does not cause isomerization to accompany the alkylation. There has been considerable discussion in the literature whether the mechanism of the reaction involves an olefin or an ester as the alkylating agent. While no experimental data can be given to prove definitely which is the actual alkylating agent, it will be shown that the seemingly anomalous results can be explained best on the assumption of the intermediate formation of esters.

SULFURIC ACID CATALYZED REACTIONS

Alkylation by olefins. The recent study (1h) made in this laboratory on the isomerization accompanying the alkylation of benzene with 3-

[1] Presented before the Division of Organic Chemistry of the American Chemical Society at Milwaukee, Wisconsin. Sept. 1938.

methylbutene-1 showed that olefins do not always react with benzene to yield the product that would be obtained if the phenyl radical added to the least hydrogenated carbon atom of the double bond and a hydrogen atom added to the other.

In all cases the reaction presumably proceeds by way of the alkyl hydrogen sulfate. The ester reacts with benzene to yield the alkylbenzene, the reaction being catalyzed by concentrated sulfuric acid. With

TABLE I

ALKYLATION PRODUCTS

	SULFURIC ACID	ALUMINUM CHLORIDE
Olefins		
Pentene-1	2- and 3-Phenylpentane	
3-Methylbutene-1	*t*-Amylbenzene	2-Methyl-3-phenylbutane
Alcohols		
n-Propyl alcohol	Isopropylbenzene	*n*-Propylbenzene
Isoamyl alcohol	*t*-Amylbenzene	No alkylation
Naphthene		
Cyclopropane	*n*-Propylbenzene at 0° Isopropylbenzene at 65°	*n*-Propylbenzene regardless of temperature
Alkyl Halide		
n-Propyl chloride		Mixture of *n*- & isopropylbenzene

weak acid at low temperatures esters are formed but do not react with benzene (1c). Isomerization of the intermediate ester may occur prior to alkylation, resulting, with 3-methylbutene-1, in the formation of *t*-amylbenzene rather than of 2-methyl-3-phenylbutene.

$$(CH_3)_2\text{—}CH\text{—}CH\text{=}CH_2 + H_2SO_4 \rightleftarrows (CH_3)_2CH\text{—}\underset{\displaystyle OSO_3H}{\underset{|}{CH}}\text{—}CH_3$$

$$\uparrow\downarrow$$

$$(CH_3)_2\underset{\displaystyle OSO_3H}{\underset{|}{C}}\text{—}CH_2CH_3 \rightleftarrows [(CH_3)_2C\text{=}CHCH_3] + H_2SO_4$$

With pentene-1, the primary reaction-product is more stable, isomerization is slower, and a mixture of 2- and 3-phenylpentanes is formed. Here, the rate of alkylation is almost the same as that of isomerization.

Alkylation by alcohols. In the presence of sulfuric acid the primary product of the reaction is again the monoalkyl sulfate. As before, this may or may not undergo isomerization, depending on the conditions. Thus, *n*-propyl alcohol reacts with benzene in the presence of 80% sulfuric acid at 65° to yield isopropylbenzene. Similarly, isoamyl hydrogen sulfate undergoes isomerization even at 0° in the presence of 96% sulfuric

acid (isoamyl alcohol yields *t*-amylbenzene). On the other hand, *n*-amyl hydrogen sulfate undergoes only partial isomerization (*n*-amyl alcohol yields a mixture of 2- and 3-phenylpentanes). It may be expected, then, that *n*-propyl alcohol would yield *n*-propylbenzene in the presence of sulfuric acid at 0°. However, no alkylation takes place at this low temperature.

Alkylation by naphthenes. The fact that the alkylation of benzene with cyclopropane in the presence of sulfuric acid yields isopropylbenzene when the reaction is carried out at 65°, and *n*-propylbenzene when it is carried out at 0°(2b), may be considered to show that the alkylation takes place *via* the ester. The alkyl hydrogen sulfate, which is more stable at the lower temperature, is isomerized at higher temperatures, a result that was predicted on the basis of the mechanism discussed above.

Recently Simons and co-workers (1i, 2c, 3k, 4f) have shown that the alkylation of aromatic hydrocarbons is catalyzed by hydrogen fluoride. The unusual catalytic behavior of hydrogen fluoride, compared with that of other hydrogen halides, probably lies in the fact that hydrogen fluoride reacts with olefins to form alkyl acid esters similar to those obtained with sulfuric acid. Thus, the mechanism of hydrogen fluoride catalyzed reactions may be formulated as shown in I and II.

I. $$RCH{=}CH_2 + HF_nH_{n-1} \rightarrow RCH(F_nH_{n-1})-CH_3$$

II. $$C_6H_6 + RCH(F_nH_{n-1})-CH_3 \rightarrow C_6H_5CH(CH_3)R + H_nF_n$$

ALUMINUM CHLORIDE CATALYZED REACTIONS

Any mechanism advanced for the interpretation of the catalytic action of aluminum chloride in the alkylation of aromatic hydrocarbons must explain the following facts:

1. The presence of hydrogen chloride is essential for the alkylation of aromatics with olefins or naphthenes when aluminum chloride is used as a catalyst.

2. Alkylation of benzene with alcohols in the presence of aluminum chloride is not accompanied by isomerization.

3. Alkylation of benzene with cyclopropane in the presence of aluminum chloride-hydrogen chloride yields *n*-propylbenzene and not isopropylbenzene.

4. Alkylation of benzene with alkyl halides in the presence of aluminum chloride is often accompanied by isomerization, especially at higher temperatures.

Two mechanisms are proposed for the alkylation of aromatic hydrocarbons: the first applies to the alkylation of aromatics with olefins, naphthenes, or alkyl halides; the second, to the alkylation by alcohol.

Alkylation by olefins. The first step in the alkylation of aromatic hydrocarbons with olefins in the presence of aluminum chloride-hydrogen chloride is assumed to be the formation of a complex similar to sodium aluminum chloride.

$$AlCl_3 + HCl \rightarrow AlCl_3HCl \quad \text{or} \quad \left[\begin{array}{c} :\ddot{Cl}: \\ :\ddot{Cl}:\ddot{Al}:\ddot{Cl}: \\ :\ddot{Cl}: \end{array} \right]^- H^+$$

It may be assumed that hydrogen aluminum tetrachloride forms esters, analogous to those obtained with sulfuric acid, and that these react with the aromatic hydrocarbons.

$$RCH{=}CH_2 + HAlCl_4 \rightarrow \underset{\displaystyle ClAlCl_3}{\overset{\displaystyle |}{RCH{-}CH_3}}, \quad i.e., \quad \left[\begin{array}{c} Cl \\ ClAlCl \\ Cl \end{array} \right]^- R^+$$

$$C_6H_6 + \underset{\displaystyle ClAlCl_3}{\overset{\displaystyle |}{RCH{-}CH_3}} \rightarrow C_6H_5CH\begin{array}{l} \diagup\, CH_3 \\ \diagdown\, R \end{array} + HAlCl_4$$

However, unlike the alkyl sulfates, the alkyl tetrachloraluminates apparently isomerize slowly, if at all. Hence, for example, isopropylethylene reacts with benzene in the presence of aluminum chloride-hydrogen chloride to yield 2-methyl-3-phenylbutane and not *t*-amylbenzene.

Alkylation by naphthenes. By reacting cyclopropane with benzene in the presence of aluminum chloride-hydrogen chloride catalyst, *n*-propylbenzene is obtained; this is true whether the reaction is carried out at 0° (2a) or at 71°. The fact that no isopropylbenzene is found in the reaction-product excludes the possibility that *n*-propyl chloride was an intermediate in this reaction, since the latter on reacting with benzene yields both *n*- and iso- propylbenzene.

The mechanism of the alkylation of benzene with naphthenes involves the formation, not of alkyl halides but of alkylaluminum tetrachloride, which, as deduced above, does not undergo isomerization.

$$\begin{array}{l} CH_2{-}CH_2 \\ \diagdown\ \diagup \\ \quad CH_2 \end{array} + HAlCl_4 \rightarrow CH_3{-}CH_2{-}CH_2{-}ClAlCl_3$$

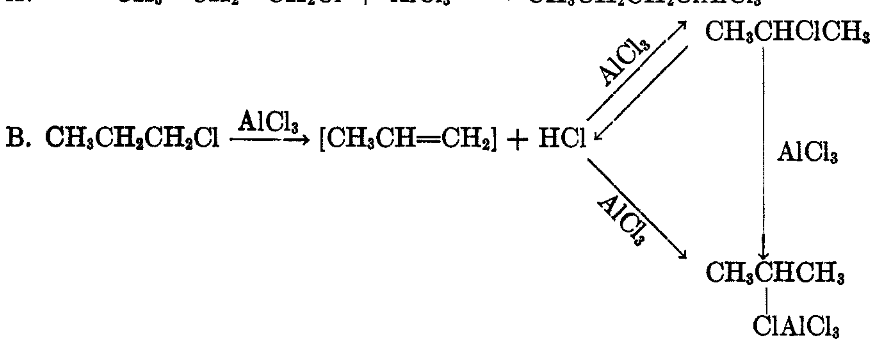
$$CH_3{-}CH_2{-}CH_2ClAlCl_3 + C_6H_6 \rightarrow C_6H_5CH_2{-}CH_2{-}CH_3 + HAlCl_4$$

That sulfuric acid and aluminum chloride do not bring about the formation of the same end-product in the alkylation of benzene with naphthenes is shown also in the results obtained with methylcyclobutane. In the presence of aluminum chloride (2a), isoamylbenzene and other isomers were formed, and *t*-amylbenzene was very probably not one of these. On the other hand, when the reaction was catalyzed by sulfuric acid (2b), only *t*-amylbenzene was obtained. Its formation was explained on the basis of the isomerization of the intermediate amyl hydrogen sulfate.

Alkylation by alkyl halides. Konowalow (4b, 4c), in investigating the alkylation of benzene with alkyl halides in the presence of aluminum chloride, showed that isomerization often accompanied the alkylation, especially at higher temperatures. Our own experiments have indicated that *n*-propyl chloride, on reacting with benzene in the presence of aluminum chloride at $-6°$, yields monopropylbenzene consisting of 60% of *n*-propylbenzene and 40% isopropylbenzene; when the reaction is carried out at $+35°$, 40% of *n*-propyl- and 60% of isopropyl-benzene is obtained.

In the alkylation of aromatics with alkyl halides, aluminum chloride being a dehydrohalogenating catalyst, two competitive reactions take place. At lower temperatures, reaction A predominates; at higher temperatures, B.

A. $CH_3—CH_2—CH_2Cl + AlCl_3 \longrightarrow CH_3CH_2CH_2ClAlCl_3$



The recent observations of Bowden (6c) on the alkylation of benzene by various esters (formates, acetates, sulfates, etc.) in the presence of aluminum chloride may be explained in a similar manner. The fact that the *n*-propyl ester yielded *n*-propylbenzene while the *n*- and iso- butyl compounds yielded *sec*.- and *t*-butylbenzene, respectively, finds analogy in the fact that *n*-propyl chloride yields a mixture of *n*-propyl- and isopropyl-benzene at even as high a temperature as 35°, whereas with isobutyl chloride only *t*-butylbenzene is formed even at a temperature as low as $-18°$. On the other hand, McKenna and Sowa (6b) state that in the presence of boron fluoride, *n*-propyl formate condenses with benzene to yield isopropylbenzene.

It is worth while to point out that there are exaggerated reports in the literature concerning the ability of aluminum chloride to cause isomerization during alkylation. Thus, for example, Calloway (7) states: "Propyl, butyl, and amyl halides react to yield, largely, branched alkyl substances. Generally, regardless of the configuration of the alkyl halide, the final product contains an alkyl group of the highest possible branching." Calloway gives the following equation:

$$\text{"}C_6H_6 + n\text{- or iso-}C_4H_9Cl \longrightarrow \textit{tert.}\text{-}C_4H_9C_6H_5\text{"}$$

However, none of his references describes the preparation of *t*-butylbenzene from *n*-butyl chloride. Indeed, except with neopentyl chloride (8), there has been no evidence for the branching (*i.e.*, the migration of a methyl group) of the alkyl radical of the halide during alkylation of benzene in the presence of aluminum chloride.

Alkylation by alcohols. A consideration of the experimental evidence indicates that the mechanism of the alkylation of benzene with primary alcohols in the presence of aluminum chloride is similar to that proposed by Tzukervanik (3e) for secondary alcohols, in contrast to that for tertiary alcohols. Thus,

$$n\text{-}C_3H_7OH + AlCl_3 \longrightarrow n\text{-}C_3H_7OAlCl_2 + HCl$$

$$n\text{-}C_3H_7OAlCl_2 + C_6H_6 \xrightarrow[AlCl_3]{} n\text{-}C_3H_7C_6H_5 + HOAlCl_2$$

Recently, Norris and Ingraham (3i) have studied the alkylation of benzene with methyl and ethyl alcohols. They state that in the study of the mechanism of the condensation which they will report in detail later, it was shown that the alcohols react with aluminum chloride to form compounds having the formula $ROAlCl_2$, which decompose when heated to produce RCl and AlOCl. In the presence of aluminum chloride, the usual Friedel-Crafts synthesis then takes place. This mechanism can scarcely be considered satisfactory for *n*-propyl alcohol, since the formation of propyl chloride by the decomposition of propoxyaluminum chloride would result in the formation of isopropylbenzene, as well as of *n*-propylbenzene.

For similar reasons, the mechanism proposed by Tzukervanik for alkylation by tertiary alcohols (3d) (*i.e.*, the decomposition of the alkoxyaluminum chloride to yield an olefin and hydroxyaluminum chloride) cannot be applied to the reaction with primary alcohols.

EXPERIMENTAL

Materials. All the chemicals with the exception of the pentenes were obtained from commercial sources and, when necessary, were purified by the usual methods. Pentene-1 was prepared according to the directions of Hurd and Goldsby (9). The preparation of the 3-methylbutene-1 is described in a previous paper (1h).

TABLE II

BENZENE, G.	ALKYLATING AGENT		CATALYST		PROCEDURE REFERENCE NO.	TEMP., °C.	TIME, HOURS	MONOALKYLBENZENE	
	Kind	Grams	Kind	Grams				Yield, %	Identified as
30	Pentene-1	20.9	H_2SO_4 (96%)	28.5	(1c)	4–6	1.2	65	55–60% 2-Phenylpentane 40–45% 3-Phenylpentane
50	*n*-Propyl alcohol	38.0	H_2SO_4 (96%)	90	(3b)	4–5	6.0	Traces	Benzene and propyl sulfate were the products isolated
50	*n*-Propyl alcohol	38.2	H_2SO_4 (80%)	400 cc.	(3b)	65	6.0	45	Isopropylbenzene
60	Isoamyl alcohol	55.7	H_2SO_4 (80%)	400 cc.	(3b)	65	6.0	36	*t*-Amylbenzene
80	Cyclopropane	23.5	H_2SO_4 (80%)	400 cc.	(2b)	65	5	58	Isopropylbenzene
35	3-Methylbutene-1	17.0	$AlCl_3$	10		4–6	1.7	12	2-Methyl-3-phenylbutane
120	*n*-Propyl alcohol	20.0	$AlCl_3$	87	(3f)	110	10	26	*n*-Propylbenzene
35	*n*-Amyl alcohol	25	H_2SO_4 (80%)	500 cc.	(3b)	70	6	60	60–65% 2-Phenylpentane 35–40% 3-Phenylpentane
120	Isoamyl alcohol	44	$AlCl_3$	87	(3f)	65–130	6–15	None	No alkylation
78	Cyclopropane	21.3	$AlCl_3$	10	(2a)	71	6	48	*n*-Propylbenzene
160	*n*-Propyl chloride	80	$AlCl_3$	10	(4b)	−6	5	41	60% *n*-Propylbenzene 40% Isopropylbenzene
160	*n*-Propyl chloride	80	$AlCl_3$	10	(4b)	35	5	48	40% *n*-Propylbenzene 60% Isopropylbenzene

Sulfuric acid catalyzed reactions. The alkylations were carried out following procedures described by Ipatieff, Corson, and Pines for the reaction with olefins (1c) and with naphthenes (2b), and by Meyer and Bernhauer for the reaction with alcohols (3b). In general, a mixture of benzene and sulfuric acid was stirred in a flask equipped with a mercury-sealed stirrer, a reflux condenser, and either a dropping-

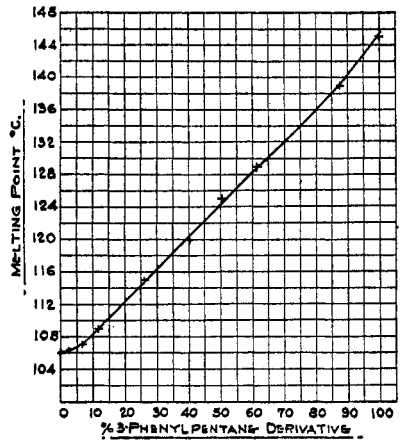


FIGURE I. MELTING POINT CURVE FOR MIXTURES OF THE MONACETAMINO DERIVATIVES OF 2- AND 3-PHENYLPENTANE

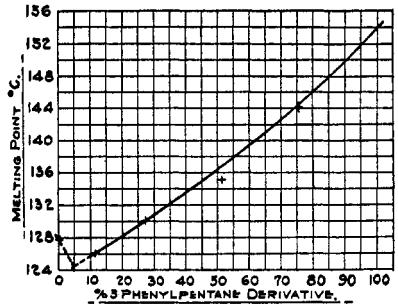


FIGURE II. MELTING POINT CURVE FOR MIXTURES OF THE MONOBENZAMINO DERIVATIVES OF 2- AND 3-PHENYLPENTANE

funnel for introducing the liquid alkylating agents or an inlet tube reaching to the bottom of the flask for introducing the cyclopropane. The reaction conditions are given in Table II. The hydrocarbon product was separated from the acid layer, made alkaline, and steam distilled. The distillate was dried and fractionated through a vacuum-jacketed, total reflux column (10).

Aluminum chloride catalyzed reactions. The general procedure used in the alkyla-

tions with 3-methylbutene-1, cyclopropane, and propyl chloride was similar to that described above for the sulfuric acid catalyst, except that steam distillation of the product was unnecessary. With the first two alkylating agents, anhydrous hydrogen chloride was added during the reaction at a rate of 300 cc. per hour.

The alkylation with *n*-propyl alcohol was carried out according to the directions of Tzukervanik and Vikhrova (3f). In a three-liter flask fitted with a mercury-sealed stirrer and a condenser, 20 g. (0.33 mole) of *n*-propyl alcohol, 120 g. (1.5 moles) of benzene, and three drops of water were placed. Aluminum chloride (87 g., 0.68 mole) was added during one hour by way of the condenser. The aluminum chloride dissolved, yielding a pale yellow solution, which gradually turned golden-yellow and then brown as more catalyst was added. When all the aluminum chloride had been added, the dark brown solution was stirred for one hour and allowed to stand overnight. It was then heated under reflux at 110–120° for ten hours, during the first part of which there was a copious evolution of hydrogen chloride. The product was worked up in the usual manner and distilled. The yield was 10.5 g. (26% of the theoretical) of monopropylbenzene.

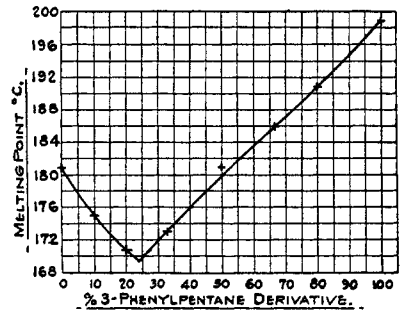


FIGURE III. MELTING POINT CURVE FOR MIXTURES OF THE DIACETAMINO DERIVATIVES OF 2- AND 3-PHENYLPENTANE

The monoalkylbenzenes were identified by the preparation of their mono- and diacetamino derivatives (11). The mixtures of *n*- and iso- propylbenzene were analyzed by the fractional crystallization (11a) of the diacetamino derivative. The relative quantities of the two isomers were estimated by weighing the crystals; the purity of the fractions was checked by observing the crystals under the polarizing microscope.

With the mixtures of 2- and 3- phenylpentanes, it was not possible to separate the derivative into its components. The melting point curves (Figures I, II, and III) were, therefore, prepared and used in determining the composition of the mixtures.

SUMMARY

The alkylation of benzene with olefins, alcohols, and naphthenes in the presence of sulfuric acid leads to the formation of alkylbenzenes different from those obtained when the reactions are catalyzed by aluminum chloride.

In the presence of sulfuric acid, isomerization accompanies the con-

densation of olefins with benzene; pentene-1 yields a mixture of 2- and 3- phenylpentanes; 3-methylbutene-1 yields *t*-amylbenzene. In the presence of aluminum chloride no isomerization occurs; isopropylethylene yields 2-methyl-3-phenylbutane.

Isomerization occurs during the alkylation of benzene with alcohols when the reaction is catalyzed by sulfuric acid, but not when aluminum chloride is used as catalyst; *n*-propyl alcohol yields isopropylbenzene in the presence of the acid and *n*-propylbenzene in the presence of the metal halide.

Isomerization does not accompany the alkylation of benzene with naphthenes in the presence of aluminum chloride; cyclopropane yields *n*-propylbenzene only. In the presence of sulfuric acid isomerization occurs, provided that sufficiently high temperatures are used; cyclopropane yields isopropylbenzene when the reaction is carried out at 65°.

The condensation of alkyl halides with benzene by aluminum chloride leads to a mixture of isomers. Even when the alkylation is made at 35°, much *n*-propylbenzene results from the reaction of *n*-propyl chloride and benzene.

The mechanism of the alkylations is discussed.

RIVERSIDE, ILL.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

THE KINETICS OF THE FORMATION OF THE GRIGNARD REAGENT. II. THE RATE OF REACTION WITH ETHYL BROMIDE

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In a previous paper (1) it was shown that, after an induction period, the rate of reaction of magnesium with ethyl bromide was approximately proportional to the concentration of ethyl bromide and the surface of the metal. It was also shown that under the experimental conditions employed a contact was necessary to produce uniform reaction. The results were not very reproducible and this was ascribed to the nature of the surface of the metal and the inefficiency of the contact. The present paper reports an attempt to improve the contact, a method for eliminating the induction period, and a study of the various contact materials as well as of the effect of dimethylaniline on the reaction. It will be shown that dimethylaniline is without effect on the velocity constant after the maximum rate is reached, and that the velocity constant is independent of the material used for the contact in the cases studied. It will also be shown that the velocity constant is greater in the presence of a contact than without a contact.

EXPERIMENTAL PART

The apparatus was similar to that used in the previous study except that two flat shoes were used as contacts and greater precautions were taken to exclude air and moisture. Two shoes of plate glass, designated by (A) in Figure I, served as contacts. The shoes were supported by two bronze springs (B) and a collar (C) so that they rested in a vertical position when inserted into the reaction-vessel (D). At the same time, there was just enough spring to (B) so that the shoes assumed a parallel and symmetrical position about the magnesium cylinder (E) and the glass shaft (F) on which the cylinder was mounted. Another half ring at the position (G) prevented the shoes from spreading or coming together. The glass joints (H) were ground to fit so that no grease was necessary. The remainder of the apparatus was the same as that described in the first paper (1).

Materials Used

Kahlbaum's pure magnesium was used. The rods, machined to remove the inactive oxide skin, formed cylinders approximately 0.90 cm. in diameter and 1.35 or

[1] From the dissertation of Felix C. Gzemski, presented to the Faculty of the Graduate School of the University of Pennsylvania in partial fulfillment of the requirements for the degree of Doctor of Philosophy, April, 1937. Paper presented before the Rochester Meeting of the American Chemical Society, September, 1937.

2.50 cm. in length. In addition, the cylinders were polished with emery paper and washed with dry ether on the day of use. If the cylinders were polished and allowed to stand for several days, the surface became inactive. This statement is based on the time elapsing to the appearance of an opalescence in the solution when magnesium was reacted with ethyl bromide. For freshly prepared cylinders the time was often as short as one-half minute, as against three minutes for other cylinders.

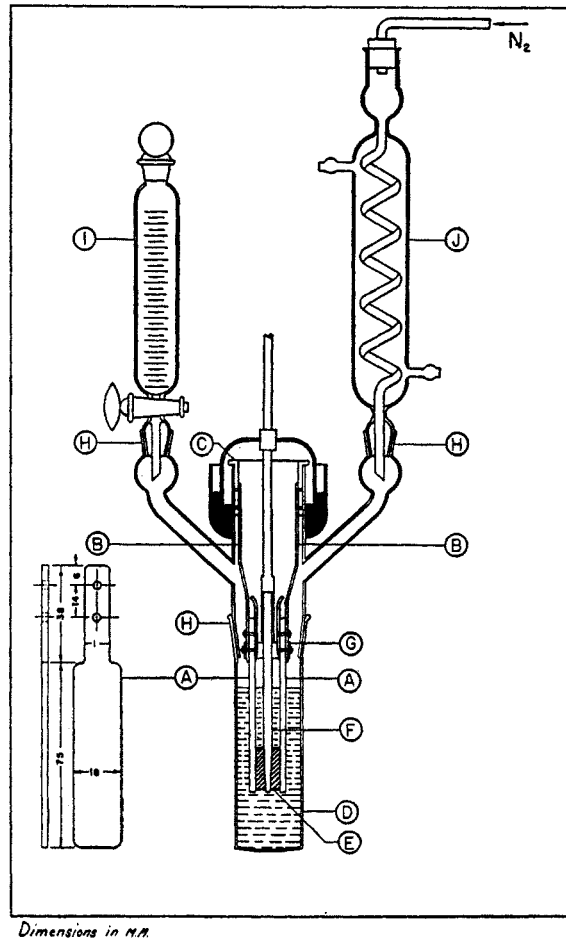

FIGURE I

Ethyl bromide was dried over phosphorus pentoxide and fractionated with a three-ball Snyder column. It was freshly distilled for each set of runs.

Ordinary commercial ether was treated with a saturated salt solution, and then stored over anhydrous calcium chloride for several days. The ether was decanted and distilled into a dry flask to which fresh sodium wire was added. After standing over sodium wire for three days, the ether was refluxed for five hours and fractionated. This treatment of the ether was repeated and it was finally stored over

sodium. A tube with glass wool at the bottom was inserted into the flask containing the dry ether and the ether was pipetted from this tube, a procedure which prevented any particles of sodium or flakes of sodium hydroxide from being drawn into the pipette. At first phosphorus pentoxide was employed in the final drying, but this step was eliminated after it was found that a dark brown substance formed on standing. Langheld (2) pointed out that ether combines with phosphorus pentoxide to form esters.

During the earlier part of the work, the ether was distilled into a specially designed separatory funnel. In every case, upon removing a sample, a positive test for water was obtained. The presence of water was detected by adding a xylene solution of basic aluminum ethoxide prepared according to the method of Henle (3), who claimed that it would detect 0.005% of water. However, when ether was pipetted from ether stored over sodium, a negative test was obtained. Later, another step was inserted into the procedure prior to the final distillation. The ether was treated with an ether solution of Grignard reagent to eliminate all Grignard-reactive substances.

Experimental Technique

All rate experiments were carried out in an oil thermostat regulated at 25 ± 0.05°. The magnesium cylinders were rotated at constant speed. The reaction-vessels, shoes, and burettes were baked at 135° and introduced into the system while warm in order to minimize the admittance of moisture. The system was swept out with dry nitrogen, and after the introduction of the solution, a small but positive pressure was maintained on the system to prevent any influx of air. The shaft was rotated at a speed of 1100 r.p.m. in all experiments. At the completion of an experiment, the magnesium cylinders were removed quickly, washed with ether, dried, and placed in a desiccator for later weighing. The solution was hydrolyzed with 0.2 *N* sulfuric acid and titrated with carbonate-free sodium hydroxide using phenolphthalein as an indicator (4).

The difference between the loss of weight of the magnesium cylinder (ΔW) and the C_2H_5MgBr formed [Mg(G)] gives the $MgBr_2$ formed [Mg(W)]. The initial concentration of ethyl bromide (expressed in terms of magnesium) is given by:

$$a = [Mg(G) + 2Mg(W)] \text{ final}$$

In this paper the assumption that the greater part of the Wurtz reaction takes place in the first interval is not made. The velocity constant is computed from the equation:

$$k = \frac{2.3\ S}{V(t_2 - t_1)} \log \frac{(a - x)_1}{(a - x)_2}$$

where S is the average surface, V the volume and $(a\text{-}x)_1$ and $(a\text{-}x)_2$ represent the concentrations of ethyl bromide at the times t_1 and t_2. Since the surface of the cylinders varied somewhat, the most convenient method of computing the velocity constant is to plot log (a-x) versus (St/V) and to read off the slope $-k/2.30$. Table I summarizes the first results obtained in the presence of dimethylaniline.

The reproducibility of the results is poor, the (a-x) values in the individual experiments often varying as much as 25%. Tentatively, we can conclude that dimethylaniline is without effect upon the velocity constant. The variations are attributed to the small ridges on the metal surface (making for poor contact over the whole surface), and to the fact that the cylinder was not always perfectly centered on the shaft.

Results with the Second Method

Finally a method was adopted which gave much more reproducible results. A known quantity of ethyl bromide was reacted to completion, a second portion was added, and the reaction measured over various intervals of time. This method eliminates any induction period for the part measured, removes moisture and other Grignard-reactive substances, and during the first period an adaptation of the metal cylinder to the glass shoes takes place. The method makes necessary careful sets of experiments carried to completion so that Mg(G) and Mg(W) are known at the initial and final times. Table II gives such a series of experiments.

Table II shows that the amount of ethyl bromide delivered can be accounted for quantitatively, and that the ratio of Wurtz to Grignard increases with increasing concentrations of ethyl bromide. These results are qualitatively in agreement with those of Gilman (5).

Tables III and IV give the results for cylinders of two different lengths, and for three different initial concentrations of ethyl bromide. The reproducibility is good and the graphs of log (a-x) versus (St/V) show that the line intersects the time axis at log a. The velocity constants in column seven are calculated from the time of addition of the second portion of ethyl bromide. It will be noted that the velocity

TABLE I

EFFECT OF DIMETHYLANILINE

V = 50 cc. T = 25°

AVERAGE LENGTH CYLINDERS, CM.	AVERAGE SURFACE CYLINDERS, CM.^{2}	DIMETHYLANILINE, MOLES PER LITER	INITIAL CONCENTRATION C_2H_5Br, MOLES PER LITER	FINAL YIELD, GRIGNARD PER CENT	k
2.50	7.18	0.0	0.133	90	0.88
2.50	7.55	0.0078	0.133	92	0.80
2.50	7.38	0.0156	0.133	91	0.88

constant for the short bars is greater than the constant for the long bars. In computing k only the surface of the side of the cylinder was used. If the total surface is used, the constants for both lengths of bar are the same. There was, however, no observable reaction on the ends except at the border of the shaft. These observations are in agreement with the earlier experiments (1), and the higher constant for the shorter bars is attributed to the better tangential contact.

An examination of the Wurtz-Grignard ratios for the forty-five individual runs yields the following information: For the experiments with one addition of ethyl bromide, the yield of Grignard is low for the five minute determinations (81%), and then increases to a final yield of 90%. This is in qualitative agreement with our earlier observations, where, however, lower yields were obtained (1). For the experiments with short bars reported in Table II, we have final yields for initial concentrations of 0.065 and 0.19 molar ethyl bromide only, namely, 93 and 85%. Table V summarizes the yields for short and long bars.

From Table V the following conclusions can be drawn.

1. For equal surface the higher the initial concentration of ethyl bromide the lower the yield of Grignard reagent.

2. The yield of Grignard reagent is constant throughout the reaction of the second portion of ethyl bromide. Our calculation includes the products formed in the

TABLE II

REACTION OF ETHYL BROMIDE WITH MAGNESIUM TO COMPLETION

Volume 50 cc. Temp. 25°. Surface, 3.5–4.0 cm.²

Ethyl bromide reacted—0.00327 mole, 0.065 mole per liter

TIME (MIN.)	GRAMS OF Mg REACTED			
	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$
50	0.0765	0.0729	0.0036	0.049
50	.0761	.0740	.0021	.028
50	.0748	.0734	.0014	.019
40	.0766	.0738	.0028	.038
Average	0.0760	0.0735	0.0025	0.034
			Yield 92.5%	

Surface, 7.5–8.0 cm.²

Ethyl bromide reacted—0.00665 mole, 0.133 mole per liter

50	0.1525	0.1439	0.0086	0.060
50	.1530	.1439	.0091	.063
50	.1533	.1463	.0070	.048
50	.1527	.1472	.0055	.037
45	.1530	.1451	.0079	.054
45	.1525	.1451	.0074	.051
Average	0.1528	0.1453	0.0076	0.052
			Yield 90%	

Surface, 3.5–4.0 cm.²

Ethyl bromide reacted—0.00993 mole, 0.198 mole per liter

50	0.2210	0.2054	0.0156	0.076
50	.2202	.2017	.0185	.092
60	.2224	.2048	.0176	.086
60	.2253	.2039	.0214	.105
Average	0.2222	0.2039	0.0183	0.090
			Yield 84.5%	

EFFECT OF THE CONCENTRATION OF ETHYL BROMIDE ON THE WURTZ-GRIGNARD RATIO

I MOLE C_2H_5Br DELIVERED	II MOLE C_2H_5Br REACTED $\frac{Mg(G) + 2Mg(W)}{24.32}$	III PER CENT GRIGNARD (Based on II)	IV PER CENT WURTZ (Based on II)	V PER CENT ACCOUNTED FOR
0.00327	0.00323	93.6	6.4	98.8
.00665	.00660	90.5	9.5	99.2
.00993	.00990	84.7	15.3	99.8

reaction of the first portion, but the same conclusion can be drawn from Tables III and IV where the yields are calculated separately for the second portion.

Effect of Dimethylaniline

Although the experiments in Table I indicated that dimethylaniline had no effect on the velocity constant, it was thought desirable to reinvestigate the effect of dimethylaniline under the new experimental conditions. In these experiments, the

TABLE III

RATE OF REACTION OF ETHYL BROMIDE WITH LONG BARS OF MAGNESIUM

Mg cylinder length 2.50 cms. Volume 50 cc.

0.00665 mole ethyl bromide reacted to completion
0.00327 mole ethyl bromide reacted to time (t)

TIME	S	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
2.5_2[a]	7.03	0.0300	0.0300			1.45
5.0_2	7.43	.0488	.0476	0.0012	0.025	1.37
7.5_4	7.24	.0582	.0580	.0002	.003	1.30
10.0_2	7.22	.0663	.0642	.0021	.033	1.41
15.0_2	6.97	.0760	.0716	.0044	.061	
Average k = 1.38 cm./min.						
0.00665 mole ethyl bromide reacted to completion .00665 mole ethyl bromide reacted to time (t)						
5.0_4	7.49	0.0982	0.0941	0.0041	0.044	1.38
10.0_6	7.24	.1295	.1217	.0078	.064	1.37
Average k = 1.38 cm./min.						
0.00327 mole ethyl bromide reacted to completion .00993 mole ethyl bromide reacted to time (t)						
5.0_2	7.26	0.1529	0.1451	0.0078	0.054	1.50
7.5_2	7.17	.1835	.1688	.0147	.087	1.58
10.0_2	7.20	.1964	.1850	.0114	.062	1.37
15.0_2	7.06	.2139	.2003	.0136	.068	1.33
20.0_2	7.06	.2216	.2103	.0113	.054	1.23
Average k = 1.40 cm./min.						

[a] Subscript gives number of duplicate experiments.

dimethylaniline was added after the first portion of ethyl bromide had reacted to completion. Table VI summarizes the results.

The failure of dimethylaniline to affect the velocity constant leads to the conclusion that, although ethyl bromide reacts with magnesium quite energetically in benzene solutions of dimethylaniline, it does not necessarily follow that in ether small quantities will have an effect. There is still the possibility that dimethylaniline acts as a cleaning agent for the surface. The experiments in Table VI do

not offer any evidence on this point, as the surface had already been cleaned by reaction with the first portion of ethyl bromide.

The Effect of the Nature of the Contact Substance on the Velocity Constant

Johnson and Adkins (6) and Gilman (7, 8) studied the effect of metals on the Wurtz-Grignard ratio. Copper was studied more intensively than other metals

TABLE IV

REACTION OF ETHYL BROMIDE WITH SHORT BARS OF MAGNESIUM

Mg cylinder length 1.35 cms. Volume 50 cc.

0.00327 mole ethyl bromide reacted to completion
.00327 mole ethyl bromide reacted to time (t)

TIME	S	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
5_3	3.65	0.0319	0.0304	0.0015	0.050	1.60
10_3	3.78	.0537	.0507	.0030	.059	1.71
15_3	3.91	.0641	.0602	.0039	.065	1.70
20_5	3.68	.0679	.0641	.0038	.059	1.65
Average k = 1.66 cm./min.						
0.00327 mole ethyl bromide reacted to completion .00665 mole ethyl bromide reacted to time (t)						
5_2	3.58	0.0661	0.0621	0.0040	0.064	1.62
10_2	3.57	.1018	.0967	.0051	.053	1.57
15_2	3.68	.1274	.1195	.0079	.066	1.69
20_3	3.91	.1373	.1274	.0099	.078	1.60
25_4	3.69	.1405	.1319	.0086	.065	1.57
Average k = 1.61 cm./min.						
0.00327 mole ethyl bromide reacted to completion .00993 mole ethyl bromide reacted to time (t)						
5_2	3.72	0.0947	0.0890	0.0057	0.064	1.47
10_2	3.65	.1548	.1416	.0132	.093	1.62
15_5	3.66	.1859	.1698	.0161	.095	1.62
20_2	3.52	.1975	.1820	.0155	.085	1.43
25_4	3.57	.2110	.1935	.0175	.085	1.64
30_4	3.70	.2148	.1987	.0161	.081	1.41
Average k = 1.54 cm./min.						

since it affected the Grignard reaction to a greater extent. In some experiments, copper powder was added to the magnesium, and in others, a copper-magnesium alloy was used. According to Gilman and Heck, certain copper-magnesium alloys react more rapidly than pure magnesium. It is an established fact that the presence of copper modifies the Wurtz-Grignard ratio. To determine the effect of the nature of the contact substance, the glass shoes were replaced by metal ones made after the same pattern. Completion experiments were not carried out for each metal and

consequently the Wurtz-Grignard ratios given in Table VII apply to the total product.

For the silver contact, thin silver sheets were used with a glass shoe as a backing. The use of a magnesium shoe gave very interesting results. The shoes were weighed

TABLE V

EFFECT OF CONCENTRATION ON THE YIELD OF GRIGNARD

Short Bars

FIRST PORTION		EtBr, MOLE PER LITER	YIELD SECOND PORTION							AVERAGE
EtBr, mole per liter	Yield, Grignard per cent		Time in minutes							
			5	10	15	20	25	30	35	
0.065	93	0.065	92	92	90	93				92
.065	93	.133	91	91	90	89	90			90
.065	93	.198	89	88	87	89	87	87	87	88

Long Bars

			Time in minutes						
			2.5	5	7.5	10	15	20	
0.13	90	0.065	93	93		93	90		92
.13	90	.133		91		89			90
.065		.198		91	87	89	89	90	89

TABLE VI

EFFECT OF DIMETHYLANILINE ON THE RATE OF REACTION OF ETHYL BROMIDE

0.00327 mole of ethyl bromide reacted to completion

.00327 mole of ethyl bromide reacted to time (t)

TIME	S	Me_2NPh	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
5_2	3.83	0.0078	0.0317	0.0284	0.0033	0.116	1.54
5_2	3.68	.0157	.0337	.0319	.0018	.056	1.62
5_2	3.74	.0235	.0343	.0311	.0032	.103	1.67
5_2	3.68	.0470	.0321	.0300	.0021	.070	1.56
10	4.17	.0078	.0578	.0553	.0025	.045	1.75
10	3.91	.0157	.0539	.0523	.0016	.031	1.78
10	3.80	.0314	.0544	.0516	.0028	.054	1.68
10	4.17	.0627	.0568	.0542	.0026	.048	1.69

Me_2NPh = moles/liter of dimethylaniline

Average k = 1.66 cm./min.

before and after the experiment and a loss in weight was found. The magnesium plate reacted only at the contact, a groove being observed in the shoe at the end of each experiment. Table VIII summarizes the results.

In the experiments reported in Table VIII, no allowance is made for the change

TABLE VII

THE EFFECT OF CONTACT MATERIAL ON THE RATE OF REACTION OF ETHYL BROMIDE

Aluminum

0.00327 mole of ethyl bromide reacted to completion
.00327 mole of ethyl bromide reacted to time (t)

TIME	S	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
5_2	3.97	0.0346	0.0309	0.0037	0.060	1.61
10_2	4.06	.0510	.0454	.0056	.069	1.58
15	3.79	.0618	.0556	.0062	.073	1.77
Average k = 1.65 cm./min.						
Copper						
5	4.35	.0303	.0224	.0079	.109	1.68
10	3.77	.0474	.0388	.0086	.104	1.65
15	4.02	.0581	.0510	.0071	.077	1.54
Average k = 1.62 cm./min.						
Silver						
5_3	4.06	.0388	.0363	.0025	.049	1.89
10_3	4.02	.0565	.0503	.0062	.040	1.89
15_1	4.07	.0670	.0645	.0025	.036	1.77
Average k = 1.85 cm./min.						

TABLE VIII

THE EFFECT OF MAGNESIUM CONTACT

TIME	ΔW_1	ΔW_2	ΔW_3	S	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
5_2	0.0351	0.0941	0.0168	3.98	0.0351		0.012	1.50
10_2	.0524	.1083	.0201	3.87	.0524		.015	1.42
15	.0619	.1222	.0157	4.12	.0604	0.0015	.030	1.35
Average k = 1.42 cm./min.								

ΔW_1 = total loss in weight of magnesium for the time interval *t*.

ΔW_2 = total weight of magnesium dissolved from cylinder for reaction to completion of 0.003228 mole of ethyl bromide, plus the amount dissolved during the time interval *t* following.

ΔW_3 = total weight of magnesium dissolved from magnesium shoes under the same conditions as ΔW_2.

S = surface of the cylinder.

in surface with time. It will be noted that the velocity constant is somewhat less than the average obtained with the glass shoes, while for the other metals, with the exception of silver, there is little change in the velocity constant. However, an examination of Tables VII and VIII and the summary given in Table IX indicates

TABLE IX

THE EFFECT OF CONTACT ON THE VELOCITY CONSTANT AND ON THE WURTZ-GRIGNARD RATIO

0.00327 mole of ethyl bromide reacted to completion
.00327 mole of ethyl bromide reacted to time (t)

CONTACT	$\frac{Mg(W)}{Mg(G)}$	YIELD, GRIGNARD PER CENT	k
Aluminum	0.067	89	1.65
Copper	.097	84	1.62
Silver	.042	91	1.85
Magnesium	.019	96	1.42
Glass	.058	89	1.66

0.00327 mole of ethyl bromide reacted to completion
.00665 mole of ethyl bromide reacted to time (t)

Aluminum	.086	85	1.54
Copper	.103	83	1.51
Silver			
Magnesium	.046	92	1.59
Glass	.065	88	1.61

TABLE X

THE REACTION OF ETHYL BROMIDE WITH SHORT BARS OF MAGNESIUM IN THE ABSENCE OF A CONTACT

Mg cylinder length 1.25 cm. Volume, 50 cc.

0.00327 mole of ethyl bromide reacted to completion in presence of contact
0.00327 mole of ethyl bromide reacted to time (t) in the absence of a contact

TIME	S	ΔW	Mg(G)	Mg(W)	$\frac{Mg(W)}{Mg(G)}$	k
5_3	3.73	0.0312	0.0308	0.0004	0.013	1.50
10_4	3.76	.0449	.0439	.0010	.023	1.25
15_3	3.48	.0550	.0533	.0017	.032	1.27
20_2	3.29	.0625	.0611	.0014	.023	1.28
Av. k = 1.32 cm./min.						

0.00327 mole of ethyl bromide reacted to completion in presence of contact
0.00665 mole of ethyl bromide reacted to time (t) in absence of a contact

5_2	3.40	.0557	.0512	.0045	.088	1.38
10_4	3.56	.0872	.0817	.0055	.067	1.31
15_2	3.43	.1095	.1045	.0050	.048	1.21
20_2	3.30	.1197	.1124	.0073	.065	1.21
Av. k = 1.28 cm./min.						

an appreciable decrease in the yield of Grignard reagent for the experiments with copper and aluminum. The decrease in yield with copper is in accord with the findings of Johnson and Adkins (6).

In order to determine if the contact was necessary after the initiation of the reaction, the experimental procedure was modified in the following way. The contact (A) and the glass shaft (F) (Figure I) were shortened so that after reaction with a portion of ethyl bromide in ether solution, the cylinder of magnesium could be lowered below the contact, and the reaction with a second portion of ethyl bromide studied. Previous experiments had shown that exposure of the cylinder to air after activation decreased the reactivity. Table X summarizes the rate experiments conducted in the absence of a contact.

The velocity constants in Table X are lower than those in Table IV, and k decreases with time. In addition, the individual experiments are not so reproducible in the absence of a contact.

DISCUSSION

Perhaps the most striking result of this investigation is the fact that changing the contact material does not alter the velocity constant. This eliminates any theory of local elements (10) as an explanation of the contact action. The possibility of an oxygen concentration cell (9), or the presence of peroxides, is eliminated, as the ether was distilled from the Grignard reagent and reacted with a first portion of Grignard reagent before the rate was measured. The possibility that the reacting surface is at a much higher temperature than 25° has already been mentioned (1) but discarded. That uniform reaction takes place without activation by a contact is refuted by the appearance of the surfaces, and by the experiments with magnesium shoes. The shoes presented a large surface of magnesium, but reaction took place only at the contact of shoes and cylinder.

In their study of photovoltaic effects, Dufford (11) and Harty (12) found that the direct-current resistance of a solution of Grignard reagent was greater than the alternating-current resistance. From this observation it appears probable that the electrodes were coated with a resistant layer of adsorbed molecules. Clark (13) has demonstrated, by means of x-rays, the presence of an adsorbed layer of organic halogen compounds on metals. The adsorption results in actual chemical reaction at higher temperatures (14). Such a mechanism is not impossible as a mode of activation of the ethyl bromide before reaction, but it is difficult to say just what rôle the shoe might play.

Our own picture of the reaction is that the shoe ruptures the coating, allowing the reaction of ethyl bromide and magnesium to start. Moreover, the shoe tends to prevent contamination of the surface by the products. During the initial period, the percentage yield of Grignard reagent based on the ethyl bromide reacted is probably relatively low

(70–80%), due in part to hydrolysis of the Grignard reagent and in part to the formation of Wurtz products. After approximately 50% has reacted, the yield is practically constant to the end of the reaction, and will remain so for subsequent runs at the same concentration, provided the accumulation of the reaction-products does not decrease the amount of clean or active surface of the metal available for reaction. This point of view is supported by the results reported in Table X.

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SUMMARY

1. An improved method of studying the dissolution of magnesium in ethyl ether solutions of ethyl bromide has been found. This method gives reproducible results.

2. Uniform and reproducible reaction takes place only at a contact. The rate of reaction is proportional to the concentration of ethyl bromide.

3. The contact initiates the reaction.

4. The nature of the contact substance does not appreciably alter the velocity constant for the substances studied but it does alter the yield of ethylmagnesium bromide in some cases.

5. The yield of ethylmagnesium bromide has been computed for all experiments and the various factors affecting the yield have been discussed.

PHILADELPHIA, PA.

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MOLECULAR REARRANGEMENTS INVOLVING OPTICALLY ACTIVE RADICALS. VIII. THE WOLFF REARRANGEMENT OF OPTICALLY ACTIVE DIAZOKETONES

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In 1912 Wolff (1) described a rearrangement which diazoketones undergo when they are treated with silver oxide in ammoniacal solution.

$$R{-}\overset{\overset{O}{\|}}{C}{-}CHN_2 \xrightarrow[NH_3]{Ag_2O} R{-}CH_2{-}\overset{\overset{O}{\|}}{C}{-}NH_2 + N_2$$

In recent years this rearrangement has received considerable attention, and has been developed by Arndt and co-workers (2) as a general synthetic method for lengthening the carbon-carbon chain. It has also been shown that the transformation is catalyzed by finely divided metals such as silver, copper, and platinum.

Of the mechanisms that have been proposed for this rearrangement, the one formulated by Eistert (3) is of special interest. In the presence of the catalyst, the intermediate (II) follows the course of the reaction indicated by equations (b) and (c). In the absence of the catalyst, and in the presence of water and an acid such as formic acid, it adds water to give a keto alcohol as indicated in equation (d).

(a)
$$R{:}\overset{\overset{O}{\|}}{\underset{\cdot\cdot}{C}}{:}\overset{\overset{H}{\cdot\cdot}}{\underset{\cdot\cdot}{C}}{:}N{:::}N: \rightarrow R{:}\overset{\overset{O}{\|}}{\underset{\cdot\cdot}{C}}{:}\overset{\overset{H}{\cdot\cdot}}{\underset{\cdot\cdot}{C}} + N_2$$

II

(b)
$$R{:}\overset{\overset{O}{\|}}{\underset{\cdot\cdot}{C}}{:}\overset{\overset{H}{\cdot\cdot}}{\underset{\cdot\cdot}{C}} \xrightarrow[\text{anionic migration}]{\text{catalyst}} R{:}\overset{\overset{H}{\cdot\cdot}}{C}{::}C{::}\overset{\cdot\cdot}{O}$$

III

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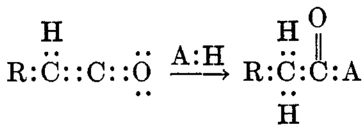
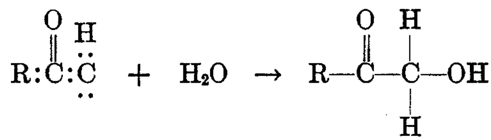
(c)  (A:H=NH_3; H_2O; RNH_2; ROH)

(d) 

Evidence that a ketene (III) is formed as an intermediate in rearrangements of this type has been submitted by Staudinger and Hirzel (4). These investigators were able to isolate the ketene formed in the rearrangement of diazoacetoacetic ester. A similar result has been reported by Schroeter (5). Usually, however, the rearrangement is conducted in the presence of water, ammonia, alcohol, or an amine, and consequently an acid, an amide, an ester, or a substituted amide, as the case may be, is the first product of the reaction that can be isolated.

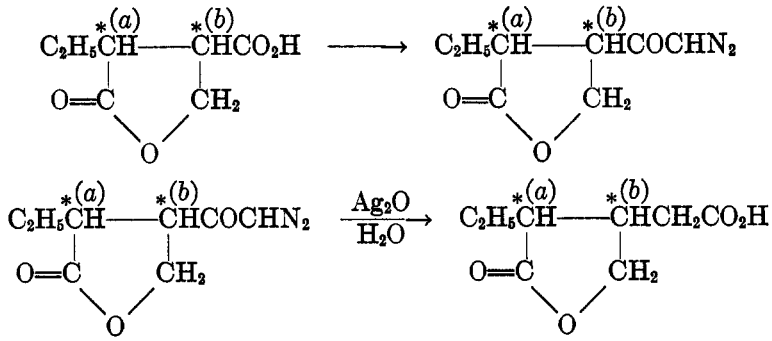
In studying the above proposed mechanism, it was of interest to us to note that this formulation closely parallels that now generally accepted for the Curtius rearrangement of the acid azides (6), where the first intermediate corresponding to the ketene is an isocyanate. The Curtius rearrangement, together with the related Hofmann and Lossen rearrangements of amides and hydroxamic acids respectively, has been extensively studied in recent years, and in the earlier papers of this series (7) describing experimental results on compounds in which the rearranging group is an optically active radical, it was shown that in every case the migrating group retained its asymmetry during the rearrangement process, and that the reaction was accompanied by no appreciable racemization.

In this paper it is our purpose to present for consideration the results of a similar study on the behavior of optically active diazoketones when they undergo the Wolff rearrangement, with a view of showing to what extent the formal parallelism between this rearrangement and the Curtius rearrangement may be accepted. *d*-Benzylmethyldiazoacetone, $(C_6H_5CH_2)(CH_3)CHCOCHN_2$, was chosen for these studies, since the work of Wallis and co-workers (6, 7) on the Curtius, Hofmann, and Lossen rearrangements was carried out on optically active compounds which contain the benzylmethylcarbinyl radical. This diazoketone, α_D^{20} + 134.3°; 1 dm. tube without solvent, was prepared by the action of diazomethane on *d*-benzylmethylacetyl chloride, α_D^{20} + 24.80°; 1 dm. tube without solvent. Similarly, an optically impure *levo* modification, α_D^{20} − 14.03°, 5 cm. tube without solvent, was obtained from an incompletely resolved *levo*-benzylmethylacetic acid.

Treatment of the completely resolved *dextro*-rotatory diazoketone with aqueous formic acid gave the corresponding keto alcohol with no appreciable racemization. Portions of the diazoketone were then subjected to the Wolff rearrangement under two sets of conditions. In the first series of experiments a small amount of silver ion was used as a catalyst. The diazoketone was dissolved in methyl alcohol which had been saturated previously at room temperature with ammonia gas. A small amount of silver nitrate was added, and then a rapid rearrangement occurred. On working up the product, an optically active β-methyl-β-benzylpropionamide was obtained in a chemically pure state with an inversion of the sign of rotation. It was soon observed, however, that partial racemization had taken place during the rearrangement process. Thus, by crystallization methods, it was possible to obtain pure fractions of the amide ranging in activity from $[\alpha]_D^{20} - 2.63°$ to $[\alpha]_D^{20} - 10.80°$ (benzene).

In the second series of experiments the diazoketone was dissolved in a 30% aqueous dioxane solution containing some sodium thiosulfate. The latter was added to prevent precipitation of the silver salt of the organic acid which is subsequently formed. A small amount of silver oxide was then added as a catalyst, and a rapid rearrangement took place. The substituted propionic acid so obtained, however, showed no appreciable rotation. Its amide was also found to be completely inactive. In this instance the asymmetric group completely loses its asymmetry during rearrangement—a fact that stands out in sharp contrast to observations in studies on the Curtius, Hofmann, and Lossen rearrangements. In these rearrangements no appreciable racemization accompanies the reaction.

These results are also of interest in connection with certain experiments of Preobrashenski, Poljakowa, and Preobrashenski (8). In their work on the synthesis of *d*-homopilopic acid from *d*-pilopic acid:

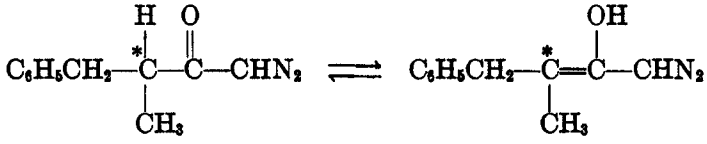


these investigators reported that the Wolff rearrangement takes place with no racemization. It should be remembered, however, that the mole-

cule studied has two asymmetric carbon atoms, one of which (*a*) is not affected by the rearrangement process and thus may influence the stereochemical course of the reaction as a whole. Moreover, these workers reported rotations on materials only after they were prepared for analysis. Thus, it may be that in this case also, rearrangement is accompanied by partial or complete racemization of the asymmetric center (*b*), one of the two possible products being lost in the mother liquors during recrystallization.

In the interpretation of their results obtained in studies on the Curtius, Hofmann, and Lossen rearrangements, Wallis and his co-workers put forward the belief that optical stability is most easily explained on the basis of an electronic mechanism involving a shift of the group with its pair of electrons. This did not imply, however, that the migrating group is a carbanion. On the contrary, evidence was obtained (9) by them to show that at no time is the migrating group ever free from the sphere of influence of the rest of the molecule. Hence, if the Wolff rearrangement proceeded according to the mechanism suggested by Eistert as outlined above, which is strictly analogous to that of the Curtius rearrangement, then a similar retention of optical activity by the migrating group would have been expected. The behavior of *d*-benzylmethyldiazoacetone on rearrangement, however, shows that this is not the case. Partial or complete racemization of the migrating group occurs, depending upon the conditions of the experiment.

This striking difference in behavior suggests many possible interpretations. At first thought it might be argued that the racemization is due to the occurrence during reaction of a tautomerism involving the hydrogen atom on the asymmetric carbon atom in the diazoketone or in the intermediate products.



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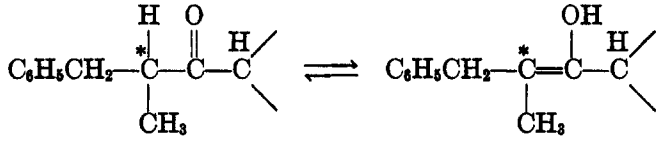
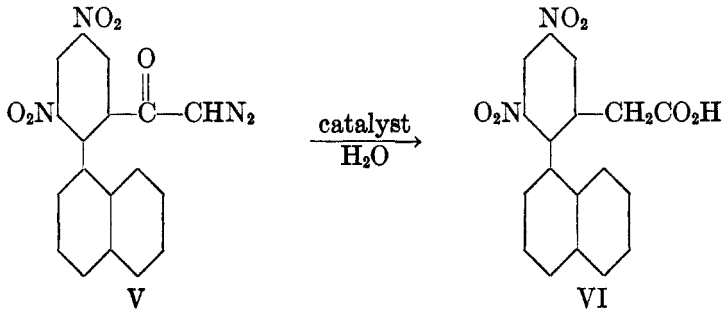


We are inclined, however, to reject this interpretation. The diazoketone is reasonably stable optically, even on distillation, and exhibits no such tautomerism in the solutions employed in the experiments; these solutions

are quite stable unless metallic catalysts are introduced. Furthermore, certain experiments on the optically active diazoketone, methylethylphenyldiazoacetone, $(CH_3)(C_2H_5)(C_6H_5)C—CO—CHN_2$, where such tautomerism can be ruled out, indicate here also that racemization accompanies the rearrangement. It may also be pointed out that the intermediates in the Curtius, Lossen, and Hofmann rearrangements of derivatives of *d*-benzylmethylacetic acid should have an equal opportunity for displaying this sort of tautomerism; yet this apparently never happens during the rearrangement process.

The explanation of the difference in behavior of a migrating asymmetric group in the two types of rearrangement is more probably to be sought in some divergence of the detailed mechanisms in the two cases. For example, both Curtius and Wolff rearrangements may proceed by a process of internal oxidation and reduction such that at no time is the migrating group free, but that in the former the asymmetric carbon atom retains at all times its complete octet of electrons, while in the latter it is at some point left with only a sextet of electrons. It has been pointed out by Wallis (10), that such a sextet of electrons is, in general, incapable of preserving intact the asymmetry of a carbon atom in such an intramolecular process and leads to extensive or complete racemization, or sometimes by a special mechanism to Walden inversion. It is also possible that the rearrangement, when catalyzed by silver ions, may be an ionic process involving separation of the asymmetric group as a carbanion or carbonium ion respectively, depending on the conditions of experiment (dielectric constant of the medium, catalyst, *etc.*). The properties and optical stability of such ions have been investigated in recent years (11), and it has been found that carbonium ions are on the whole more liable to racemization than carbanions. Such reactions are markedly influenced by the solvent and by other ions present in the solution. If the energies of ionization in the two different ways are comparable, then one or both types of ionization may be expected, the relative extent of each depending on the activation energies of each process, which will depend on the particular nature of the reaction-medium. Thus it is possible that the rearrangement of *d*-benzylmethylacetyldiazomethane in methyl alcohol saturated with ammonia leads to a product not completely racemized because the process involves carbanions extensively as intermediates, while the rearrangement in aqueous dioxane leads to a completely racemized product, since the intermediates are largely carbonium ions. It is interesting to note in this connection that the silver ion in the first case is present as a complex cation ($[Ag(NH_3)_2]^+$), while in the second it is present as a complex anion ($[AgS_2O_3]^-$). We propose to investigate further whether this is of real significance.

In conclusion we should like to point out that the decision between the alternatives discussed in the preceding paragraph, could be definitely made, were data available on the Wolff rearrangement of the same character as those obtained by Wallis and Moyer (9) for the Hofmann rearrangement. For instance, the optically active diazoketone (V) should rearrange into the acid (VI) without loss of optical activity unless the



V VI

mechanism involves the definite separation of the optically active radical into a free fragment, in which case racemization due to free rotation around the axial C—C bond should result. A study of this type has not yet been made, but the diazoketone (V) is now being prepared in this laboratory and its behavior will be discussed in a later paper. The influence of dielectric constant of the medium is also being investigated, since this also will make itself evident if the reaction is ionic. The connection, however, between rate of reaction and dielectric constant is difficult to establish in this case, since the reaction rate is also very sensitive to the catalyst. It must be remembered that the rôle of the catalyst is as yet completely unknown, although it may be noted in passing that those catalysts satisfactory for the Wolff rearrangement are among those known to be effective in weakening the carbon-carbon and carbon-hydrogen bonds (*i.e.* the metallic hydrogenation-dehydrogenation catalysts) and may owe their efficacy to the promotion of reactions of the types discussed above at their surfaces.

EXPERIMENTAL

Preparation of d-*benzylmethyldiazoacetone.* This compound was prepared from *d*-benzylmethylacetic acid. The acid used in these experiments was prepared according to the method of Conrad (12), with a few modifications due to Jones and Wallis (6). It was resolved into its enantiomorphs by the method of Kipping and Hunter (13). In a 5 cm. tube without solvent, the acid displayed a rotation α_D^{20} +11.35°. It was converted into its chloride by the method of Pickard and Yates (14). The chloride boiled at 89–90° (1.7 mm.). In a 5 cm. tube without solvent it gave a rotation α_D^{20} +12.40°. From the acid chloride, the diazoketone was then prepared according to the method of Arndt and Eistert (2) for the general prepara-

tion of diazoketones from acid chlorides. The acid chloride (10 g.) was dissolved in 25 cc. of pure dry ether, and added drop by drop over a period of one-half hour, with mechanical stirring, to a solution of 8 g. of diazomethane in 400 cc. of dry ether, prepared according to the directions of Arndt and Amende (15). The solution was kept at 0° during the addition of the chloride and for one-half hour thereafter. Finally it was allowed to come to room temperature and was stirred for an additional two hours. After filtration of the solution to remove polymethylenes, the solvent was removed. The diazoketone was obtained as a clear, yellow oil, which was freed from the last traces of solvent by heating on the water-bath at 60° for one hour under a pressure of 15 mm.

The diazoketone so prepared showed no trace of chloride either in the Beilstein test or on treatment with silver nitrate in ethyl alcohol. It was readily soluble in alcohol, ether, acetone, and benzene, insoluble in water. It was not obtained in crystalline form. When kept in a glass-stoppered bottle, the inner surface of which was free from etching, in a refrigerator, it was stable for an indefinite period. In a 5 cm. tube without solvent it gave a rotation α_D^{20} +67.2°.

The filtrates from the fractional crystallizations of the quinine salt of benzylmethylacetic acid were worked up and a mixed *levo* acid was obtained. This was converted to the corresponding mixed *levo* diazoketone by the method just described for the preparation of the pure *dextro* modification. Its rotation in a 5 cm. tube without solvent was α_D^{20} −27.90°. At 0.08 mm. pressure on a bath at 95–100°, the diazoketone distilled over with slight decomposition. An analysis of the product for nitrogen gave:

Calc'd for $C_{11}H_{12}N_2O$: N, 14.89. Found: N, 14.17.

Hydrolysis of the mixed l-*diazoketone to 4-phenyl-3-methylbutan-2-on-1-ol.* Three grams of the mixed *l*-diazoketone was treated with 30 cc. of 50% formic acid solution at room temperature. Nitrogen was violently evolved, and the solution became intensely orange-yellow. After one hour the reaction had stopped, and the solution was filtered, diluted with water, and extracted with ether. The ether extract was treated with concentrated sodium bicarbonate solution until neutral. It was then washed with water, dried over anhydrous sodium sulfate, filtered, and the ether removed on a water-bath. The residual brownish liquid was distilled at 56–62° at 0.002 mm. pressure. Yield 2 g. or 70.4% of the theory. In a 5 cm. tube without solvent the keto alcohol showed a rotation α_D^{20} −14.03°. For identification a sample of the freshly distilled keto alcohol was treated with *p*-nitrobenzoyl chloride and a small amount of pyridine. The *p*-nitrobenzoate was crystallized from a mixture of alcohol and petroleum ether. Melting point of pure product, 73°.

Anal. Calc'd for $C_{18}H_{17}NO_5$: C, 66.05; H, 5.20.
Found: C, 65.94; H, 5.12.

Rearrangement of the d-*diazoketone in methanol saturated with ammonia.* Thirty-five cubic centimeters of methanol was saturated with dry ammonia gas at 20°. Three grams of *d*-benzylmethyldiazoacetone was then added, whereupon the solution deepened in color to orange-red but remained clear. To the solution was added slowly and with shaking, 10 cc. of a saturated solution of silver nitrate in 80% (aqueous) methanol. Evolution of nitrogen commenced at once. After two hours no further evolution of nitrogen could be observed. The solution was then freed from solvent under reduced pressure on the water-bath at 30°, and the oily residue was extracted with ether until only a small amount of silver nitrate and silver powder remained. The ether solution was decolorized with animal charcoal, filtered, and dried over anhydrous sodium sulfate. On removal of the ether from the dried solu-

tion, a straw-colored oil was left, which was taken up in benzene and examined for optical activity. A solution of the substance in 10 cc. of benzene showed a rotation of α_D^{20} +0.5° (2 dm. tube). On addition of an equal amount of light petroleum ether, crystals of β-benzyl-β-methyl-propionamide separated. Some 2.5 g. of crude crystals was obtained. The mother liquor still exhibited a positive rotation. On evaporation of the solvent, a yellow oil remained which refused to crystallize. This was again subjected to a treatment with ammonia and silver in methanol as described above. This time, when the solvent was finally removed, a crystalline product was obtained, which was united with the first fraction. Three recrystallizations from a 50% solution of light petroleum ether in benzene gave one gram of leafy white crystals of melting point 80–81°. It had $[\alpha]_D^{20}$ −9.30° in benzene (0.156 g. of the substance in 5.00 cc. of solution gave α_D^{20} −0.58° in a 2 dm. tube).

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.54; H, 8.5.
Found: C, 74.34; H, 8.3.

The mother liquors from the recrystallizations were worked up and 0.5 g. of additional amide obtained. Melting point: 78–89°; $[\alpha]_D^{20}$ −2.63° (0.114 g. of amide in 5.00 cc. of benzene gave α_D^{20} −0.12°).

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53.
Found: C, 74.43; H, 8.54.

This indicates that the product was partially racemic. This was confirmed by the change of specific rotation of a portion on recrystallization from water. The crystals, separated and dried, had a specific rotation $[\alpha]_D^{20}$ −7.21°, while the amide left in the mother liquor had a rotation $[\alpha]_D^{20}$ −10.80°.

Rearrangement of the d-*diazoketone in 25% (aqueous) dioxane.* Three grams of *d*-benzylmethyldiazoacetone was dissolved in 25 cc. of dioxane. To this solution was added, with shaking, 80 cc. of a suspension of freshly precipitated silver oxide in 100 cc. of 5% sodium thiosulfate solution. Reaction commenced at once, as evidenced by a rapid evolution of nitrogen, the solution rapidly turning red. The mixture was shaken for ten minutes and then heated to 50° on the water-bath for two or three minutes. Reaction was then complete. The excess silver oxide was filtered out, and the solution extracted several times with small portions of ether. These extracts were discarded. The clear aqueous solution was acidified carefully with dilute hydrochloric acid, saturated with sodium chloride, and extracted four times with ether. The ether extracts were united and extracted several times with a solution of 2 *N* sodium hydroxide. This effected a separation of the organic acid from sulfur precipitated by the action of hydrochloric acid on sodium thiosulfate.

The united sodium hydroxide extracts were acidified with hydrochloric acid, saturated with sodium chloride, and extracted with ether as before. The ether solution of the organic acid was decolorized with animal charcoal, filtered, and dried over anhydrous sodium sulfate. On final removal of the ether, 2 g. of a straw-colored oil was obtained which was completely *optically inactive.*

The β-benzyl-β-methylpropionic acid itself was not obtained in crystalline form. For analysis it was converted to the acid chloride by treatment with thionyl chloride. The chloride was then added drop by drop with stirring to 100 cc. of concentrated ammonium hydroxide at 0°. The mixture was allowed to stand overnight, and the precipitated amide was recrystallized from 50% benzene-petroleum ether solution. Three recrystallizations sufficed to give a pure product of sharp melting point 83°.

Anal. Calc'd for $C_{11}H_{15}NO$: C, 74.54; H, 8.53.
Found: C, 74.55; H, 8.47.

Rearrangement of d-*methylethylphenyldiazoacetone.* This diazoketone was prepared by a method similar to that outlined above for *d*-benzylmethyldiazoacetone. Five grams of an incompletely resolved methylethylphenylacetic acid, $[\alpha]_D^{20}$ +6.90°, prepared by the method of Wallis and Bowman (10), was converted to the acid chloride by reaction with thionyl chloride. The chloride so prepared was dissolved in 200 cc. of dry ether and treated with an excess of diazomethane. After the reaction was completed the excess of diazomethane and the solvent were removed at 30° under diminished pressure. Five grams of a yellow viscous oil was obtained. Qualitative tests showed it to be free from halides.

Two grams of the material was dissolved in 15 cc. of pure dioxane, and to the solution was added slowly 40 cc. of a mixture of 2 g. of freshly precipitated silver oxide in 100 cc. of 5% aqueous solution of sodium thiosulfate. A reaction began immediately as evidenced by the evolution of nitrogen, and the color of the reaction-mixture changed rapidly to deep red. After two hours the reaction was complete. The solid silver-silver oxide mixture was then removed by filtration, and the filtrate was extracted several times with ether. Both ether extract and aqueous solution were optically inactive. From the aqueous solution was obtained on acidification 0.5 g. of an optically inactive acid.

We wish to take this opportunity to thank Merck and Company, Rahway, New Jersey, for certain of the analyses published in this paper and also to thank Professor F. Arndt, Universite Kimya Enstitusei, Istanbul, for helpful suggestions made to one of us at the commencement of this work.

SUMMARY

Benzylmethyldiazoacetone has been prepared in a pure *dextro* and a mixed *levo* modification.

Evidence is submitted to show that: (a) On treatment with acids in the absence of a catalyst, this compound gives an optically active keto alcohol without appreciable racemization.

(b) On treatment with ammonia in the presence of a catalyst, the compound undergoes a Wolff rearrangement to give a partially racemized β-methyl-β-benzylpropionamide.

(c) On treatment with water in the presence of a catalyst, the compound undergoes a Wolff rearrangement to give an optically inactive β-methyl-β-benzylpropionic acid.

Methylethylphenyldiazoacetone has been prepared in a mixed *dextro* modification. When this compound undergoes the Wolff rearrangement in the presence of water and a catalyst, an optically inactive acid likewise results.

A discussion of these results is given with special reference to the relation of the detailed mechanism of the Wolff rearrangement to that of the Curtius, Hofmann, and Lossen rearrangements, in which the benzylmethyl-

carbinyl radical retains its asymmetry without appreciable racemization during the rearrangement process.

OXFORD, ENGLAND
PRINCETON, N. J.

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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE STRUCTURE OF ACETOCODEINE[1]

LYNDON SMALL AND JAMES E. MALLONEE[2]

Received January 6, 1940

It was observed by Knoll and Co. about 1905 (1) that codeine reacts with warm "sulfoacetic acid" (a solution of concentrated sulfuric acid in acetic anhydride) in such manner that the alcoholic hydroxyl group is acetylated, and, in addition, the codeine molecule undergoes substitution by a second acetyl group. In contrast to the acetyl group at the hydroxyl, the second acetyl has ketonic properties, and cannot be removed by hydrolysis, whence Knorr (2) believed that the new group was substituted in the aromatic ring of codeine, at the same position as the bromine atom or the nitro group of bromocodeine or nitrocodeine respectively. This view was supported by the fact that acetocodeine, like bromocodeine, does not undergo nitration, an indication that the preferred nitration position is already occupied. Knorr assumed, on grounds not stated, that these derivatives all carried the substituent at the 1 position. Later investigators (6) considered that substitution in the morphine or codeine molecule may take place at the 2 position, a belief that was perhaps based on the probable ortho-orienting influence of the morphine phenolic hydroxyl at position 3. Schöpf and Pfeifer (3), however, have suggested that bromination of dihydrocodeinone takes place at position 1. Direct proof of the position of bromination was offered by Small and Turnbull (4), through identification of the degradation product of bromocodeine (and consequently of bromomorphine) with synthetic 1-bromo-3,4-dimethoxyphenanthrene.

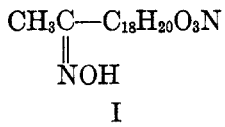
More recently, Ochiai and Nakamura (5) have taken up the structural problem outlined by Small and Turnbull (6) and have demonstrated, through conversion to 1-bromocodeine, that the aminocodeine (m.p. 228°) resulting from reduction of Anderson's nitrocodeine (m.p. 221°) (7) has the amino group in the 1 position. By a parallel procedure, the

[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

[2] Mallinckrodt Fellow in Alkaloid Chemistry 1937–39.

aminocodeine (m.p. 95–96.5°) resulting from reduction of nitrocodeine (m.p. 116.5–117.5°) obtained from the supposed nitrosomorphine of Wieland and Kappelmeier (8) was shown to be 2-aminocodeine. Anderson's nitrocodeine was first reduced by Vongerichten and Weilinger (9) with tin in glacial acetic acid. Acetylation took place simultaneously with reduction; the product that they describe as "diacetylaminocodeine" is, in the light of Ochiai's proof, 1-acetylamino-6-acetylcodeine.

If acetocodeine actually has the acetyl group in the aromatic ring, the obvious method for proof of position of the group is the Beckmann rearrangement of the oxime. If acetocodeineoxime has the structure I, the rearrangement would lead to II, and Ochiai's aminocodeines would be of no service.



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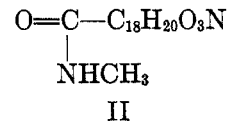

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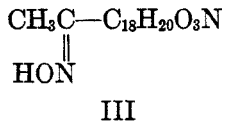

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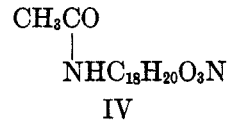

IV

If, on the other hand, the oxime is of the other possible form III, the rearrangement must lead to the N-acetyl derivative IV of one of the known aminocodeines.

To carry out the desired structural proof, aceto-6-acetylcodeine was chosen, since its oxime, in contrast to that of acetocodeine, is a crystalline, well-defined compound. Attempts to accomplish the rearrangement of aceto-6-acetylcodeineoxime with concentrated sulfuric acid, or phosphorus pentachloride, under the customary conditions resulted in unchanged material, or in extensive decomposition. With "Beckmann's mixture," at room temperature, the rearrangement proceeded smoothly, to give an excellent yield of acetylamino-6-acetylcodeine. This compound differed from the "diacetylaminocodeine" of Vongerichten and Weilinger in that it crystallized in the form of a trihydrate, whereas Vongerichten reported an anhydrous base. The rearrangement-product gave satisfactory analytical values, however, and was identical with 1-acetylamino-6-acetylcodeine prepared according to Vongerichten's directions from 1-aminocodeine.

Although these results leave little doubt about the structure of the Beckmann rearrangement product, it was desirable to eliminate the possibility of criticism arising from the disagreement with Vongerichten's

experiments. The acetylamino-6-acetylcodeine from the rearrangement was therefore subjected to hydrolysis. The product was 1-aminocodeine, corresponding in melting point and rotatory power with 1-aminocodeine prepared by reduction of Anderson's (m.p. 221°) nitrocodeine, the structure of which was demonstrated by Ochiai and Nakamura. Acetocodeine therefore carries the acetyl group in the 1 position of the codeine aromatic ring. Reduction-products from acetocodeine will be described in a later paper.

EXPERIMENTAL

1-Aminocodeine was prepared by electrolytic reduction of 1-nitrocodeine in 20% sulfuric acid solution (10). From 10 g. of 1-nitrocodeine, 5 g. of crude 1-aminocodeine was obtained. Purification was difficult because of the low solubility of aminocodeine in organic solvents, and was best effected by repeated sublimation in a high vacuum. The pure base had the melting point 226–228° (evac. tube) and showed $[\alpha]_D^{27}$ −178.7° (water, $c = 0.91$). We were unable to obtain significant amounts of aminocodeine by reduction with sodium hydrosulfite, as described by Ochiai.

Acetylation of aminocodeine by the method of Vongerichten gave a base that crystallized from 60% alcohol in lustrous rectangular plates of melting point 112–115° (Vongerichten described needles, m.p. 120°, anhydrous). In alcohol, 1-acetylamino-6-acetylcodeine showed $[\alpha]_D^{26}$ −220.3°, −220.8° ($c = 1.16, 1.02$). Analysis of the same compound, obtained from the Beckmann rearrangement described below, indicated that it was the trihydrate.

1-Aceto-6-acetylcodeine, prepared according to the method of Knoll and Co., appeared to be solvated, since the purest samples sintered strongly at 125°. Drying at 100° in a vacuum resulted in a product having the previously observed melting point, 146–147°.

The preparation of the oxime of 1-aceto-6-acetylcodeine coincided with the description of Knorr, Hörlein, and Staubach (2), except that the oxime hydrochloride invariably began to separate as silky needles after a few hours, and the mixture became solid within 24 hours. The crystals (m.p. 240°, decomp.) were sucked dry and dissolved in water, and the oxime base was precipitated with sodium carbonate. From 10 g. of aceto-6-acetylcodeine, 10.2 g. of crude oxime was obtained.

Rearrangement of 1-aceto-6-acetylcodeineoxime. The action of concentrated sulfuric acid on the oxime gave only unidentifiable, non-basic material. Treatment with phosphorus pentachloride in boiling ether, petroleum ether, or benzene, gave either starting material, or tarry products, depending upon the solvent used.

One gram of the oxime was dissolved in 10 cc. of glacial acetic acid containing 2 cc. of acetic anhydride, and dry hydrogen chloride was bubbled in for two hours. After one and one-half hours standing, the solution was poured on ice, and sodium carbonate solution was added to alkalinity. The precipitate obtained weighed 1.05 g. after drying. It contained a trace of high-melting material (m.p. 210–230°, perhaps aminocodeine) that was removed by crystallization from 60% alcohol. The pure 1-acetylamino-6-acetylcodeine had the melting point 112–115° (with foaming) and gave no depression of melting point when mixed with the acetylation product from aminocodeine described above. In alcohol solution it showed $[\alpha]_D^{26}$ −214° ($c = 0.95$). The compound was a trihydrate, and lost its water, even in a high vacuum, only at the melting point.

Anal. Calc'd for $C_{22}H_{26}N_2O_5 + 3\ H_2O$: C, 58.4; H, 7.1; H_2O, 11.9.
Found: C, 58.5; H, 7.0; H_2O, 10.4.

Two grams of acetylaminoacetylcodeine obtained from the Beckmann rearrangement was heated with 3 *N* hydrochloric acid at 90° for 1.5 hours. The aminocodeine was isolated as in the preparation from nitrocodeine, and weighed 1.3 g. (93% yield). It melted (crude) at 223–226° and showed no depression in mixed melting point with the authentic sample. After sublimation in a high vacuum the hydrolysis product had $[\alpha]_D^{27}$ −181.1° (water, c = 0.81).

SUMMARY

Acetocodeine carries the acetyl group in the 1 position. This has been proved by Beckmann rearrangement of aceto-6-acetylcodeineoxime, and identification of the product as 1-acetylamino-6-acetylcodeine.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF COLUMBIA UNIVERSITY]

3,5-DIMETHYL-, 2-ETHYL-5-METHYL-, AND 3-ETHYL-5-METHYL- PHENANTHRENE. A CONTRIBUTION TO THE ABNORMAL SELENIUM DEHYDROGENATION OF STROPHANTHIDIN[1]

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In 1932 Jacobs and Fleck (1) subjected strophanthidin to dehydrogenation with selenium with the purpose in mind of establishing the long-suspected relationship between the cardiac aglycones and the sterols by the formation of the so-called Diels' hydrocarbon which has come to be recognized as methylcyclopentanophenanthrene. Instead of this substance they reported the isolation of a hydrocarbon, the analytical figures for which indicated a formula of $C_{16}H_{14}$. Later ultra-violet absorption spectra (2) and x-ray (3) studies on this hydrocarbon indicated a phenanthrene nucleus bearing a close resemblance to retene. In a reinvestigation of the dehydrogenation of strophanthidin with selenium, Elderfield and Jacobs (4) found that the nature of the products formed was closely dependent on the experimental procedure used. If the reaction was carried out with slow initial heating of the reaction-mixture and at a final temperature of 320–340° the Diels' hydrocarbon could be readily isolated. However, when the mixture was heated as rapidly as possible to 360° and then held at that temperature, they reported the isolation of two unknown hydrocarbons, both of which gave analytical figures corresponding to $C_{16}H_{14}$, in addition to a small amount of the Diels' hydrocarbon. The phenanthrene nature of the two new hydrocarbons was indicated by the formation of quinones and quinoxalines.

In view of the uncertainty concerning the identity of these two hydrocarbons and because of the apparent abnormality in the course of the dehydrogenation reaction induced by a comparatively slight change in the experimental conditions, it seemed desirable to re-open the question with the aim of definitely identifying the two hydrocarbons and thus to throw some light on the changes accompanying their formation. The latter end assumes increased importance because of the wide-spread use

[1] The material used in this paper forms part of a dissertation submitted by Ernest E. Lewis in partial fulfillment of the requirements for the degree of Doctor of Philosophy in the faculty of pure science of Columbia University.

of the selenium dehydrogenation method and the reliance placed on results gained thereby.

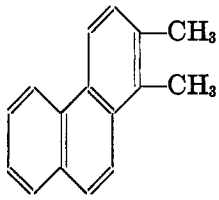
We have repeated the dehydrogenation of strophanthidin according to Elderfield and Jacobs (4) and have been able to isolate one hydrocarbon which we believe to be pure and which furnished analytical figures corresponding to $C_{16}H_{14}$, or possibly $C_{17}H_{16}$. Its melting point, 131–132°, does not correspond to that of either of the Elderfield and Jacobs hydrocarbons, which melted at 127° and 124–125° respectively. This may be taken to indicate that the former workers did not have at hand two pure hydrocarbons, but rather two samples of the same hydrocarbon with different amounts of contaminating impurities, a view which is strengthened by our failure to isolate any second hydrocarbon. A final decision on this point, however, must be reserved for the future.

Limited by the small amount of pure material available, we were unable to carry out structural studies on the hydrocarbon by oxidative degradation as originally intended, and we have therefore turned to the synthetic approach. The analytical results obtained with the hydrocarbon and its quinone favor the formula, $C_{16}H_{14}$, although analyses of its picrate and trinitrobenzene derivative favor $C_{17}H_{16}$. In either event, it is difficult to make a decision with certainty because of the small difference in analytical figures corresponding to the two formulas. At the start we were inclined to favor the $C_{16}H_{14}$ possibility, because of the known instability of the addition compounds, but evidence to be presented renders the $C_{17}H_{16}$ alternative more likely.

Proceeding on the plausible assumption that the hydrocarbon is an alkylated phenanthrene, only dimethyl- or ethyl- phenanthrenes need be considered in connection with the $C_{16}H_{14}$ formula. From a consideration of the structure of strophanthidin (I) the most logical points of attachment for alkyl groups in a phenanthrene appear to be the 1 and 2 positions (II). Alkyl residues in these positions could then result simply from a rupture of ring IV during dehydrogenation, whereas the appearance of alkyl groups in any other position of the phenanthrene nucleus would require more or less extensive rearrangements. The investigations of Haworth, Mavin, and Sheldrick (5) and of Mosettig and van de Kamp (6), which resulted in the synthesis of all the dimethyl-, ethyl-, and methylethyl- phenanthrenes with substituents in these positions, rather definitely eliminate them from further consideration. The strophanthidin hydrocarbon therefore must result from some rearrangement involving wandering of one or more alkyl groups.

As a point of departure in considering such possibilities we have postulated that the aldehyde group on C atom 10 of the strophanthidin molecule might undergo a shift to C atom 1 (the 5 position in the resulting

phenanthrene) in a manner similar to the shift taking place during the conversion of strophanthidin to trianhydrostrophanthidin (7). A methyl group in position 5 of phenanthrene would then result, barring further rearrangements as discussed later. The second alkyl group in the hydrocarbon, if this is $C_{16}H_{14}$, could then be (a) a methyl group in the 3 position, by wandering of the angular methyl group on C atom 13 of strophanthidin, and leading to the unknown 3,5-dimethylphenanthrene (III), or (b) a



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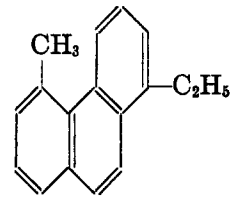

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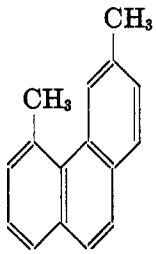

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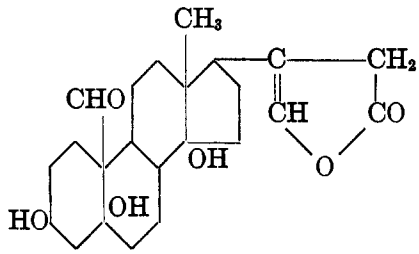

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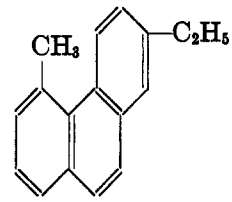

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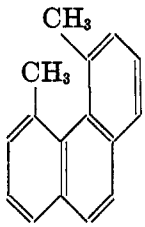

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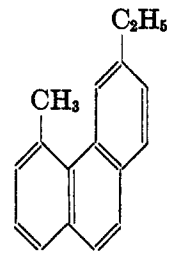

VII

methyl group in the 4 position of phenanthrene, arising from the more remote and less predictable migration of a methyl group, and leading to the unknown 4,5-dimethylphenanthrene (IV). All other dimethylphenanthrenes are known and are not identical with the strophanthidin hydrocarbon. Of the $C_{17}H_{16}$ possibilities with a methyl group in the 5 position, 1,2,5-trimethylphenanthrene and 1-, 2-, or 3- ethyl-5-methylphenanthrene (V, VI, VII) need be considered on the basis of the above hypothesis.

In this paper we report the synthesis of 3,5-dimethyl-, 2-ethyl-5-methyl, and 3-ethyl-5-methyl- phenanthrene. None of these hydrocarbons is identical with the strophanthidin hydrocarbon. The synthesis of 4,5-dimethylphenanthrene was attempted unsuccessfully, which confirms the idea first advanced by Haworth, and Sheldrick (5c) on the basis of studies of models that this substance is incapable of formation by ring closure reactions. The synthesis of 1-ethyl-5-methylphenanthrene was abandoned because of the excessive cost of the requisite intermediates. In all of these syntheses we have used the classical Pschorr method, since retention of the 5-methyl group would not be expected if a dehydrogenation method were used (5). The details of the various syntheses are apparent from the experimental part. In the attempted synthesis of 4,5-dimethylphenanthrene it was necessary to block the 1 position of the expected phenanthrene with a removable group in order to force the ring closure to take place as desired. For this purpose bromine was used. However, while no tangible product could be isolated from the ring closure reaction, the experience gained in this unsuccessful synthesis was valuable in that it showed the impossibility of ring closure by the Pschorr method leading to a 4,5-dialkylphenanthrene. In the subsequent synthesis of 2-ethyl-5-methylphenanthrene, therefore, it was unnecessary to block the 1 position since ring closure on that carbon atom is extremely unlikely. Both ethylmethylphenanthrenes were liquids and were characterized by their trinitrobenzene and trinitrotoluene addition-compounds.

From the non-identity of the strophanthidin hydrocarbon with any of the dimethylphenanthrenes and with any of the known ethylphenanthrenes (the 4-derivative is still unknown) we conclude that the former is probably $C_{17}H_{16}$. While 4-ethylphenanthrene cannot be rigidly excluded, the low melting points of the known ethylphenanthrenes (all below 70°) taken in conjunction with the unlikely migration of an alkyl group to this position on steric grounds render it very improbable. Of the $C_{17}H_{16}$ possibilities it seems probable that those bearing a methyl group in the 5 position, with the exception of 1,2,5-trimethylphenanthrene, may be eliminated. This leaves as possibilities 1-, 2-, or 3-propylphenanthrene, and alkylphenanthrenes analogous to those discussed above containing a methyl group in the 8 position as a result of a *trans*-migration of a C-5 methyl group in accordance with the experience of Haworth, Mavin, and Sheldrick (5). Of these, 1-propylphenanthrene (5) and 1,2,8-trimethylphenanthrene (8) are known to be non-identical with the strophanthidin hydrocarbon. The synthesis of the other possibilities is being continued.

We wish to express our appreciation to S. B. Penick and Company, of New York City, for the generous gift of the strophanthus seeds from which the strophanthidin used in this work was prepared.

EXPERIMENTAL

All melting points are corrected for stem exposure.

Dehydrogenation of strophanthidin. An intimate mixture of 300 g. of strophanthidin and 450 g. of selenium was heated very rapidly in an atmosphere of nitrogen to 340° and the melt was maintained at 340–360° for 32 hours. The cooled melt was ground and extracted with ether in a continuous extractor. The material extracted by the ether was distilled at 0.1 mm. pressure and 67.5 g. of distillate boiling from 100° to 300° was collected. This was redistilled through an 8-in. vacuum jacketed Vigreux column at 0.1 mm. and the following fractions were taken: below 130°, 7.1 g. of liquid; 130–170°, 35.2 g. of solid with a bluish fluorescence; 170–210°, 17.6 g. of solid; above 210°, 7.6 g. of solid.

The fraction boiling from 130–170° was dissolved in ether, ethereal picric acid was added, and the solvent was removed. The residue was thoroughly extracted with petroleum ether and the undissolved picrates were decomposed by shaking their ethereal solution with sodium carbonate solution. After removal of the ether, 9 g. of crystalline hydrocarbon mixture was obtained. After 90 recrystallizations from alcohol according to the triangle scheme, a fraction weighing 1.7 g. and melting constantly at 127–128° was obtained. An equal weight of 1,3,5-trinitrobenzene was added and the addition-compound was recrystallized from alcohol saturated with trinitrobenzene. After 25 recrystallizations, the addition compound formed long, yellow, matted needles which melted constantly at 168.5–170.5°. Elderfield and Jacobs (4) report a melting point of 151–153° for one of their hydrocarbon trinitrobenzene addition-compounds.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_6$: C, 63.7; H, 4.4.
Calc'd for $C_{16}H_{14}\cdot C_6H_3N_3O_6$: C, 63.0; H, 4.1.
Found: C, 63.6; H, 4.3.

The addition-compound was taken up in benzene and passed through a column of aluminum oxide (General Chemical Co., reagent grade) which retained the trinitrobenzene but permitted the hydrocarbon to pass through (9). The hydrocarbon obtained from the effluent of the column was recrystallized from alcohol and melted constantly at 131–132°. It weighed 1.0 g. Elderfield and Jacobs (4) report melting points of 124–125° and 127°, respectively, for the two hydrocarbons described by them.

Anal. Calc'd for $C_{17}H_{16}$: C, 92.7; H, 7.3.
Calc'd for $C_{16}H_{14}$: C, 93.2; H, 6.9.
Found: C, 93.0, 93.3, 93.3, 93.2, 93.2, Ave., 93.2; H, 7.1, 6.9, 7.0, 6.9, 6.9, Ave., 7.0.

The *picrate* of this hydrocarbon formed long, orange rectangular plates and melted constantly at 142–144° after recrystallization from alcoholic picric acid. Elderfield and Jacobs (4) report melting points of 126–127° and 140–141° for their two hydrocarbon picrates.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_7$: C, 60.7; H, 3.9; N, 9.7.
Calc'd for $C_{16}H_{14}\cdot C_6H_3N_3O_7$: C, 61.6; H, 4.3; N, 9.4.
Found: C, 61.5; H, 4.3; N, 9.5.

The *quinone* from the hydrocarbon formed brownish-red prisms from alcohol and melted at 207–208°. Elderfield and Jacobs (4) report melting points of 203–205° and 208–209° for their quinones.

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 61.6; H, 5.6.
Calc'd for $C_{16}H_{12}O_2$: C, 61.3; H, 5.1.
Found: C, 61.3; H, 5.4.

3,5-Dimethylphenanthrene

p-Toluylacetic acid was prepared by hydrolysis of *p*-xylyl cyanide (10) by the general method of Adams and Thal (11) in 45% yield. It boiled at 159° at 15 mm. and melted at 93–94°, the latter value agreeing with that of Strassmann (12).

α-(4'-Methylphenyl)-2-nitro-3-methylcinnamic acid. Thirty-seven and six-tenths grams (0.2 moles) of the potassium salt of *p*-toluylacetic acid (dried at 120°), 33 g. (0.2 moles) of carefully dried 2-nitro-*m*-tolualdehyde (13), and 204 g. (2 moles) of freshly distilled acetic anhydride were digested with vigorous stirring for 8 hours at 105–110°. The acetic anhydride was decomposed at 100° by careful addition of water and the reaction-mass was poured into 1 l. of cold 5% hydrochloric acid. After standing overnight, the solid acid was collected, washed with water, and recrystallized first from glacial acetic acid and then from alcohol. It melted at 250.5–251.5°. Yield: 38.4 g. or 65%.

Anal. Calc'd for $C_{17}H_{15}NO_4$: C, 68.7; H, 5.1; N. 4.7.
Found: C, 68.7; H, 5.3; N, 4.8.

α-(4'-Methylphenyl)-2-amino-3-methylcinnamic acid. Thirty-six grams of the above nitro acid was suspended in 500 cc. of warm dilute ammonia and the suspension was stirred into a boiling mixture of 240 g. of hydrated ferrous sulfate, 500 cc. of water, and 500 cc. of concd. ammonia. Boiling was continued for an hour and the mixtures were then allowed to stand overnight. The combined filtrate and washings from the iron hydroxide was acidified to Congo red with hydrochloric acid, and the amino acid was collected and recrystallized from 70% methanol. It melted at 176.5–177.5°. Yield: 27.2 g. or 84%.

Anal. Calc'd for $C_{17}H_{17}NO_2$: C, 76.4; H, 6.4; N, 5.2.
Found: C, 76.6; H, 6.6; N, 5.5.

3,5-Dimethyl-10-phenanthroic acid. Fifteen grams of the above amino acid was suspended in 150 cc. of 15% alcoholic hydrogen chloride and stirred for an hour at 0°. To the suspension 20 cc. of freshly distilled isoamyl nitrite was added and stirring was continued for another hour. The solution was then added to a suspension of 1 g. of copper powder in a solution of 50 g. of sodium hypophosphite in 50 cc. of water containing 2 drops of sulfuric acid (14). A violent evolution of nitrogen occurred and the phenanthroic acid separated. After stirring for 30 minutes with gentle heating, the solution was cooled and the acid was collected. After reprecipitation from its filtered solution in sodium hydroxide it was recrystallized with Norit from 80% methanol, from which it formed fine white needles melting at 216–217°. Yield: 10 g. or 71%.

Anal. Calc'd for $C_{17}H_{14}O_2$: C, 81.6; H, 5.6.
Found: C, 81.4; H, 5.7.

3,5-Dimethylphenanthrene. Five grams of the phenanthroic acid was dissolved in 30 cc. of quinoline and 0.5 g. of basic copper carbonate was added. The mixture was refluxed in an oil-bath at 240–260° for 1 hour, cooled, diluted with ether, and extracted with dilute hydrochloric acid until free from quinoline. The residue, after removal of the ether, was crystallized with Norit from methanol. The hydrocarbon formed white plates which melted at 53.5–54.5°. Yield: 2.6 g. or 63%.

Anal. Calc'd for $C_{16}H_{14}$: C, 93.2; H, 6.9.
Found: C, 93.0; H, 6.9.

The *picrate* formed orange needles from alcohol and melted at 139–139.5°.

Anal. Calc'd for $C_{16}H_{14} \cdot C_6H_3N_3O_7$: C, 60.7; H, 3.9; N, 9.7.
Found: C, 60.7; H, 4.0; N, 9.6.

The *styphnate* formed short, yellow-orange needles from alcoholic styphnic acid and melted at 124–125°.

Anal. Calc'd for $C_{16}H_{14} \cdot C_6H_3N_3O_8$: C, 58.7; H, 3.8; N, 9.3.
Found: C, 58.9; H, 4.1; N, 9.4.

3,5-Dimethylphenanthraquinone melted at 124.5–125.5° after recrystallization from "Skellysolve D."

Anal. Calc'd for $C_{16}H_{12}O_2$: C, 81.3; H, 5.1.
Found: C, 81.1; H, 5.3.

3,5-Dimethylphenanthrenequinoxaline formed pale yellow needles on crystallization from chloroform-alcohol and melted at 173–173.5°.

Anal. Calc'd for $C_{22}H_{16}N_2$: C, 85.7; H, 5.2; N, 9.1.
Found: C, 85.6; H, 5.3; N, 9.3.

2-Ethyl-5-methylphenanthrene

m-*Allylethylbenzene.* The Grignard reagent prepared from *m*-bromoethylbenzene (15) was condensed with allyl bromide according to the method of Hurd and Bollman (16) for the preparation of *o*-allyltoluene. *m*-Allylethylbenzene was obtained in 65% yield, and boiled at 88° at 18 mm.

Anal. Calc'd for $C_{11}H_{14}$: C, 90.3; H, 9.7.
Found: C, 90.3; H, 9.8.

m-*Ethylphenylacetic acid.* This was prepared by oxidation of the above allyl compound with cold, dilute aqueous potassium permanganate according to the general method of Hill and Short (17). The acid was obtained in 24% yield and melted at 62–63° after crystallization from ligroin. Mayer and English (18) gave a melting point of 62–64° for the acid prepared by hydrolysis of the nitrile. The above method seems preferable, despite the lower yield, because of the accessibility of the starting material.

α-(3'-Ethylphenyl)-2-nitro-3-methylcinnamic acid was prepared in 57% yield by condensation of *m*-ethylphenylacetic acid with 2-nitro-*m*-tolualdehyde as in the previous case. It formed white prisms from alcohol and melted at 144.5–145.5°.

Anal. Calc'd for $C_{18}H_{17}NO_4$: C, 69.4; H, 5.5; N, 4.5.
Found: C, 69.3; H, 5.5; N, 4.8.

α-(3'-Ethylphenyl)-2-amino-3-methylcinnamic acid was prepared from the nitro acid by reduction with ferrous hydroxide as before. It formed lemon-yellow, hexagonal prisms from 70% methanol and melted at 146.5–147.5°. Yield: 85%.

Anal. Calc'd for $C_{18}H_{19}NO_2$: C, 76.8; H, 6.8; N, 5.0.
Found: C, 77.0; H, 6.8; N, 5.1.

2-Ethyl-5-methyl-10-phenanthroic acid was prepared by ring closure of the above amino acid exactly as before. The acid formed white needles on crystallization first from acetic acid and then from methanol, and melted at 171.5–172.5°. Yield: 30%.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.8; H, 6.1.
Found: C, 81.5; H, 6.3.

2-Ethyl-5-methylphenanthrene. An intimate mixture of 2.4 g. of the above phenanthroic acid and 2.4 g. of copper powder was heated in a side-arm test tube at atmospheric pressure until the temperature reached 350° when the phenanthrene began to distill. The distillation was completed under reduced pressure, and 1 g., or 50%, of a light yellow oil which darkened on exposure to air was obtained. The oil was quite soluble in hot alcohol, methanol, acetic acid, and ligroin, but on cooling, the hydrocarbon appeared as a liquid which could not be crystallized. Since it could be purified only with difficulty, no analyses are given, but the hydrocarbon did give well-defined addition-compounds. No better success attended the use of other decarboxylation methods.

The *trinitrobenzene derivative* formed fine, lemon-yellow needles and melted at 111–112°.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_6$: C, 63.7; H, 4.4; N, 9.7.
Found: C, 63.5; H, 4.5; N, 9.8.

The addition-compound was decomposed by passing its solution in benzene over aluminum oxide. The phenanthrene was thus obtained as a light yellow oil which still resisted all attempts at crystallization. The *trinitrotoluene derivative* formed light yellow needles and melted at 49–50°.

Anal. Calc'd for $C_{17}H_{16}\cdot C_7H_5N_3O_6$: C, 64.4; H, 4.7; N, 9.4.
Found: C, 64.6; H, 4.9; N, 9.6.

The *picrate* proved to be unstable. Although it melted constantly at 101–102°, analyses indicated some decomposition.

Anal. Calc'd for $C_{17}H_{16}\cdot C_6H_3N_3O_7$: C, 61.5; H, 4.3.
Found: C, 62.6; H, 4.4.

Attempts to prepare the quinone and quinoxaline from the phenanthrene failed to yield any crystalline substances.

3-Ethyl-5-methylphenanthrene

p-*Bromoethylbenzene* was prepared by bromination of ethylbenzene in the cold according to Schramm (19). The crude product was washed with concd. sulfuric acid in order to remove a small amount of the more easily sulfonated ortho isomer. The para derivative boiled at 86–88° at 15 mm. Schramm (19) reports 202–204° at 760 mm.

p-*Allylethylbenzene*, boiling at 94–95° at 23 mm. (yield: 63%), *Anal.* Found: C, 90.3; H, 9.9, and p-*ethylphenylacetic acid*, melting at 88–89° from petroleum ether (yield: 27%), were prepared like the meta derivatives. Stamatoff and Bogert (20) report the latter acid, prepared *via* the chloromethylation of ethyl benzene, as melting at 88.5–89.5°.

Likewise, *α-(4'-ethylphenyl)-2-nitro-3-methylcinnamic acid*, melting at 182.5–184.5° (yield: 50%), *Anal.* Found: C, 69.2; H, 5.5; N, 4.7, *α-(4'-ethylphenyl)-2-amino-3-methylcinnamic acid*, melting at 167–168° (yield: 77%), *Anal.* Found: C, 76.6; H, 7.1; N, 5.1, and *3-ethyl-5-methyl-10-phenanthroic acid*, melting at 186–187° (yield: 57.5%), *Anal.* Found: C, 82.0; H, 6.2, were prepared exactly as in the preceding example.

3-Ethyl-5-methylphenanthrene. Decarboxylation of the above phenanthroic acid resulted in the formation of an oil in 42% yield, the properties of which paralleled those of 2-ethyl-5-methylphenanthrene. The *trinitrobenzene derivative* melted at 124–125°, *Anal.* Found: C, 63.9; H, 4.5; N, 9.8, and the *trinitrotoluene derivative* melted at 74–76°, *Anal.* Found: C, 64.2; H, 4.8; N, 9.6. The *picrate* melted constantly at 111°, but again analysis indicated some decomposition; *Anal.* Found: C, 62.5; H, 4.6. Attempts to prepare a crystalline quinone and quinoxaline were likewise unsuccessful.

Attempted preparation of 4,5-dimethylphenanthrene

Chloromethyl-p-*bromotoluene.* The mixture of 2- and 3- chloromethyl-*p*-bromotoluene was prepared according to Fieser and Seligman (21). A 54% yield of material boiling at 128° and 12 mm. was obtained.

Cyanomethyl-p-*bromotoluene* was prepared in the usual manner by treatment of the chloro derivative with sodium cyanide. A partial separation of the isomers could be effected by fractional distillation, the 3-isomer boiling at 150–154° and the

2-isomer boiling at 161–165° at 12 mm. However, no attempt at complete separation was made at this point.

2-Bromo-5-methylphenylacetic acid. The various cyanide fractions were hydrolyzed as usual and the resulting acids were fractionally crystallized from alcohol. The identity of the isomeric phenylacetic acids was established by oxidation to known phthalic acids with alkaline permanganate. 2-Bromo-5-methylphenylacetic acid melted at 122–123° and yielded on oxidation 4-bromoisophthalic acid which melted at 300° with decomposition. Claus (22) reports an uncorrected melting point of 287° for the latter acid. Willgerodt (23) gives 82° as the melting point for 2-bromo-5-methylphenylacetic acid obtained by rearrangement of the corresponding acetyl derivative by means of ammonium polysulfide in sealed tubes, followed by hydrolysis of the resulting acid amide mixture. He, however, offers no proof of structure for his acid, nor does he give analytical figures. Our acid gave the following:

Anal. Calc'd for $C_9H_9BrO_2$: C, 47.2; H, 4.0.
Found: C, 47.4; H, 4.0.

3-Bromo-6-methylphenylacetic acid melted at 93.5–94.5°, and yielded on oxidation 4-bromophthalic acid melting at 166°, which agrees with the melting point reported by Fries and Hübner (24) for the latter.

Anal. Found: C, 47.2; H, 4.1.

α-(2'-Bromo-5'-methylphenyl)-2-nitro-3-methylcinnamic acid melting at 190–191° from 70% methanol (yield: 67%),

Anal. Calc'd for $C_{17}H_{14}BrNO_4$: C, 54.3; H, 3.8; N, 3.7,
Found: C, 54.3; H, 3.8; N, 4.0,

and *α-(2'-bromo-5'-methylphenyl)-2-amino-3-methylcinnamic acid* melting at 214–215° from 50% alcohol (yield: 85%),

Anal. Calc'd for $C_{17}H_{16}BrNO_2$: C, 59.0; H, 4.7; N, 4.1,
Found: C, 59.2; H, 4.8; N, 4.3,

were prepared as in the preceding cases.

Attempted ring closure to 1-bromo-4,5-dimethyl-10-phenanthroic acid. Ring closure of the above amino acid was tried using a variety of procedures involving changes in the method of diazotization, copper treatment, solvent, and temperature. In all cases a gummy product was obtained from which no pure material could be isolated. An attempted chromatographic purification through a column of aluminum oxide resulted in the formation of eight more or less well-defined rings, elution of which gave no tangible pure products. Likewise, treatment of the crude product of the reaction with diazomethane and benzoyl chloride failed to yield any pure derivative of a phenol. Attempted decarboxylation of the crude product, both by the quinoline and copper powder methods, as well as attempted oxidation of the decarboxylated material to a quinone, also led to no tangible products.

The micro-analyses here reported were performed by Mr. Saul Gottlieb of these laboratories.

SUMMARY

1. The abnormal dehydrogenation of strophanthidin with selenium has been reinvestigated and one apparently pure hydrocarbon (other than the Diels' hydrocarbon) has been isolated. The empirical formula corresponds to $C_{16}H_{14}$ or $C_{17}H_{16}$, of which we favor the latter.

2. 3,5-Dimethyl-, 2-ethyl-5-methyl-, and 3-ethyl-5-methyl- phenanthrene have been synthesized and shown to be not identical with the strophanthidin hydrocarbon.

3. The impossibility of the formation of 4,5-dialkylphenanthrenes by ring closure reactions has been confirmed for 4,5-dimethylphenanthrene.

NEW YORK, N. Y.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

MIGRATION OF THE CARBAMYL RADICAL IN 2-AMINOPHENOL DERIVATIVES

L. CHAS. RAIFORD AND KLIEM ALEXANDER

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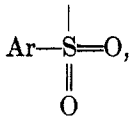
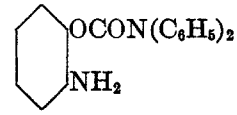
When two different acyl radicals derived from carboxylic acids are introduced into an *ortho*-aminophenol, only one mixed diacyl derivative can generally be obtained, regardless of the order of introduction of these groups; and in this product the heavier and more acidic acyl is usually found attached to nitrogen. To account for these facts, migration of acyl from nitrogen to oxygen must occur in one of these reactions (1). This rearrangement takes place most frequently during acylation, but in some instances it occurs when the diacyl derivative is partially hydrolyzed (2).

If one of the acyls is derived from a sulfonic acid and has the composition



Ar—S(=O)=O, isomeric mixed diacyl derivatives are obtained when the groups are introduced in different orders and no rearrangement takes place (3), which shows that the migration in question depends, to some extent, on the composition and structure of the acyls. On this account, it was of much interest to test acylating agents other than those previously studied. In this report, results obtained by the use of certain derivatives of carbamic acid will be given.

Herzog (4) noted that diphenylcarbamyl chloride reacts readily with phenols to give high yields of solid derivatives that crystallize well, and hence is a suitable reagent for use in identification of such hydroxy compounds. Of particular interest is his statement concerning the behavior of this reagent with 2-aminophenol. Here he isolated a product that melted at 177°, and for which complete analysis indicated that only one position had been acylated. Without further proof he assumed that acyl was attached to oxygen and that the product had the structure shown below.



Previous to this time, Lellmann and Bonhöffer (5) reduced the 2-nitrophenyl ester of diphenylcarbamic acid, m.p., 112–114°, and obtained a compound that melted at 189–191°, which gave satisfactory analysis for carbon and hydrogen, and to which they, also, assigned the structure given above. But the previous work of Böttcher (6) and the later work of Ransom (7) proved that reduction of 2-nitrophenyl benzoate and 2-nitrophenyl ethyl carbonate gave phenolic compounds that were identified as 2-benzoylaminophenol and 2-hydroxyphenylurethane, respectively. This clearly indicates that the 2-aminophenyl-O-esters, which are the first reduction-products in such cases, are not stable, and that they readily rearrange to the isomeric N-acyl derivatives.[1] It is also interesting to note that the latter may suffer further change. Moore (8), working in this laboratory, found that reduction of the methyl, ethyl, *n*-propyl, and *n*-butyl 2-nitro-4-bromo-5-methylphenyl carbonates gave the 2-amino compounds which, under the usual laboratory conditions, promptly rearranged to the isomeric 2-hydroxyphenylurethanes as had previously

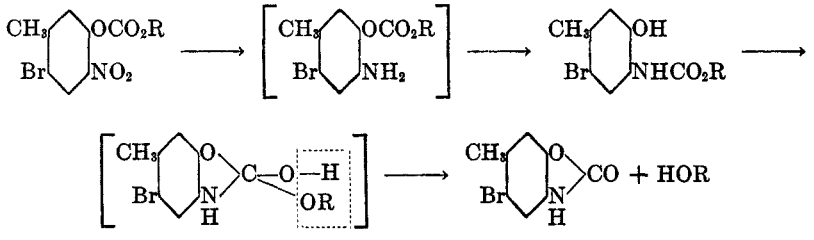
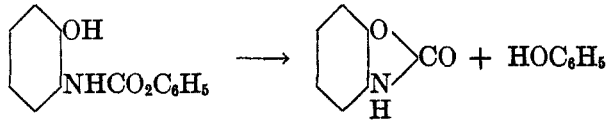


FIGURE I

been shown by Ransom for 2-nitrophenyl ethyl carbonate, and by Stieglitz and Upson (9) for the methyl ester. In addition, Moore found that under similar conditions portions of the urethanes containing the ethyl, propyl, and butyl radicals lost the elements of the related alcohols and suffered ring closure to give the corresponding benzoxazolone as shown in Figure I. The latter change is of the same type as that observed by Raiford and Inman (10), who found that when the N-carboaryloxy derivatives of *o*-aminophenol and its substitution-products are dissolved in caustic alkali solution they are converted into benzoxazolone, and a phenol is liberated. In some instances the change takes place slowly when the product is stored at room temperature (11), as indicated.



[1] Ransom (7, p. 43) found that under special conditions he was able to isolate 2-aminophenyl ethyl carbonate and to observe its rearrangement directly.

As a proof of the structure of their product, Lellmann and Bonhöffer state that when it was heated eight to ten hours at 190° it decomposed into benzoxazolone and diphenylamine. But the observations cited above show that benzoxazolone ring formation may easily occur when acyl is bound to nitrogen and the hydroxyl group is exposed, consequently the interpretations of Herzog, and of Lellmann and Bönhoffer are questioned.

To test this point, the work of the last named authors was repeated. 2-Nitrophenol was converted into the diphenylcarbamic ester, and the product was found to have the melting point 113–114°, and other physical properties reported by them. Reduction of this ester gave a compound that likewise melted at the point recorded for their supposed amino com-

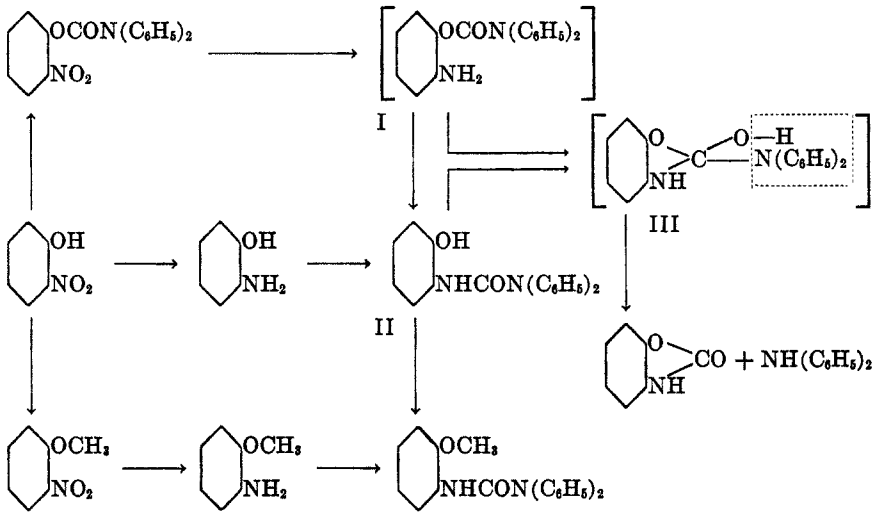


FIGURE II

pound, but whose chemical behavior was not in agreement with the structure they assigned. The substance was soluble in cold dilute solution of caustic alkali, and from this solution acids precipitated it in unchanged form, which indicates a phenol. The presence of the hydroxyl group was further indicated by the fact that the product in question was obtained by the direct action of diphenylcarbamyl chloride on 2-aminophenol, and also by the fact that treatment of it with diazomethane gave the same methyl ether as that obtained by interaction of *o*-anisidine with diphenylcarbamyl chloride, all of which supports structure II rather than I (see Figure II). In addition, the closure of the benzoxazolone ring may have taken place through the intermediate III, but it is probable that the latter could have been formed quite as readily from II as from I. Finally, when the compound melting at 190–191° was refluxed with 2 *N* alcoholic potash,

it was converted into benzoxazolone and diphenylamine, both of which were identified by mixed melting point determinations with authentic samples. Diphenylamine was obtained in nearly quantitative amount. Analogous results were obtained by the use of halogen substitution-products of 2-nitrophenol.

Diacyl derivatives containing the diphenylcarbamyl radical. In view of the facts stated above, it was of much interest to test the behavior of the diphenylcarbamyl radical in the formation of mixed diacyl derivatives of *o*-aminophenol. It was found that when a warm 1,4-dioxane solution of diphenylcarbamyl chloride was added to a warm solution of 2-acetylaminophenol (III, Figure III) in a mixture of pyridine and dioxane, a product (IV) was obtained that contained both the expected acyl radicals.

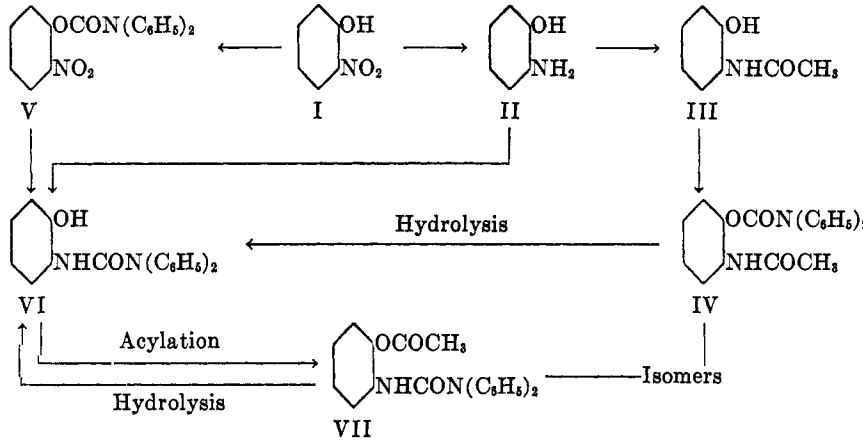


FIGURE III

Hydrolysis of this compound with alcoholic potash caused the loss of acetyl and gave an almost quantitative yield of product (VI), which had previously been obtained by the reduction of 2-nitrophenyl diphenylcarbamate, and in this case was also prepared by the direct action of diphenylcarbamyl chloride on *o*-aminophenol. During the hydrolysis of (IV) the diphenylcarbamyl radical must have migrated from oxygen to nitrogen. These relations are shown in Figure III for one pair of acyls with *o*-aminophenol. Similar results were obtained when acetyl was replaced by benzoyl, and also when the 4-bromo substitution-product of 2-aminophenol was used as the free base.

As noted above, when the 2-nitrophenyl ester of diphenylcarbamic acid was reduced, the resulting amino compound rearranged at once to the isomeric carbamylaminophenol. This made it a matter of interest to test the behavior of an ester containing an acyl of somewhat different com-

position. Accordingly, 2-nitrophenyl methylphenylcarbamate, first obtained by Lellmann and Benz (12), was prepared. When this compound was reduced by hydrochloric acid solution of stannous chloride (13), as used by Raiford and Colbert with 3-nitro-4-hydroxydiphenyl, no solid separated as it did with the diphenylcarbamic ester. With the latter, reduction was followed by rearrangement, consequently this difference in behavior suggested that in the compound in question migration of acyl may not have occurred and that the product might contain an exposed amino group as indicated by the formula used by Lellmann and Benz, who offered no proof of structure. Repetition of the experiment with a larger quantity of starting material gave the same result.

The presence of an exposed amino radical was indicated by the behavior toward nitrous acid. One portion of the solution thus obtained evolved nitrogen when it was warmed, and a second was coupled with β-naphthol to give a deep red precipitate of azo dye. To test this view further the compound in question was converted into the 4-tolylsulfonyl derivative and the product formed was compared with that obtained when 2-aminophenyl 4-tolylsulfonate was treated with methylphenylcarbamyl chloride. It was found that the resulting compounds had different melting points and that they gave different products when hydrolyzed.[2]

The failure of 2-aminophenyl methylphenylcarbamate to rearrange immediately in the reaction-mixture in which it was formed made it a matter of much interest to study the action of the related acid chloride on an *ortho*-aminophenol. In this case it was found that treatment of 2-aminophenol with one molecular proportion of methylphenylcarbamyl chloride in the presence of dimethylaniline, heating the mixture nearly to the boiling point for a few moments on the steam-bath, and then allowing it to stand overnight, gave an 84% yield of a monoacylated compound.[3] This substance was soluble in caustic alkali solution and from this liquid it was precipitated unchanged by acids. It was identified as 2-methylphenylcarbamylaminophenol. When the acylation was carried out in

[2] It had previously been shown by Raiford and Shelton, and others whose work was cited by them (3), that when the N-sulfonyl and O-sulfonyl derivatives of *ortho*-aminophenol were converted into diacylated compounds by introduction of other acyl radicals, isomers were always obtained in the cases thus far examined. Likewise, when these products were hydrolyzed the sulfonyl radical was found on nitrogen in every case in which it had been attached there in the starting material, while in those instances where it had been bound to oxygen in the starting material it was lost by hydrolysis and the other acyl was found on nitrogen. No rearrangement took place either during acylation or hydrolysis.

[3] In a previous trial in which the reaction-mixture was heated for several hours over the steam-bath about 80% of the aminophenol was converted into benzoxazolone.

the presence of pyridine instead of dimethylaniline, a mixture of 2-methylphenylcarbamylaminophenol and 2-aminophenyl methylphenylcarbam-

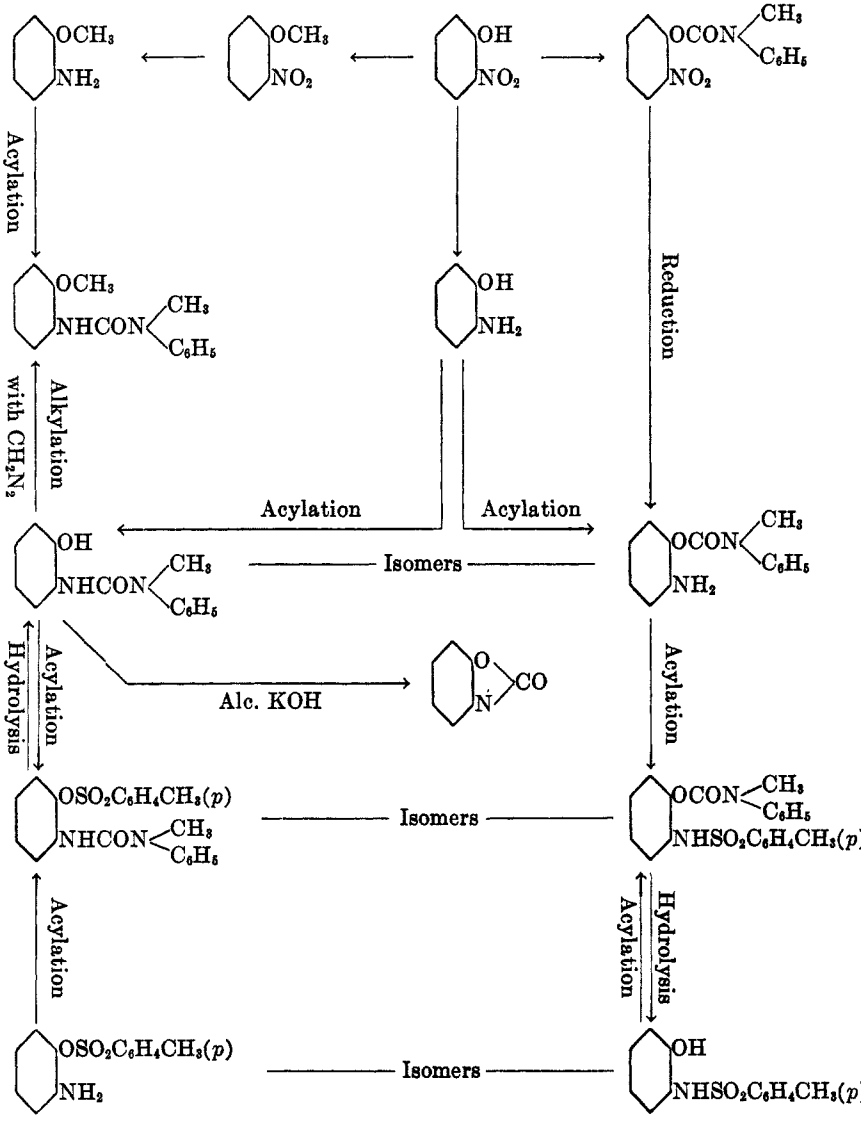


FIGURE IV

ate was obtained, in the proportions of 60% and 35%, respectively. Their relations are shown in Figure IV.

EXPERIMENTAL

The carbamyl chlorides. The diphenylcarbamyl chloride was Eastman's best grade and was used without further purification. Methylphenylcarbamyl chloride was first prepared by Michler and Zimmermann's (14) method, but a poor yield was obtained. The general procedure described by Shriner and Cox (15) was more satisfactory. Three hundred cubic centimeters of ethyl acetate was saturated with phosgene and into this warm liquid, while the gas bubbled through continuously, a solution of 153 g. of freshly distilled methylaniline in 600 cc. of ethyl acetate was introduced rather rapidly. Phosgene was allowed to run through for five minutes longer, the solvent was distilled until the contents of the flask showed a temperature of 140–150°, then the residue was allowed to cool and crystallize. Recrystallization of the pale brown material from ligroin (65–70°) gave large, nearly colorless rhombohedra that melted at 87–88°. The yield was 92%. The previous workers reported 88°, but recorded no yield.

2-Diphenylcarbamylaminophenol. Five grams of 2-nitrophenyl diphenylcarbamate[4] was reduced by stannous chloride as described by Raiford and Colbert (13), and the oil that separated when the reaction-mixture was diluted with several volumes of dilute hydrochloric acid stiffened into a plastic mass on standing. Repeated crystallization of this material from methanol gave nearly colorless needles that melted at 190–191°. This substance was found to be identical with the product obtained by the action of diphenylcarbamyl chloride on 2-aminophenol, and also with that produced by hydrolysis of 2-acetylaminophenyl diphenylcarbamate (see Figure III).

2-Diphenylcarbamylaminophenyl methyl ether. One gram of the above-described phenol was dissolved in 8 cc. of acetone, and an excess of diazomethane (16) dissolved in dry ether was added. The vessel was closed with a stopper bearing a capillary tube, it was held in an ice-bath for two and one-half hours, the solvent was evaporated, and the remaining solid was extracted with a small portion of ether to remove starting material. Crystallization of the residue from alcohol gave colorless plates that melted at 106–107° and that did not depress the melting point of the compound obtained by treatment of *o*-anisidine with diphenylcarbamyl chloride.

Anal. Calc'd for $C_{20}H_{18}N_2O_2$: N, 8.80. Found: N, 8.85.

2-Nitro-4-bromophenyl diphenylcarbamate. Ten and nine-tenths grams of the required nitrophenol was treated with diphenylcarbamyl chloride as previously noted. The yield was almost quantitative. The product was repeatedly crystallized from alcohol, from which it separated in nearly colorless needles that melted at 137–138°. Korczynski and Grzybowski (17), who previously prepared it, recorded no yield but reported 129–130° as the melting point. When exposed to bright light the product became deep purple in color.

Anal. Calc'd for $C_{19}H_{13}BrN_2O_4$: Br, 19.36. Found: Br, 19.30.

Reduction of the above compound was brought about by treatment of a hot 1,4-

[4] This was prepared in 95% yield from equimolecular proportions of *o*-nitrophenol and diphenylcarbamyl chloride by a modification of Fischer's method [*Ber.*, **53**, 1625 (1920)]. A dry chloroform solution of the acid chloride was added to a pyridine solution of the nitrophenol, the mixture was warmed on the steam-bath for a few minutes and allowed to stand for twenty-four hours. Chloroform was distilled and the residue was poured into dilute hydrochloric acid. Repeated crystallization of the product from alcohol gave nearly colorless needles that melted at 113–114°, and agreed in properties with the compound isolated by Lellmann and Bonhöffer (5).

dioxane solution of it with a hydrochloric acid solution of stannous chloride as indicated above. After the rearranged product, 2-diphenylcarbamylamino-4-bromophenol, had been removed, the purple filtrate was diluted with water until precipitation was complete. The solid obtained, which represented about one-third of the reduction-product, was highly colored and obviously impure. Crystallization from benzene, which involved considerable loss, gave fine, nearly colorless needles that melted at 216–218°, and which did not depress the melting point of an authentic sample of 4-bromobenzoxazolone, m.p. 215° (18).

2-Diphenylcarbamylamino-4-bromophenyl methyl ether. Three-tenths gram of the above N-acyl derivative was dissolved in a few cc. of chloroform in a test tube and treated with diazomethane. Recrystallization of the product from carbon tetrachloride gave brownish rhombohedra that melted at 155–156°. This compound did not depress the melting point of the product, m.p. 155–156°, especially prepared for this comparison by the action of diphenylcarbamyl chloride on 2-amino-4-bromophenyl methyl ether.

Anal. Calc'd for $C_{20}H_{17}BrN_2O_2$: Br, 20.15. Found: Br, 20.14.

The analytical data and other properties for a number of *o*-aminophenol derivatives containing the diphenylcarbamyl radical are given in Table I.

2-Nitrophenyl methylphenylcarbamate. A pyridine solution of 23.4 g. of 2-nitrophenol was treated with a chloroform solution of 30 g. of methylphenylcarbamyl chloride, and the reaction-mixture was worked up as previously noted. Crystallization of the product from alcohol gave slightly yellowish needles that melted at 111–112°. The yield of purified material was 95%. Lellmann and Benz (12), who first prepared this compound from the potassium salt of the nitrophenol, reported the melting point 110°, but recorded no yield. Reduction of this compound with a hydrochloric acid solution of stannous chloride gave 2-aminophenyl methylphenylcarbamate, m.p. 105–106°, which was identified as indicated above. The previous authors recorded 103° but gave no proof of structure.

Action of methylphenylcarbamyl chloride on 2-aminophenol. To a warm solution of 10.9 g. of 2-aminophenol and 25 cc. of dimethylaniline in 20 cc. of 1,4-dioxane was added 17 g. of the acid chloride in 90 cc. of dioxane, the mixture was warmed nearly to the boiling point for a few minutes, and then set aside. A viscous, oily phase separated. The mixture was shaken vigorously at frequent intervals for about two hours, and allowed to stand overnight. Considerable solid was formed in this way. The mixture was then poured into about 600 cc. of dilute hydrochloric acid, the whole was shaken well, and the solid collected. Crystallization from alcohol gave nearly colorless needles that melted at 171–172°, and which were identified as 2-methylphenylcarbamylaminophenol (Table II).

Methylphenylcarbamylaminophenyl methyl ether. One gram of the product just described, in acetone solution, was treated with an excess of ether solution of diazomethane. The product was dissolved in ether, the liquid was shaken with 5% solution of sodium hydroxide, then with water. Evaporation of ether from the remaining liquid gave nearly colorless transparent crystals that melted at 77–78°. They did not depress the melting point of the product, m.p. 77–78°, obtained by action of methylphenylcarbamyl chloride on *o*-anisidine.

Anal. Calc'd for $C_{15}H_{16}N_2O_2$: N, 10.93. Found: N, 10.77.

Acylation of 2-aminophenol with methylphenylcarbamylchloride in the presence of pyridine. Ten and nine-tenths grams of 2-aminophenol was dissolved by warming in 20 cc. of pyridine. Seventeen grams of the acid chloride was dissolved in about 30 cc. of pyridine, but very soon crystals of pyridine-acyl-halide complex began to separate and in a few minutes the mixture had set to a solid mass of crystals. These

TABLE I

DIACYL DERIVATIVES OF *ortho*-AMINOPHENOLS

(a) 2-Aminophenol; (b) 2-amino-4-bromophenol

POSITION OF ACYL	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
(a)									
N-acetyl-O-diphenylcarbamyl	95	Alcohol	Pale brown prisms	150–153[b]	$C_{21}H_{18}N_2O_3$			8.09	8.07
N-diphenylcarbamyl-O-acetyl	82	Alcohol	Nearly colorless granules	119–121	$C_{21}H_{18}N_2O_3$			8.09	8.20
N-diphenylcarbamyl-O-diphenylcarbamyl	60	Benzene-ligroin[c]	Colorless needles	184–185	$C_{32}H_{25}N_3O_3$			8.41	8.21
N-diphenylcarbamyl[d]	76	Methanol	Colorless needles	190–191	$C_{19}H_{16}N_2O_2$			9.21	9.09
N-benzoyl-O-diphenylcarbamyl	98	Alcohol	Colorless prisms	153–154	$C_{26}H_{20}N_2O_3$			6.86	7.07
N-diphenylcarbamyl-O-benzoyl	76	Chloroform and alcohol[e]	Colorless cubes	210–212	$C_{26}H_{20}N_2O_3$			6.86	6.87
(b)									
N-acetyl-O-diphenylcarbamyl	80	Benzene	Colorless needles	176–178	$C_{21}H_{17}BrN_2O_3$	18.82	18.75		

N-diphenylcarbamyl-O-acetyl	70	Alcohol	Colorless hexagonal plates	117–118	$C_{21}H_{17}BrN_2O_3$	18.82	18.90		
N-diphenylcarbamyl[h]	40	Methanol-ethanol[f]	Colorless needles	199[g]	$C_{19}H_{15}BrN_2O_2$	20.88	20.87		
N-diphenylcarbamyl-O-diphenylcarbamyl	64	Ethanol-butanol	Colorless needles	198[g]	$C_{32}H_{24}BrN_3O_3$	13.84	13.85		

[a] These values represent purified materials.

[b] Though this product softened at 145° and melted over a range of three degrees, analysis for nitrogen indicated that it was nearly pure.

[c] The hot saturated benzene solution was diluted with an equal volume of ligroin and allowed to cool.

[d] Monoacyl derivative; this product was also obtained by slowly adding a dioxane solution of diphenylcarbamyl chloride and dimethylaniline to a hot dioxane solution of 2-aminophenol with stirring and continued heating on a steam-bath. The product was proved to be identical with that obtained by reduction of 2-nitrophenyl diphenylcarbamate, previously prepared by Lellmann and Bonhöffer (5) and erroneously reported by them to be 2-aminophenyl diphenylcarbamate.

[e] Hot chloroform solution was slowly diluted under reflux with several volumes of alcohol.

[f] The purple-colored filtrate was diluted with water until no more solid separated, the mixture was stirred well, allowed to settle and the solid collected and dried. Crystallization from benzene gave nearly colorless needles that melted at 216–218°, and which did not depress the melting point of 4-bromobenzoxazolone, m.p., 215°, obtained by Raiford and Inman (18).

[g] A mixture of these showed a melting range of 169–180°.

[h] Monoacyl derivative.

TABLE II

DIACYL DERIVATIVES OF *o*-AMINOPHENOL CONTAINING THE METHYLPHENYLCARBAMYL RADICAL

POSITION OF ACYL	YIELD %[a]	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES			
						Sulfur		Nitrogen	
						Calc'd	Found	Calc'd	Found
N-(4-Tolylsulfonyl)-O-methylphenylcarbamyl[b]	89	Alcohol (75%)	Nearly colorless granules	125–126	$C_{21}H_{20}N_2O_4S$	8.08	8.22		
N-Methylphenylcarbamyl-O-(4-tolylsulfonyl)	80	Alcohol	Pale brown masses	111–112	$C_{21}H_{20}N_2O_4S$			7.07	7.07
2-Aminophenyl methylphenylcarbamate	41	Alcohol	Pale brown needles	105–106	$C_{14}H_{14}N_2O_2$			11.57	11.60
2-Methylphenylcarbamylaminophenol[d]	53	Alcohol	Nearly colorless needles	171–172[c]	$C_{14}H_{14}N_2O_2$			11.57	11.60

[a] These values refer to purified materials.

[b] Hydrolysis of this product with alcoholic potash gave an 88% yield of an alkali-soluble product that melted at 138–139°, and which did not depress the melting point of 2-(4-tolylsulfonylamino) phenol previously obtained by Bell (*J. Chem. Soc.*, **1930**, 1984) and specially prepared for this comparison.

[c] This value was obtained by rapid heating. Melting occurred at 150° in six minutes, and at 135° in thirty minutes.

[d] Monoacyl derivative.

were disintegrated with a rod, 20 cc. of dioxane was added, the resulting suspension was mixed with the aminophenol solution, the whole was warmed over the steam-bath until solution occurred, and it was then set aside for twenty-four hours. When the mixture was poured into 350 cc. of water containing an excess of hydrochloric acid a reddish solid separated. The yield was 60%. Crystallization of this product from alcohol[5] gave nearly colorless needles of m.p. 171–172°, which were identical with 2-methylphenylcarbamylaminophenol described above.

When the filtrate left after removal of the above product was made alkaline with sodium hydroxide, a brownish colored solid precipitated in a yield of 35%. Repeated crystallization of this from alcohol gave pale brown needles of m.p. 105–106°, which were identified as 2-aminophenyl methylphenylcarbamate, previously obtained by reduction of the corresponding nitro compound. Analytical data and other properties for a number of derivatives containing the methylphenylcarbamyl radical and prepared by standard methods are given in Table II.

SUMMARY

Reduction of 2-nitrophenyl diphenylcarbamate and its substitution-products caused migration of the diphenylcarbamyl radical from oxygen to nitrogen to give the corresponding 2-carbamylaminophenol. The structures of these compounds were established by preparing them by the direct action of the acid chloride on the required 2-aminophenols, and also by showing that the methyl ethers prepared by the action of diazomethane on the carbamylaminophenols were identical with the products obtained by treatment of the related anisidines with the required carbamyl chloride.

In the reduction of the related 2-nitrophenyl methylphenylcarbamate, the *o*-aminophenyl derivative was obtained. This product was also prepared by treatment of 2-aminophenol with methylphenylcarbamyl chloride, but in this reaction the isomeric 2-methylphenylcarbamylaminophenol was also formed.

Partial hydrolysis of a mixed diacyl derivative containing either of these carbamyl radicals attached to oxygen, and another acyl of composition R(Ph)CO bound to nitrogen, caused loss of the latter acyl and migration of the former to nitrogen. As in many other examples, the heavier acyl was ultimately found on nitrogen. When the second acyl had the composition $Ar—\overset{|}{\underset{\|}{S}}(=O)=O$ no migration was observed.

2-Methylphenylcarbamylaminophenol and 2-diphenylcarbamylaminophenol are readily decomposed by alcoholic potash to give benzoxazolone.

IOWA CITY, IA.

[5] In subsequent experiments it was found that this product may be more conveniently purified to nearly as high a degree by repeated treatment of its caustic alkali solution with an acid.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA AND THE NATIONAL INSTITUTE OF HEALTH]

STUDIES IN THE PHENANTHRENE SERIES. XXV. DIBENZO-[f,h] QUINOLINE AND 7-METHOXYDIBENZO-[f,h] QUINOLINE[1]

JOHN KRUEGER AND ERICH MOSETTIG

Received February 23, 1940

In continuation of previous investigations in the naphthoquinoline series (1), we describe in this communication the synthesis of dibenzo-[f,h]quinoline (I) and 7-hydroxydibenzo[f,h]quinoline (IV) and some of their derivatives. The quinoline bases I and IV were prepared in satisfactory yields by applying the Skraup synthesis to 9-aminophenanthrene[2] and to 3-methoxy-9-aminophenanthrene. The quinoline bases were reduced catalytically to the "py-tetrahydro" derivatives II and V. When we attempted to convert II into the methiodide of III by the previously (1b) successful procedure with potassium hydroxide and methyl iodide, only the tertiary base (III) was obtained. The fact that under these conditions no addition of methyl iodide to base III could be achieved, points to a sterically hindering effect for which the nearness of carbon atom 12 to the N-methyl group in position 1 may be responsible. Difficulties were also experienced in preparing the methiodide VIa, either from base V or base VI. In the latter reaction the yield of methiodide was low. The salt could be readily decomposed into methyl iodide and tertiary base. These observations being of qualitative nature only do not justify speculations on the influence of the hydroxyl or methoxyl group in position 7 on the quaternary salt formation.

EXPERIMENTAL

All melting points are corrected unless otherwise designated.

9-Aminophenanthrene. A mixture of 24 g. of pure 9-acetylphenanthrene[3], 19 g. of

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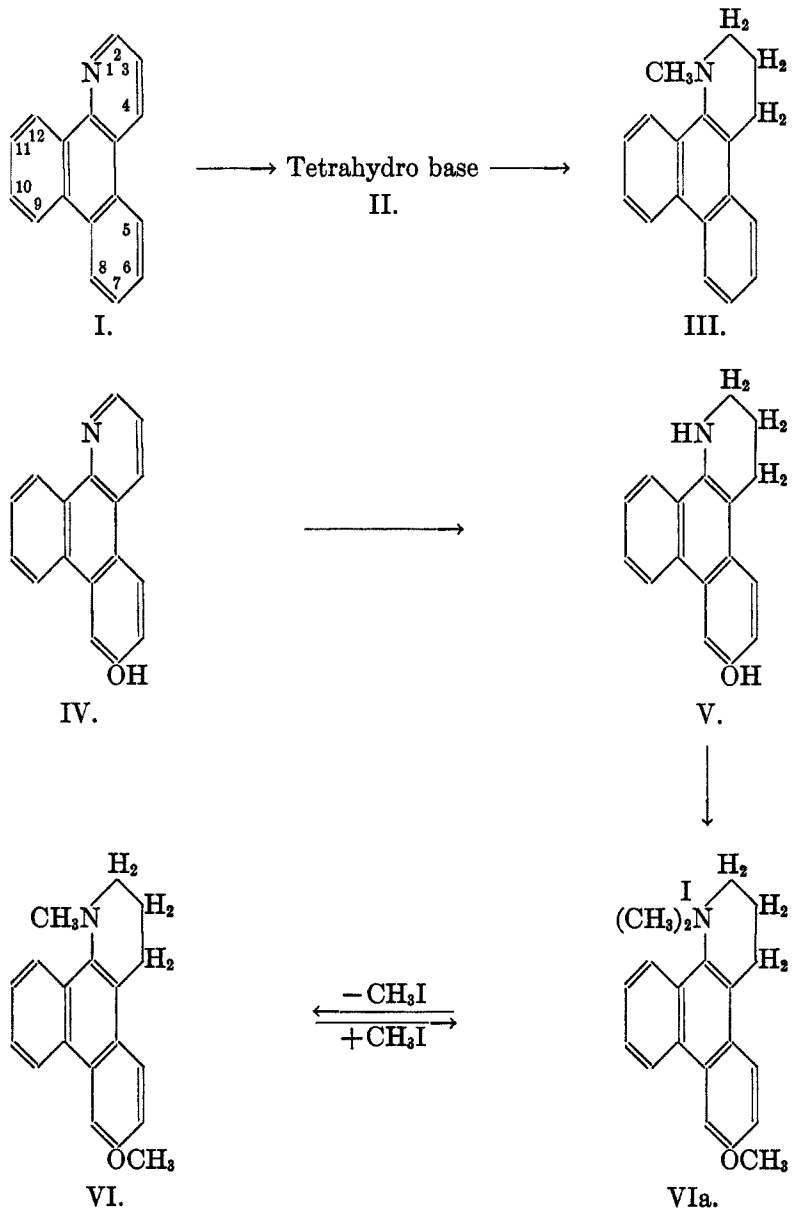
[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

[2] The synthesis of I ("phenanthroquinoline") has been reported previously by Herschmann (2).

[3] 9-Acetylphenanthrene was conveniently prepared by the method of Bachmann and Boatner [*J. Am. Chem. Soc.*, **58**, 2097 (1936)].

hydroxylamine hydrochloride, 34 cc. of pyridine, and 90 cc. of absolute ethanol was boiled for three and one-half hours. The solution was poured into water and a white



oil precipitated, which gradually became crystalline. The crystalline material weighed 26 g. and melted unsharply at 120–130°. It was dissolved in a mixture of 90

cc. of acetic acid and 60 cc. of acetic anhydride. Hydrogen chloride gas was passed rapidly through the mixture for thirty-five minutes. The flask was stoppered and allowed to stand overnight. The heavy crystalline precipitate was filtered off, and the compound was hydrolyzed by boiling in a mixture of 200 cc. of glacial acetic acid and 200 cc. of 18% hydrochloric acid. The amine hydrochloride was filtered off, suspended in hot water, and decomposed with ammonia. The base melted at 128–130°; yield 60% (calculated from the acetylphenanthrene).

Dibenzo[f,h]quinoline (I). Eighteen grams of the crude 9-aminophenanthrene, 8 cc. of nitrobenzene, and 45 cc. of glycerine were well mixed in an Erlenmeyer flask, and 18 cc. of C. P. sulfuric acid was added with thorough stirring. The mixture was heated at 145° for four hours, and was allowed to stand overnight. It was poured into water and extracted three times with ether. On addition of ammonia to the aqueous solution, a dark brown solid precipitated, which was filtered off and dried at 100°. It was sublimed at 150° in an oil-pump vacuum. The yellow base obtained crystallized from benzene in long, fine, felted yellow needles; 10 g., m.p. 167–169°. Herschmann (2) gives the m.p. 174°.

The *hydrochloride* crystallized from alcohol in white needles.

Anal. Calc'd for $C_{17}H_{12}ClN$: Cl, 13.35. Found: Cl, 13.63.

1,2,3,4-Tetrahydrodibenzo[f,h]quinoline (II). Six and one-half grams of dibenzo[f,h] quinoline in 200 cc. of glacial acetic acid absorbed the calculated amount (2 moles) of hydrogen (0.4 g. of platinum oxide as catalyst) within thirty hours. The catalyst was filtered off, and a concentrated aqueous sodium chloride solution was added to the filtrate, whereby the hydrochloride was precipitated. It was decomposed with ammonia, and the base was extracted into ether. The yield was 5.4 g. of the tetrahydro compound melting at 115–116°. The base crystallized from a benzene-petroleum ether mixture in pale yellow prisms, m.p. 117–118°.

Anal. Calc'd for $C_{17}H_{15}N$: C, 87.51; H, 6.49.
Found: C, 87.49; H, 6.45.

The *hydrochloride*, white, shiny leaflets, melted after recrystallization from aqueous hydrochloric acid at 245–247° (softening at 230°, uncorr., evac. tube).

Anal. Calc'd for $C_{17}H_{16}ClN$: Cl, 13.15. Found: Cl, 13.00.

1-Methyl-1,2,3,4-tetrahydrodibenzo[f,h]quinoline (III). To a mixture of 5.4 g. of the tetrahydroquinoline derivative and 8.5 cc. of methyl iodide was added a mixture of 9 g. of potassium hydroxide in 10 cc. of water and 50 cc. of acetone. No precipitation was observed when the mixture was allowed to stand at room temperature for three hours. On evaporation of the acetone, an oil precipitated. This was brought into solution again with acetone, 4 cc. of methyl iodide and 4.5 g. of potassium hydroxide in 5 cc. of water were added, and the mixture was heated in a Lintner bottle at 100° for one and one-half hours. The acetone was distilled off, and the oil that precipitated was extracted with ether. The residue left on evaporation of the ethereal solution became gradually crystalline and melted at 65–67° (5.2 g.). The base was most conveniently purified, practically without losses, by very slow distillation in an oil-pump vacuum at 110°. The distillate consisted of nearly colorless, broad, elongated prisms, which melted at 81–83°. The base is easily soluble in alcohol, ether, and petroleum ether.

Anal. Calc'd for $C_{18}H_{17}N$: C, 87.41; H, 6.93.
Found: C, 87.28; H, 6.97.

The *hydrochloride* was prepared in the usual manner with alcoholic hydrogen chloride. It crystallizes from an alcohol-ether mixture in balls of fine needles which gradually change to stout prisms. The melting point is rather indefinite. In a

vacuum the substance begins to melt at about 200° and gradually decomposes between 230° and 275°.

Anal. Calc'd for $C_{15}H_{18}ClN$: C, 76.16; H, 6.40.
Found: C, 76.71; H, 6.42.

No methiodide was formed when a mixture of base and methyl iodide in a small amount of acetone was allowed to stand for two days.

7-Hydroxydibenzo[f,h]quinoline (IV). The starting material for the synthesis of this compound, 3-hydroxy-9-aminophenanthrene, was prepared according to Burger and Mosettig (3), with the modification, however, that the saponification of the acetoxy compound and the reduction of 3-hydroxy-9-nitrophenanthrene were carried out in one procedure. A suspension of 18.5 g. of finely divided 3-acetoxy-9-nitrophenanthrene in 200 cc. of 50% sodium hydroxide was heated at 90° until a dark red solution was formed. A solution of 55 g. of sodium hydrosulfite was added, the temperature not being allowed to rise above 110°. After five minutes, 200 cc. of water was added, and heating at 90–95° was continued for ten minutes. The solution was diluted with water to a volume of two liters, and carbon dioxide was passed through. The heavy, yellowish precipitate was washed first with water containing some sodium hydrosulfite, and then successively with water and alcohol. The dry reduction-product weighed 13.5 g. and was used without further purification in the Skraup synthesis.

Thirteen and five-tenths grams of the above product, 15 cc. of nitrobenzene, 3.0 g. of ferrous sulfate, and 32 g. of glycerine were well mixed. Fifteen cubic centimeters of C. P. sulfuric acid was added with thorough stirring, and the mixture was heated to 145° until the reaction set in. Then the reaction was allowed to proceed without application of heat. After the reaction had subsided, the mixture was heated at 145° for thirty minutes. The dark reaction-mixture was diluted with water and extracted with ether. To the aqueous layer concentrated sodium chloride solution was added, which precipitated a brown hydrochloride. From this the base was liberated with ammonia as a gray crystalline mass. It was purified by sublimation in an oil-pump vacuum, and subsequent recrystallization from dioxane; pale yellow needles, m.p. 270–273° (evac. tube), yield 9 g. The base is sparingly soluble in alcohol, chloroform, acetone, and ether.

Anal. Calc'd for $C_{17}H_{11}NO$: C, 83.25; H, 4.51; N, 5.70.
Found: C, 83.47; H, 4.89; N, 6.06.

Hydrochloride. Two-tenths gram of the base was treated with hot dilute hydrochloric acid, some insoluble material was filtered off, and concentrated hydrochloric acid was added to the filtrate. The hydrochloride precipitated in tiny, bright yellow, felted needles (0.15 g.) that showed an indefinite melting point. The salt hydrolyzes strongly.

Anal. Calc'd for $C_{17}H_{12}ClNO$: Cl, 12.59. Found: Cl, 12.68.

7-Hydroxy-1,2,3,4-tetrahydrodibenzo[f,h]quinoline (V). Twelve grams of the above quinoline base and 1.5 g. of Chromite catalyst in 75 cc. of absolute ethanol were heated in an Adkins high-pressure hydrogenation apparatus to 150° in about one hour. Shaking at this temperature and at a pressure of 140 atm. was continued for forty minutes. From the reduction-mixture, a fraction of 8 g., melting at 228–230°, and a less pure fraction of 2.5 g., melting at 210–220°, were obtained. The tetrahydro base crystallized from absolute ethanol in pale green, hexagon-shaped crystals, which melted at 230–232°. The base may be purified also by sublimation at 180° in an oil-pump vacuum.

Anal. Calc'd for $C_{17}H_{15}NO$: C, 81.89; H, 6.07; N, 5.62.
Found: C, 81.97; H, 5.99; N, 5.73.

The *hydrochloride* was prepared in the usual manner with alcoholic hydrogen chloride. It melted, after recrystallization from aqueous hydrochloric acid, unsharply at 279–286° (uncorr.). The salt hydrolyzed readily.

Anal. Calc'd for $C_{17}H_{16}ClNO$: Cl, 12.41. Found: Cl, 12.55.

7-Methoxy-1-methyl-1,2,3,4-tetrahydrodibenzo[f,h]quinoline (VI). A mixture of 3.2 g. of base V, 8 g. of methyl iodide, 5.1 g. of potassium hydroxide, 5 cc. of water, and 30 cc. of acetone in a Lintner bottle was heated at 100° for one hour. The following day, 4 g. of methyl iodide and 2.5 g. of potassium hydroxide were added, and the mixture was heated again for one hour. The solvent was allowed to evaporate until the methiodide precipitated in brownish crystals. These were filtered off and decomposed in a water-pump vacuum at 150–170°. The tertiary base was then distilled over at 200°. The partly oily and partly crystalline distillate was dissolved in alcohol, from which the base crystallized on cooling in colorless rectangular crystals; m.p. 131.5–133°, yield 2.2 g.

Anal. Calc'd for $C_{19}H_{19}NO$: C, 82.26; H, 6.91; N, 5.05.
Found: C, 81.91; H, 6.65; N, 5.21.

The *hydrochloride* prepared in the usual manner melted at 204–206° with gas evolution. It hydrolyzes readily.

Anal. Calc'd for $C_{19}H_{20}ClNO$: Cl, 11.31. Found: Cl, 11.39.

The *methiodide* (VIa) was prepared by dissolving 0.2 g. of the N-methyltetrahydro base (VI) in a mixture of 3 cc. of acetone and 1 cc. of methyl iodide. The crystalline precipitate (0.1 g.) was collected after two days. The substance has an indefinite melting point; softening began at 145°, gas evolution took place at 175°, and the melt became clear at 200°. It resolidified on cooling and remelted at 128–130°. Apparently the methiodide is converted into the tertiary base by melting.

Anal. Calc'd for $C_{20}H_{22}INO$: I, 30.29. Found: I, 30.00.

SUMMARY

The preparation of dibenzo[f,h]quinoline and 7-methoxydibenzo-[f,h]quinoline and some of their derivatives is described.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. II. 6(α)-HYDROXY-PROGESTERONE[1]

MAXIMILIAN EHRENSTEIN AND THELMA O. STEVENS

Received April 1, 1940

As was pointed out in a previous paper (1), progesterone is the only naturally occurring compound with pronounced progestational activity. It manifests a slight "cortin" action, in that large doses are capable of maintaining the life of adrenalectomized animals (2). Desoxycorticosterone (21-hydroxyprogesterone), which was synthesized (3) previous to its isolation from the adrenal cortex (4), appears to be the simplest type of chemical compound having adrenal cortical activity. It also has a progestational effect about one-tenth that of progesterone (5). After the discovery of desoxycorticosterone, it was anticipated that this substance would alleviate equally well all the different physiological manifestations of adrenal insufficiency. More recent investigations have shown, however, that although desoxycorticosterone is highly satisfactory in maintaining the life of adrenalectomized animals, it is less effective than the other adrenal cortical hormones when, for example, the aggravation of diabetes (6) or the prevention of muscle fatigue (7) is measured. These other hormones are derivatives of desoxycorticosterone which are oxygenated at carbon atoms 11 or 17, or both.

In the light of these physiological facts it appears desirable to synthesize other compounds which are derived from progesterone or desoxycorticosterone and contain additional oxygen atoms attached to different carbon atoms of the sterol nucleus. It remains to be seen to what extent such compounds will manifest progestational or adrenal cortical action.

At least two different monohydroxyprogesterones with the hydroxyl group attached to the nucleus have been described. The 12-hydroxyprogesterone which was synthesized from desoxycholic acid (8) possesses only slight, if any, progestational action. No reference to adrenal cortical activity is given. Pfiffner (9) recently isolated from beef adrenal glands

[1] Aided by a grant from the Smith, Kline, and French Laboratories in Philadelphia.

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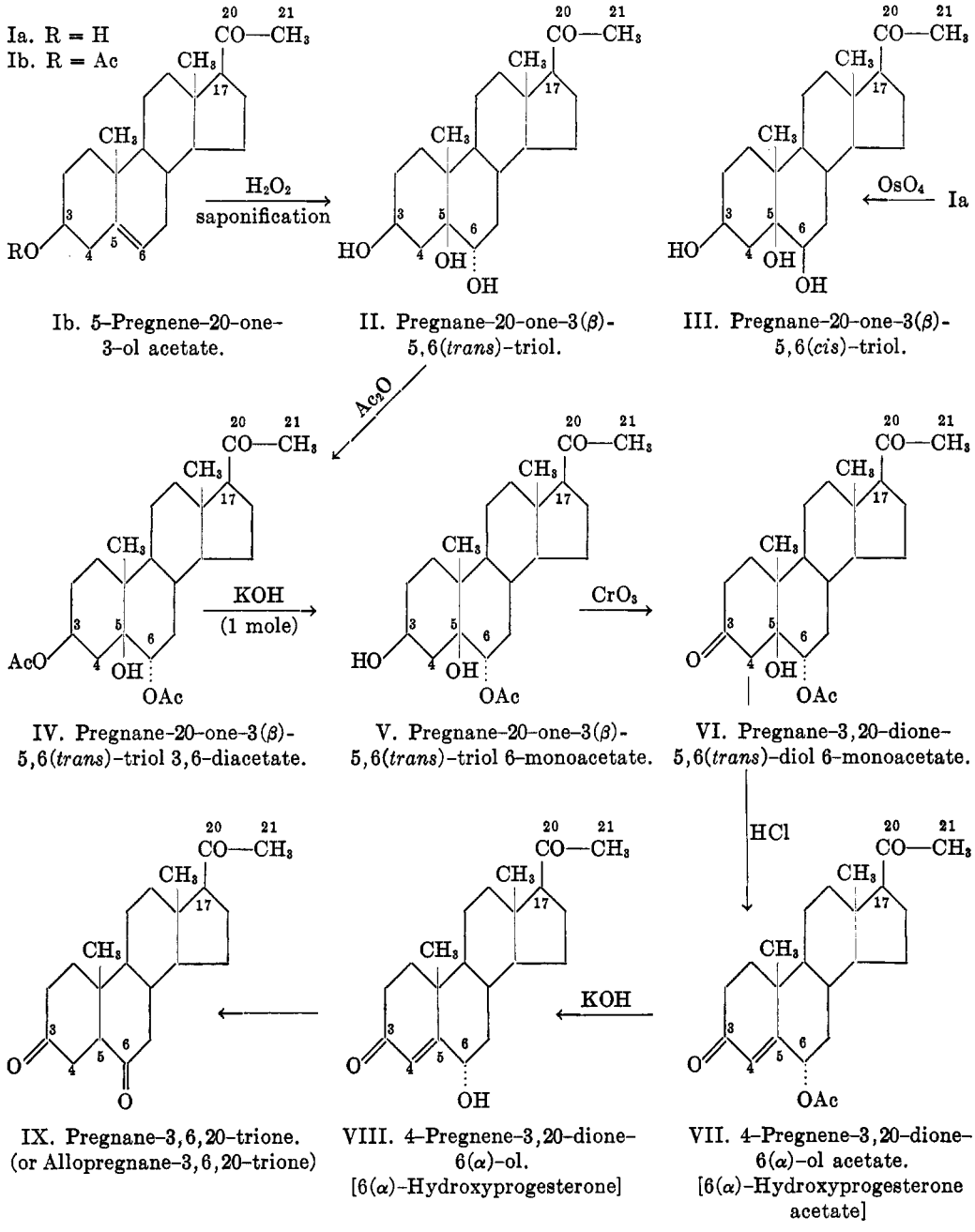
a 17-hydroxyprogesterone which probably possesses at carbon atom 17 the same configuration (β) as certain adrenal cortical hormones (17-hydroxycorticosterone, 17-hydroxy-11-dehydrocorticosterone, 17-hydroxy-11-desoxycorticosterone). It has, however, only slight, if any, "cortin" action. When it was assayed at a five milligram dose level with a modified Clauberg technique, no progestational activity was found. The attempts of other workers to obtain by synthetic methods the 17(α)-hydroxyprogesterone have thus far met with failure. Apparently this compound is unstable and undergoes rearrangement very readily (10). Two isomeric monohydroxyprogesterones were recently (11) described in which the hydroxyl group appears to be attached to carbon atom 2. They were obtained by the action of lead tetra-acetate upon progesterone. Physiological data are not available.

In a preceding paper (1) the preparation of 6-oxoprogesterone was described. It possessed no progestational activity. In the meantime, D. J. Ingle has found that this substance does not protect adrenalectomized rats against the manifestations of adrenal insufficiency when administered in doses as large as two milligrams per day.

The intermediates in the preparation of 6-oxoprogesterone were the triols II or III which were obtained by treating 5-pregnene-20-one-3-ol (I) with hydrogen peroxide or osmic acid respectively. Both triols[2] have identical stereochemical structures, presumably coprostane configurations, at carbon atom 5. They differ in configuration at carbon atom 6. The relative position of the hydroxyl groups at carbon atoms 5 and 6 is *"trans"* in compound II and *"cis"* in compound III. It ought to be possible to obtain from compounds II and III respectively two stereoisomeric 6-hydroxyprogesterones which differ only with regard to the configuration at carbon atom 6. Thus far we have been successful only in preparing a substance which is derived from compound II. By acetylation, the 3,6-diacetate was obtained (IV). Under special precautions the saponifica-

[2] Ellis and Petrow (*J. Chem. Soc.*, **1939**, 1078) recently investigated the stereochemical configuration of the cholestane-3,5,6-triols. The triol obtained by treating cholesterol with osmic acid was assigned the coprostane configuration, which is in agreement with the stereochemical considerations of our previous paper (1). The triol obtained by means of hydrogen peroxide was assigned the cholestane configuration. The fact that in our series the procedure with hydrogen peroxide apparently furnished the coprostane configuration is no contradiction. Probably the hydrogen peroxide treatment of cholesterol acetate and of 5-pregnene-20-one-3-ol acetate respectively furnished in each case a mixture of two *"trans"* forms, one possessing the coprostane configuration and the other the cholestane configuration. It appears that in the experiments with cholesterol the cholestane epimer was secured from this mixture, whereas in our experiments with pregnenonol the coprostane epimer showed the greater tendency to crystallize.



Ib. 5-Pregnene-20-one-3-ol acetate.

II. Pregnane-20-one-3(β)-5,6(*trans*)-triol.

III. Pregnane-20-one-3(β)-5,6(*cis*)-triol.

IV. Pregnane-20-one-3(β)-5,6(*trans*)-triol 3,6-diacetate.

V. Pregnane-20-one-3(β)-5,6(*trans*)-triol 6-monoacetate.

VI. Pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate.

IX. Pregnane-3,6,20-trione. (or Allopregnane-3,6,20-trione)

VIII. 4-Pregnene-3,20-dione-6(α)-ol. [6(α)-Hydroxyprogesterone]

VII. 4-Pregnene-3,20-dione-6(α)-ol acetate. [6(α)-Hydroxyprogesterone acetate]

FIGURE I

tion of one acetyl group only was carried out. We believe that the hydroxyl group was set free at carbon atom 3 rather than at carbon atom 6 for reasons which will be given later. Therefore the product of saponification has been assigned the structure of pregnane-20-one-3(β)-5,6(*trans*)-triol 6-monoacetate (V). Oxidation of this substance with chromium trioxide furnished pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (VI). Compound VI was dehydrated with the aid of dry hydrogen chloride in chloroform solution. Thereby, 4-pregnene-3,20-dione-6(α)-ol acetate [6(α)-hydroxyprogesterone acetate] (VII) was obtained. The

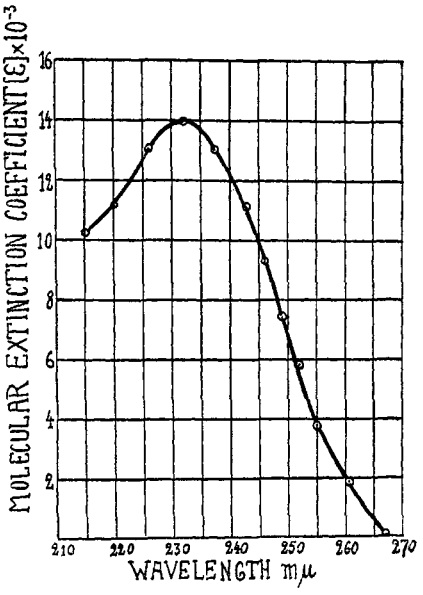


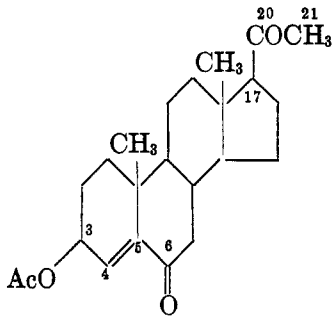
FIGURE II. Absorption curve of 6(α)-hydroxyprogesterone acetate (in absolute alcohol)

prefix α is arbitrarily used to indicate the configuration of the hydroxyl group at carbon atom 6. It would be interesting to transform hyodesoxycholic acid into a 6-hydroxyprogesterone and to establish whether the hydroxyl group at carbon atom 6 possesses the α or β configuration. The ultraviolet absorption spectrum[3] of compound VII (Figure II) is in agreement with the proposed structure of the acetate of 6(α)-hydroxyprogesterone. The wave length of the maximum (232 mμ) is somewhat short; it is, however, not inconsistent with α,β-unsaturated ketones of this type

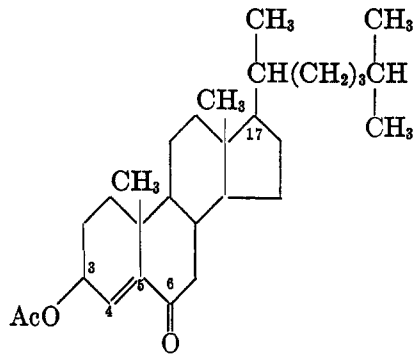
[3] We are indebted to Professor George R. Harrison and to Mr. Kent of the Department of Physics of the Massachusetts Institute of Technology for the determination of the ultraviolet absorption spectrum.

(12). The molecular extinction coefficient of about 14000 is in good agreement with the suggested structure.

If the partial saponification of the diacetate IV had taken place at carbon atom 6, the dehydration product of the saturated 3,20-diketone would have to be assigned the structure of 4-pregnene-6,20-dione-3(β)-ol acetate (X).



X. 4–Pregnene–6,20–dione–3(β)–ol acetate



XI. 4–Cholestene–6–one–3(β)–ol acetate

A compound with a corresponding structure (XI) is known in the cholestane series; it was described by Heilbron, Jones, and Spring (13). The ultraviolet absorption spectrum has the maximum at 236 mμ; the molecular extinction coefficient is as low as 6300. This latter feature appears to be noteworthy. Heilbron and his collaborators state explicitly that their compound (XI) gives a yellow coloration with tetranitromethane in chloroform solution, a reaction which is unusual for an α,β-unsaturated ketone. The fact that our compound gives no yellow color with tetranitromethane in chloroform solution is another support in favor of structure VII.

It may be mentioned that cholesterol can be transformed with the aid of hydrogen peroxide into a cholestane-3,5,6-triol. This compound probably possesses cholestane configuration. The 3,6-diacetate can be hydrolyzed to a 6-monoacetate (14). This affords another instance in which the ester group at carbon atom 3 is preferentially saponified. Although the diacetate of cholestane-3,5,6-triol and compound IV of this paper possess identical stereochemical configurations (β) at carbon atom 3, it must be borne in mind that the configurations at carbon atoms 5 and 6 are probably opposite. The two compounds are therefore stereochemically only partly analogous and the similar course of the partial saponification may only be incidental.

An attempt was made to saponify the acetate of 6(α)-hydroxyproges-

terone (VII) to the corresponding non-esterified compound (VIII). Even under mild experimental conditions the free 6(α)-hydroxyprogesterone (VIII) could not be secured. The molecule is apparently very unstable and rearranges to an isomer which is probably pregnane-3,6,20-trione (IX). This substance showed an absorption maximum at 251 mμ with a molecular extinction coefficient of about 1700 (in alcohol). There is little probability that these figures are due to the presence of some 6(α)-hydroxyprogesterone (VIII), because the acetate of the latter compound has its maximum at 232 mμ. We do not venture to decide whether the figures obtained can be attributed to pregnane-3,6,20-trione (IX) or still another isomer.

The substance obtained (IX) was accompanied by material melting over a wide range, which therefore represented a mixture. When this mixture was heated with alcoholic hydrochloric acid, it could be transformed into a homogeneous substance which proved to be identical with the above compound assumed to have structure IX. When IX[4] was treated with acetic anhydride and pyridine, it was recovered unchanged. This indicates also that it cannot be the free 6(α)-hydroxyprogesterone (VIII).

These relationships resemble those in the cholestane series, in which 4-cholestene-3-one-6-ol (14) and 4-cholestene-6-one-3-ol (13) respectively, are rearranged under the influence of alcoholic alkali or hydrochloric acid to cholestane-3,6-dione.

Experiments are under way to obtain the 6(β)-hydroxyprogesterone from pregnane-20-one-3(β)-5,6(*cis*)-triol (III). We have found that it is not feasible to subject the 3,6-diacetate, which is described in the experimental part of this paper, to the series of reactions outlined above. When partial saponification of the diacetate was attempted, it was found that the rate of hydrolysis was about the same at carbon atoms 3 and 6, so that some other means of transformation must be sought.

The acetate of 6(α)-hydroxyprogesterone (VII) was subjected to a preliminary physiological examination. We are indebted to Dr. A. W. Makepeace for testing this substance for progestational activity. Five milligrams produced a strong response (++++) in the Corner-Allen test, 3 milligrams was positive (++), and 1 milligram failed to cause a distinct uterine response. This means that the acetate of 6(α)-hydroxyproges-

[4] A very small amount of this compound was used for preparing an oxime. The resulting substance, which was not pure, melted between 165° and 170°.

Calc'd for $C_{21}H_{33}N_3O_3$ (Trioxime): N, 11.20
$C_{21}H_{32}N_2O_3$ (Dioxime): N, 7.78
Found: N, 10.03

The result of the analysis indicates that the substance must consist mainly of a trioxime, a finding which is in agreement with the above discussion.

terone is the first monohydroxyprogesterone which has been found to manifest a distinct progestational effect. At present only two other compounds with pronounced progestational activity are known, namely progesterone, which gives a positive response in the Corner-Allen test with 1 milligram, and pregneninonol (17-ethinyltestosterone, anhydrohydroxyprogesterone), which is about one-third as active[5]. Preliminary tests by D. J. Ingle indicate that adrenalectomized rats treated with 2 milligrams daily of the acetate of 6(α)-hydroxyprogesterone (VII) gain in body weight and perform more work than untreated animals. The number of tests is too small to permit a final conclusion.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa.). The readings are sufficiently near the true melting points so that no corrections have been made. All microanalyses were carried out by Mr. William Saschek, Columbia University, New York.

Pregnane-20-one-3(β)-5,6(trans)*-triol 3,6-diacetate (IV).* Pregnane-20-one-3(β)-5,6(*trans*)-triol was prepared according to the procedure given in the preceding paper (1). The average yield of three experiments was 30%. A solution of 1.94 g. of triol in 19.5 cc. of acetic anhydride was refluxed for 1.5 hours and was then poured into water. After the precipitated material had solidified to a crystalline mass, it was filtered, washed with water, and dried *in vacuo*. The crude diacetate (2.26 g.) was recrystallized from methanol. Several fractions, totalling 1.93 g., with melting points ranging between 215° and 219°, were secured. The average yield of constant-melting material of three experiments was 74%. Before analysis, the sample was repeatedly recrystallized from methanol; the melting point was 215.5–216.5°; beautiful macroscopic plates, $[\alpha]_D^{18}$ −2.0° (84.6 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{25}H_{38}O_6$: C, 69.08; H, 8.82.
Found: C, 68.68, 68.86; H, 8.68, 8.88.

Pregnane-20-one-3(β)-5,6(trans)*-triol 6-monoacetate (V).* To a solution of 1.95 g. of the above described diacetate (IV) in 136 cc. of absolute alcohol was added, over a period of two days, in 25 equal fractions, a total of 48.75 cc. of 0.1 *N* solution of potassium hydroxide in absolute alcohol (calc'd for 1 mole KOH: 44.85 cc.). Thereafter the solution was made neutral to litmus by the addition of dilute acetic acid. It was brought to a small volume *in vacuo*, and water was added to the warm concentrate until a turbidity appeared. On cooling, crystallization began almost at once. After filtering, 1.15 g. of material was secured; the melting point was 217–223°. On concentrating the mother liquor, two more crops, totalling 0.53 g., were secured; the melting points were variable, but above 200°. The fractions were dissolved separately in a little methanol; on adding ether, crystallization began at once. The total yield of material melting above 212° was 1.36 g. The average yield of fairly pure material of three experiments was 71%. A sample was again recrystallized for microanalysis. It was dissolved in a large volume of ether to which some petroleum ether was added. On concentrating to a small volume, a white crystalline precipitate appeared; platelets of various shapes melting at 222–226°.

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[5] A. Wettstein just (March 15, 1940; *Helv. Chim. Acta*, **23**, 388) described the preparation of 6-dehydroprogesterone, a compound which produced a corpus luteum hormone effect about half that of progesteron.

Anal. Calc'd for $C_{23}H_{36}O_5$: C, 70.36; H, 9.25.
Found: C, 70.20, 70.05; H, 9.35, 9.36.

Pregnane-3,20-dione-5,6(trans)*-diol 6-monoacetate* (*VI*). One hundred and sixty milligrams of fairly pure pregnane-20-one-3(*β*)-5,6(*trans*)-triol 6-monoacetate (V) was dissolved in 5.0 cc. of glacial acetic acid and the solution cooled to room temperature. Then 50 mg. of chromic oxide (calc'd for 1 atom O: 27.2 mg. CrO_3) dissolved in 2.0 cc. of 80% acetic acid was added and the mixture allowed to stand overnight. After the addition of 4 cc. of alcohol, the solution was concentrated almost to dryness *in vacuo*. To this residue water was added, giving a white precipitate, which was filtered and washed with water. The precipitate was suspended for several minutes in *N* sodium carbonate solution in order to remove any acid material present. It was again filtered, washed with water, and dried *in vacuo*; yield 131.2 mg. This crude material proved to be a mixture. It was dissolved in a rather large amount (about 15 cc.) of 95% alcohol on the water-bath and then concentrated to a somewhat smaller volume. On removing this solution from the water-bath, crystallization (glistening scales) began at once. The crystals were filtered the next day, washed and dried. The yield was 35.7 mg.; this material melted at 260–262° to a dark brown fluid. The conjecture that this substance might be impure pregnane-3,6,20-trione-5-ol [melting point 268.5–269.5°, see compound XIII of preceding paper (1)], proved to be correct. The mixed melting point of the two substances was about 264–267°. This would indicate that the starting material of this experiment contained some completely saponified pregnane-20-one-3(*β*)-5,6(*trans*)-triol (II). After the separation of the trione, the filtrate was concentrated to a very small volume. Crystallization began almost at once; two crops totalling 73.6 mg. were secured; the melting points were 214–216° and 214–215.5° respectively. The combined material was recrystallized from a small volume of 95% alcohol; scales and prisms, showing rosette arrangement, melting point 215–217.5°. The mixed melting point with the diacetate of pregnane-20-one-3(*β*)-5,6(*trans*)-triol (IV) was 175–180°; $[\alpha]_D^{17.5}$ +23.3° (18.8 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.78.
Found: C, 70.66, 70.52; H, 8.74, 7.82.

This experiment was repeated several times. A certain amount of almost pure pregnane-3,6,20-trione-5-ol was easily separated after the oxidation. The yield of the main product of the reaction could be increased to about 67%.

4-Pregnene-3,20-dione-6(*α*)*-ol acetate* ["*6*(*α*)*-hydroxyprogesterone acetate*"] (*VII*). A solution of 73.6 mg. of pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (VI) in 10 cc. of alcohol-free chloroform was cooled with ice. A moderate stream of dry hydrogen chloride was passed through it for three hours; the temperature was always kept below +4°. The solution was poured into an ice-cooled *N* sodium carbonate solution. After shaking this mixture in a separatory funnel, the chloroform phase was washed with water and dried with sodium sulfate overnight. After the removal of the solvent, a slightly yellow resin was obtained. Attempts to obtain crystals with the aid of several solvents failed. The material was eventually freed from all solvent and dried in a vacuum desiccator to constant weight; 72.1 mg., colorless glass.

The residue was subjected to chromatographic adsorption, for which it was dissolved in 5 cc. of benzene. To this solution 20 cc. of petroleum ether was added. A column[6] of 3 g. of aluminum oxide (aluminium oxide anhydrous, standardized for chromatographic adsorption acc. to Brockmann, E. Merck, Darmstadt) was

[6] Jena filter tube, with permanently fused-in glass filter disc, No. 15a G3.

prepared in the usual way with petroleum ether. The above solution was allowed to drip slowly through this column, and the adsorbed material was eluted with a series of appropriate solvent mixtures (see table). The solvents were then evaporated and the residues dried in a vacuum desiccator.

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	5 cc. benzene + 20 cc. petroleum ether	1.2	Gelatinous
2	2 cc. benzene + 8 cc. petroleum ether	0.7	Somewhat crystalline ?
3	3 cc. benzene + 7 cc. petroleum ether	1.2	Somewhat crystalline ?
4	4 cc. benzene + 6 cc. petroleum ether	2.1	Oily, trace of crystals
5	6 cc. benzene + 4 cc. petroleum ether	7.1	Oily, trace of crystals
6	8 cc. benzene + 2 cc. petroleum ether	15.3	Mainly oily, with few centers of crystallization
7	10 cc. benzene	14.0	Largely crystalline
8	10 cc. benzene	7.1	Mainly oily, several centers of crystallization
9	5 cc. benzene + 5 cc. ether	16.0	Largely crystalline
10	3 cc. benzene + 7 cc. ether	1.9	Largely crystalline
11	10 cc. ether	0.5	Trace of crystals
12	20 cc. ether	0.4	Trace of crystals
Total.....		67.5	

After some experimenting, it was found advisable to treat the crystalline residues with a mixture of ether (1 part) and petroleum ether (2 parts). Most of the resinous material went into solution, and the liquid was separated from the crystals by decantation.

YIELDS OF CRYSTALLINE MATERIAL AND MELTING POINTS

FRACTION NO.	YIELD, MG.	M.P., °C.
7	(a) 3.7; (b) 1.6	(a) 142.5–144.5°; (b) 143.5–145°
8	5.7	142–143.5°
9	7.4	144–145.5°

Because of the identical melting points all crystalline material was combined (18.4 mg. = 26.4% of the theoretical yield). It was dissolved in ether and petroleum ether was added until a turbidity appeared. The separation of clusters of crystals began almost at once. After standing overnight, the crystals (irregular-shaped stout plates) were filtered and washed with a mixture of ether and petroleum ether

(1:3). Yield 10.3 mg., melting point 145–146°. Further crops were secured from the mother liquor. $[\alpha]_D^{17.5}$ + 89.7° (20.0 mg. in 2.0 cc. of absolute alcohol).

Anal. Calc'd for $C_{23}H_{32}O_4$: C, 74.14; H, 8.66.
Found: 73.75; H, 8.48.

The ultraviolet absorption curve and the reaction with tetranitromethane have been noted in theoretical part. This dehydration experiment was successfully repeated several times.

Pregnane-3,6,20-trione (IX)? Eighty-three milligrams of 6(α)-hydroxyprogesterone acetate (VII) was dissolved in 10.2 cc. of 1% methanolic potassium hydroxide. This solution was allowed to stand at room temperature for about 48 hours. Then 80 cc. of water was added, and the alkalinity was reduced by passing in carbon dioxide. The methanol was removed *in vacuo*, and a white precipitate appeared. The solution was thoroughly extracted with freshly distilled ether and the combined ether extracts were carefully washed with water. The solution was concentrated to a small volume, omitting the usual drying with sodium sulfate. On cooling, white crystals began to form. The crystallization was increased by allowing the solution to stand in the refrigerator for about one-half hour. The crystalline precipitate was separated by decantation and immediately recrystallized by dissolving in acetone and adding ether. Two crops of crystalline material (A), totalling 10.9 mg. and melting between 195° and 227° were secured; by recrystallization, the melting point could be raised to 222–228°. The original ether solution was brought to dryness; the residue was a yellow resin. Three more crops of crystals (B) totalling 27.2 mg. were secured by dissolving the resin in acetone and adding ether. The melting points of these three crops of crystals (B) were much lower than those of the fractions (A), extended over a wide range, and could not be raised by repeated recrystallizations. A part of this low-melting material (B) was dissolved in absolute alcohol to which a few drops of concentrated hydrochloric acid was added. This solution was refluxed for about 30 minutes. After working up, at least one-third of the treated material was found to have been converted into a substance melting as high as 224–227°, and giving no depression of melting point when mixed with the high-melting substance (A), (m.p. 222–228°, see above).

An attempt was made to acetylate the substance melting at 224–227°. It was dissolved in a mixture of equal parts of acetic anhydride and pyridine; this solution was heated on the water-bath for 5 hours. The product of the reaction consisted mainly of unchanged starting material.

The sample selected for microanalysis and for the determination of the ultraviolet absorption spectrum had the melting point 226.5–230°. The analysis showed an ash content of about 2%. The analytical figures are correspondingly corrected.

Anal. Calc'd for $C_{21}H_{30}O_3$: C, 76.31; H, 9.16.
Found: C, 76.19; H, 9.10.

Pregnane-20-one-3(β)-5,6(cis)-triol 3,6-diacetate. Pregnane-20-one-3(β)-5,6(*cis*)-triol was prepared according to the procedure described in the preceding paper (1). The yield of pure material was 53%. Two hundred milligrams of this substance was refluxed with 2.0 cc. of acetic anhydride for 1.5 hours. When the solution approached room temperature, crystals began to separate. The acetic anhydride was decomposed by the addition of much water. The following day the crystalline precipitate was filtered, washed with water and dried. Yield, 215 mg. of crystals melting at 248–251°. This substance was recrystallized from 95% alcohol, from which it separated in scales melting at 251.5–252°; $[\alpha]_D^{17.5}$ + 56.6° (20.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{25}H_{38}O_6$: C, 69.08, H, 8.82.
Found: C, 68.93, 68.71; H, 8.76, 8.90.

SUMMARY

1. Pregnane-20-one-3(β)-5,6(*trans*)-triol (II) was converted into its 3,6-diacetate (IV). This substance was partially saponified to pregnane-20-one-3(β)-5,6(*trans*)-triol 6-monoacetate (V) which was then oxidized to pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate (VI). The latter compound was dehydrated to 4-pregnene-3,20-dione-6(α)-ol acetate [6(α)-hydroxyprogesterone acetate] (VII). Saponification of this substance did not yield the free 6(α)-hydroxyprogesterone (VIII), but an isomer to which must probably be assigned the structure of pregnane-3,6,20-trione (IX).

2. Pregnane-20-one-3(β)-5,6(*cis*)-triol (III) was converted into its 3,6-diacetate.

3. The acetate of 6(α)-hydroxyprogesterone (VII) manifests distinct progestational activity, and possibly slight adrenal cortical activity.

PHILADELPHIA, PA.

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[CONTRIBUTION FROM THE LABORATORIO DE QUÍMICA ORGÁNICA, FACULTAD DE CIENCIAS EXACTAS, F. Y N.]

CURTIUS DEGRADATION WITH DIPHENIC ACID HYDRAZIDES

RAFAEL LABRIOLA

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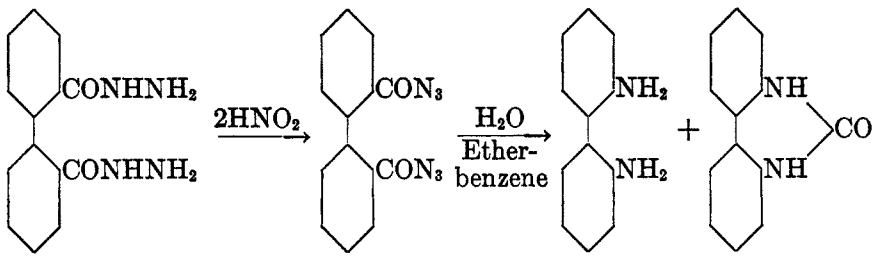
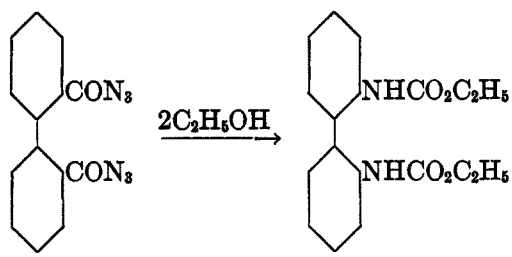
The first hydrazide obtained from diphenic acid, the dihydrazide, was prepared by Kalb and Gross (1). Later, Labriola and Catalano (2) prepared the monohydrazide and the secondary hydrazide and studied some of their reactions. The Curtius degradation of these hydrazides has now been examined and is described in this article.

When the dihydrazide (I) of diphenic acid is treated with nitrous acid, the unstable diazide precipitates. In ether-benzene solution, the diazide decomposes to form 2,2′-biphenyleneurea, the water necessary for the reaction coming from the incompletely dried ether.

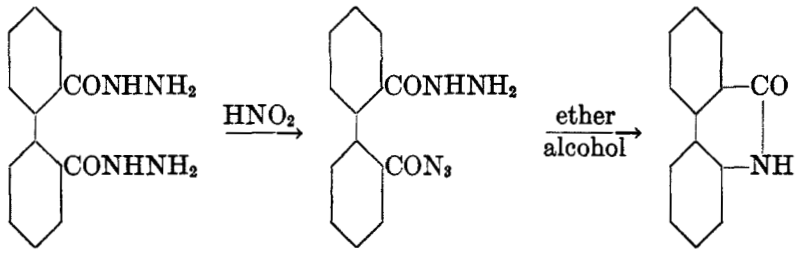


I

If the decomposition of the diazide is effected in an ether-alcohol solution, the urethane corresponding to the alcohol used is obtained. Alkaline hydrolysis of the urethanes gives 2,2′-diaminobiphenyl and 2,2′-biphenyleneurea.

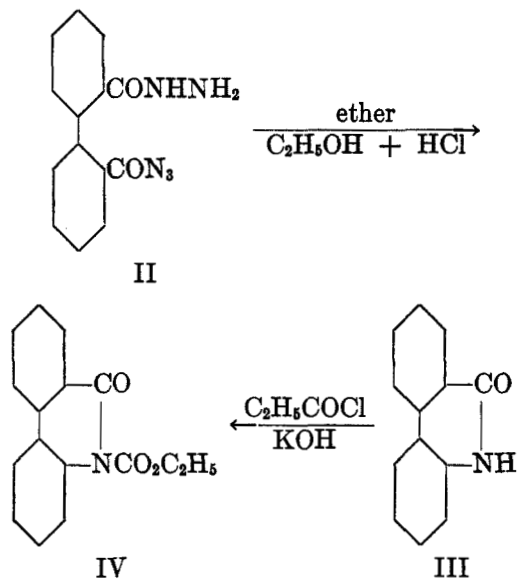


When one mole of the dihydrazide (I) is treated with one mole of nitrous acid, the azide-hydrazide (II) results. This product also is unstable, and in ether-alcohol solution decomposes to yield phenanthridone (III).



I II III

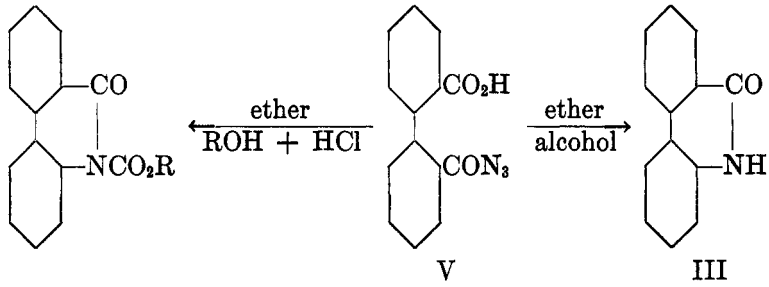
If the decomposition of the azide-hydrazide (II) is brought about by adding ethyl alcohol saturated with hydrogen chloride to its ether solution, the product is N-carbethoxyphenanthridone (IV). The constitution of (IV) was established by synthesis, from potassium phenanthridone and ethyl chlorocarbonate.



II IV III

When diphenic acid monoazide (V) is decomposed in neutral ether-alcohol solution, it, like the azide-hydrazide (II), gives phenanthridone (III). In an ether-alcohol solution containing hydrogen chloride, the monoazide (V) is transformed to N-carboalkoxyl derivatives of phenanthridone. This decomposition has been effected using methyl, ethyl, propyl,

isopropyl, cyclohexyl, allyl, and benzyl alcohols; in every case the corresponding ester was obtained.



V III

EXPERIMENTAL

Diphenic acid dihydrazide. With the following method, constant yields were obtained. Twenty-one grams of dimethyl diphenate was distributed in three tubes, 6 cc. of hydrazine hydrate was added to each and the sealed tubes were heated during 8 hours at 150–160°. The contents were combined, and the remaining hydrazine was removed by distillation. The residue was dissolved in hot water, and the filtered solution was boiled with decolorizing charcoal. It was then filtered, evaporated to dryness on the water-bath, and the solid recrystallized from alcohol; m.p. 210–211°; yield 52–55%.

Diphenic acid diazide. To a solution of 1 g. of diphenic acid dihydrazide in 15 cc. of *N* hydrochloric acid, 6 cc. of 10% sodium nitrite solution was slowly added. A precipitate formed, which was filtered and dissolved in ether. It decomposed immediately, liberating nitrogen. For this reason the analysis gave low values for this element.

Anal. Calc'd for $C_{14}H_8N_6O_2$: N, 28.7. Found: N, 25.5.

By decomposition with 50% sulfuric acid, 18% of nitrogen was liberated. Calculated for a diazide: 19.1%. The ethereal solution of this diazide, washed with sodium bicarbonate and dried with calcium chloride, was employed for the decomposition.

Decomposition in ether-benzene. Equal volumes of the ethereal diazide solution and benzene were mixed, and after 24 hours the solvent was evaporated. The residue was extracted with hydrochloric acid, and the remaining insoluble fraction recrystallized from acetic acid. It proved to be diphenyleneurea, melting at 308°. From the hydrochloric acid solution, 2,2′-diaminobiphenyl was obtained, melting at 80–81°.

Identification of both compounds was effected by mixed melting point. 2,2′-Diphenyleneurea was prepared according to Niementowsky (3), who gives the melting point 310°. A determination of its molecular weight indicated a non-polymerized structure.

Anal. Calc'd for $C_{13}H_{10}N_2O$: M. w., 210. Found: M. w., 222.
(11.2 mg. in 142 mg. of camphor, Δt 14.2°)

Decomposition in ethanol. Diurethane. By substituting ethanol for benzene in the above described reaction, a residue was obtained which proved to be biphenyldiamine bis(ethylurethane); needles melting at 131° after recrystallization from alcohol.

Anal. Calc'd for $C_{18}H_{20}N_2O_4$: C, 65.85; H, 6.05; N, 8.53.
Found: C, 65.56; H, 6.05; N, 8.51.

2,2'-Biphenyldiamine bis(methylurethane). This was obtained when methanol was used; needles melting at 145°.

Anal. Calc'd for $C_{16}H_{16}N_2O_4$: N, 9.33. Found: N, 9.43.

Hydrolysis of the urethanes. One-half gram of the urethane was boiled for 15 minutes with 5% alcoholic sodium hydroxide solution, and then acidified with hydrochloric acid. A precipitate formed which was found to be 2,2'-diphenyleneurea, melting at 308–309° after recrystallization. From the water solution made alkaline, 2,2'-diaminobiphenyl was isolated by extraction with ether; m.p. 81°.

Diphenic acid monoazide-monohydrazide. One gram of dihydrazide was dissolved in 15 cc. of *N* hydrochloric acid. Ether was added, and then, with vigorous agitation, 3 cc. of 7% sodium nitrite solution. The ether was separated, washed with sodium bicarbonate solution, and the ethereal solution was employed for decomposition. The monoazide-monohydrazide is very unstable, and decomposition takes place, as indicated by liberation of nitrogen, even on evaporation of the ethereal solution.

Decomposition of the monoazide-monohydrazide. With neutral alcohol, phenanthridone melting at 286–288° was isolated. With ethanolic hydrogen chloride, N-carboethoxyphenanthridone was obtained, melting at 143–144°.

Diphenic acid monoazide. Decomposition. The monoazide was prepared according to Labriola and Catalano (2). Its properties are similar to those of the diazide, which decomposes quickly with liberation of nitrogen.

Anal. Calc'd for $C_{14}H_9N_3O_3$: N, 15.7. Found: N, 13.9.

By decomposition with 50% sulfuric acid, 8.7% of nitrogen was liberated. Calculated for a monoazide: 10.4%.

Decomposition with alcohols. When ethanol (96%) was added to the ethereal solution of the azide, phenanthridone was obtained. When saturated solutions of hydrogen chloride in methanol, ethanol, *n*-propanol, isopropanol, allyl alcohol, cyclohexanol, or benzyl alcohol were employed for the decomposition of the azide, the corresponding esters of phenanthridone-N-carboxylic acid were isolated.

ALCOHOL	FORMULA	M.P., °C.	ANALYSIS					
			Calc'd			Found		
			C	H	N	C	H	N
Methanol	$C_{15}H_{11}NO_3$	127	71.14	4.34		71.24	4.60	
Ethanol	$C_{16}H_{13}NO_3$	143–144	71.91	4.86		71.34	4.89	
n-Propanol	$C_{17}H_{15}NO_3$	76			4.98			4.85
Isopropanol	$C_{17}H_{15}NO_3$	123			4.98			5.20
Allyl alcohol	$C_{17}H_{13}NO_3$	93–94	73.11	4.65		73.11	4.92	
Cyclohexanol	$C_{20}H_{19}NO_3$	151	74.76	5.91		74.99	6.20	
Benzyl alcohol	$C_{21}H_{15}NO_3$	134	76.59	4.49		76.38	4.53	

Ethyl phenanthridone-N-carboxylate. Three-tenths gram of phenanthridone was fused with the calculated quantity of potassium hydroxide. An excess of ethyl chlorocarbonate was added, and the mixture heated in a sealed tube at 120° during 4 hours. The reaction-product was treated with dilute hydrochloric acid, the solution evaporated to dryness, and the potassium chloride eliminated with water.

The remaining solid was recrystallized from alcohol, and melted at 143°. It was identical (mixed melting point) with the substance isolated by degradation of the azide in ethanolic hydrogen chloride solution. On boiling with dilute alcoholic sodium hydroxide, or with hydrazine hydrate solution, the carbethoxy group was eliminated and phenanthridone, melting at 292°, was produced.

SUMMARY

The Curtius degradation of diphenic acid monohydrazide and dihydrazide has been studied.

Decomposition of the diazide produced in neutral solution 2,2′-diaminobiphenyl and 2,2′-diphenyleneurea. In alcoholic acid solution the diurethanes were formed.

Decomposition of the monoazide-monohydrazide and of the monohydrazide in neutral ethanolic-ethereal solution yielded phenanthridone; in alcoholic hydrogen chloride solution the esters of phenanthridone-N-carboxylic acid were obtained.

BUENOS AIRES, ARGENTINA

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(2) LABRIOLA AND CATALANO, *Anales asoc. quím. argentina*, **25**, 121 (1937).
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[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH, AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

THE HALOGENO-MORPHIDES AND -CODIDES, AND THE MECHANISM OF THE MORPHINE-APOMORPHINE TRANSFORMATION[1]

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The halogenomorphides and halogenocodides are formed when the secondary alcoholic hydroxyl group of morphine or codeine is replaced by a halogen atom. Although the compounds occupy a position of considerable importance in the development of the morphine structural theory, and are the source of the morphine and codeine isomers, there has been no direct proof of structure offered for any single member of the series.

The related pair, α-chloromorphide and α-chlorocodide, are the principal products obtained when morphine and codeine, respectively, are treated with thionyl chloride or phosphorus pentachloride. The halogen atom has tacitly been assumed to take the place of the hydroxyl that is known to occupy the 6-position, although it has been shown (1,2,3) in recent years that replacement of a group at this point in the nucleus often involves an α,γ-shift, as a result of which the new group may appear at position 8. In carrying out numerous kilogram-scale preparations, we have observed that the α compounds are not the only products of the reaction, but are accompanied by the β-halogeno derivatives to the extent of 10% to 15% of the total yield. In the codeine series, α- and β-chlorocodides were obtained in part in the form of a new molecular compound of constant properties, that could not be separated into the components by fractional crystallization, although α- and β-chlorocodides themselves differ considerably in solubility. Separation through salts, a method previously employed successfully for similar molecular compounds in the

[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

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morphine series (4), also failed, but the nature of the compound could be shown by preparing it from equal amounts of α- and β-chlorocodides.

The nature of the isomerism between β-chloromorphide or β-chlorocodide and the respective α-chloro derivatives has often been in question (5). It now appears most probable that the β series arises from the α series through an α,γ-shift of halogen, and has the unsaturated center at the 6,7-position. This 8-halogeno structure was postulated several years ago by Schöpf without any experimental evidence (6)[4]. The fact that bromocodide cannot be caused to isomerize in the sense of the α- to β-chlorocodide change (7), indicates that the bromo series may have the same structure as the β-chloro series, although there is no obvious reason why an α-bromo series should not exist. Fluoromorphides have not been prepared, and the iodo compounds have been very little studied.

The present investigation was started in 1933, with the object of establishing definitely the position of the halogen atom in the various known halogeno derivatives mentioned above. Because of difficulties involving rearrangements and anomalous reactions, it has been only partly successful.

It is apparent that halogenation of dihydrocodeine can involve no rearrangement beyond a probable Walden inversion, and that the halogen atom in chlorodihydrocodide must have the same position, although not necessarily the same configuration, as the hydroxyl group in the starting material. There exists, however, no proof of a structural similarity between α-chlorocodide and chlorodihydrocodide, *i.e.*, that no rearrangement takes place in the conversion of codeine to α-chlorocodide. We have now found that by imposition of suitable conditions, namely, hydrogenation of α-chlorocodide hydrochloride in glacial acetic acid, the usual complete reductive elimination of chlorine can be so repressed that a 52% yield of chlorodihydrocodide can be obtained. The remainder of the material is accounted for as tetrahydrodesoxycodeine (40%) and dihydrodesoxycodeine-D (7.5%). This relationship of α-chlorocodide to chlorodihydrocodide leaves no doubt that the halogen atom in the former is actually located on carbon 6.

The evidence for the β-chloro and the bromo series is less satisfactory. Replacement reactions indicate in general that the members of these two series are of the same type. Hydrolysis of β-chlorocodide and of bromocodide yields predominantly isocodeine (8), and reaction of either halogeno compound with secondary amines appears to result exclusively in 6-amino derivatives (1), just as mercaptolysis gives only 6-alkylthio derivatives (2). It is, however, remarkable that in large-scale hydrolysis of bromocodide

[4] The argument of Schöpf, adduced from the work of Small and Cohen on the catalytic reduction of β-chlorocodide, is not very convincing, for α-chlorocodide can likewise be hydrogenated to yield, in part, tetrahydrodesoxycodeine.

we have never observed regeneration of any trace of codeine, which might be expected to appear with its diastereoisomer, isocodeine. These replacement reactions might be interpreted as indicating the 6-position for halogen, but we believe that they favor rather the 8-position, chiefly on the ground, that in the α series, where the structure is known, replacement of halogen involves preferentially the α,γ-shift.

In view of the above cited parallelisms between the β-chloro and bromo compounds, it is somewhat surprising to find, that while α-chloromorphide and bromomorphide in acetic acid react with great ease with hydriodic acid to give the same iodomorphide, β-chloromorphide is quite indifferent, even under more vigorous conditions.

Attempts to locate the halogen of β-chlorocodide by substitution and reduction procedures gave negative results. Whereas dihydrocodeine is transformed smoothly to 6-chlorodihydrocodide by phosphorus pentachloride, dihydroisocodeine yields only a phosphorus-containing compound, probably an ester. Dihydropseudocodeine and dihydroallopseudocodeine both react to give a single 8-chlorodihydrocodide. As a minor product of the same reaction, a non-phenolic base containing two halogen atoms is formed. This may be assumed to be 1,8-dichlorodihydrocodide. Thionyl chloride does not act on the alcoholic hydroxyl of the dihydrocodeine isomers, but chlorinates instead the aromatic nucleus[5], presumably at the 1-position (9). The monochlorodihydrocodeine isomers so obtained are transformed with great ease back to the dihydrocodeine isomers by sodium and alcohol reduction, a reaction quite general for morphine derivatives halogenated in the aromatic ring, but not for those carrying halogen elsewhere in the nucleus.

The apparent impossibility of obtaining all four isomeric chlorodihydrocodides effectively blocks direct determination of the structure of β-chlorocodide. After long investigation, it was found that β-chlorocodide could be hydrogenated, as the hydrochloride in alcoholic hydrogen chloride solution, with retention of the halogen atom in a small portion of the product. While the β-chlorodihydrocodide obtained could not be brought to satisfactory analytical purity, it is obviously different from either 6-chlorodihydrocodide or 8-chlorodihydrocodide. This still leaves the alternative configuration at the 6- or 8-position as a possibility, and there seems to be little prospect of proving the β-chlorocodide structure by this method.

8-Chlorodihydrocodide proved to be exceptionally unreactive. Drastic

[5] Späth and Spitzer, *Ber.*, **59**, 1477 (1926), observed nuclear chlorination in the preparation of picolinic acid chloride with impure thionyl chloride, which they remark upon as surprising, since picolinic acid is not an especially easy substance to chlorinate.

sodium and alcohol reduction, and prolonged electrolytic reduction, left it unchanged, while autoclave treatment with sodium methoxide did not remove hydrogen chloride[6], but effected only demethylation at position 3, to give 8-chlorodihydromorphide[7]. Elimination of hydrogen chloride was ultimately accomplished with sodium and cyclohexanol (to give desoxycodeine-D) and is described in the following paper (10).

Attempts to replace the hydroxyl of the dihydrocodeine isomers with bromine met with only partial success. Dihydrocodeine, with phosphorus tribromide, usually yielded phosphorus-containing products, although in one experiment a phosphorus-free phenolic product was obtained that had the composition of a demethylated bromodihydrocodide. As in attempted chlorinations, dihydroisocodeine gave always products that contained phosphorus. From dihydropseudocodeine, 8-bromodihydrocodide was obtained in poor yield, while dihydroallopseudocodeine apparently suffered bromination and loss of hydrogen bromide, together with demethylation at the 3-methoxyl group (10). These reactions contributed little to the solution of the problem, since catalytic hydrogenation of bromocodide under a wide variety of conditions gave principally halogen-free products. The structure of bromomorphide, like that of β-chloromorphide, must rest for the present on speculations and analogy. Experiments now in progress on the reaction of phenylmagnesium bromide with these halogeno compounds may contribute evidence on the question.

POLYHALOGEN DERIVATIVES. THE MECHANISM OF APOMORPHINE FORMATION

In devising a better route to the powerful drug dihydrodesoxymorphine-D ("Desomorphine"), discovered in the Virginia laboratory in 1930[8], Kurt Warnat (Hoffmann-La Roche, Basel) made the interesting discovery that morphine, in warm concentrated hydrochloric acid, adds a molecule of hydrogen chloride at the 4,5-oxide ring, and suffers replace-

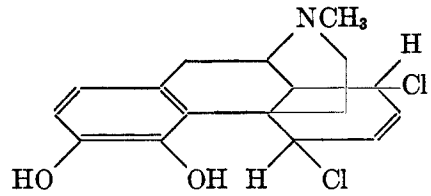
[6] Under parallel conditions, 6-chlorodihydrocodide and 6-chlorodihydromorphide lose hydrogen chloride to give desoxycodeine-C and desoxymorphine-C. Small and Cohen, *J. Am. Chem. Soc.*, **53**, 2214 (1931); Small and Morris, *J. Am. Chem. Soc.*, **55**, 2874 (1933).

[7] The demethylating action of sodium alkoxide in the morphine series has been previously noted by Small, Turnbull, and Fitch, *J. Org. Chem.*, **3**, 212 (1938); Small and Morris, *J. Am. Chem. Soc.*, **55**, 2876 (1933).

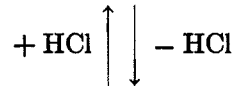
[8] Dihydrodesoxymorphine-D was prepared by Small and Eilers in November 1930 and submitted for pharmacological tests on July 21, 1932. The publications, Small, Yuen, and Eilers, *J. Am. Chem. Soc.*, **55**, 3863 (1933); Small, U. S. Patent, 1,980,972, (Nov. 13, 1934) embody later improvements in the preparation.

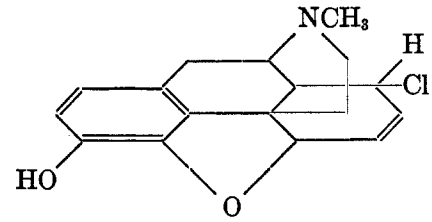
ment of the alcoholic hydroxyl by chlorine in a manner parallel to that involved in the formation of β-chloromorphide (11).

With the kind permission of Dr. Warnat, the unpublished details of the reaction are here communicated. Warnat formulates the dichlorodihydrodesoxymorphine as in formula I, and as proof advances the formation of a diacetyl derivative and the facile conversion of I to β-chloromorphide (II) in the presence of alkali. We observe that this transformation proceeds with such ease that it is not possible to isolate the base,



I. Dichlorodihydrodesoxymorphine





II. β-Chloromorphide

dichlorodihydrodesoxymorphine, from its hydrochloride, for the ring-closure takes place even in the presence of sodium bicarbonate. Indeed, no alkaline agent is necessary, for if the very sparingly soluble hydrochloride is merely boiled with water for ten minutes, it passes completely into solution, and the solution becomes strongly acid. By concentration under diminished pressure, the hitherto unknown β-chloromorphide hydrochloride is obtained in good yield. The ease of ring-closure is remarkable in view of the fact that the 4-hydroxyl is so weakly acidic that it does not react with diazomethane; a monomethyl ether is formed, which is transformed to β-chlorocodide by sodium bicarbonate, and hence must have had the 4-hydroxyl free.

We find that β-chloromorphide is an intermediate step in the con-

version of morphine to dichlorodihydrodesoxymorphine. This is evident from the fact that β-chloromorphide can be used instead of morphine as the starting material for the reaction, and is demonstrated more convincingly by our observation that if the reaction between morphine and hydrochloric acid is interrupted at the first appearance of crystals of dichlorodihydrodesoxymorphine hydrochloride, the hydrochloric acid solution contains approximately equal amounts of morphine and β-chloromorphide.

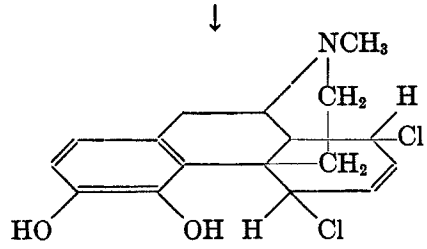
β-Chloromorphide has long been recognized as being an intermediate in the transformation of morphine to apomorphine (12). It is, however, only the first step in the process, the second intermediate being dichlorodihydrodesoxymorphine, for experiment shows that the dichloro compound, under the conditions imposed in the morphine-apomorphine reaction, gives a yield of apomorphine quite comparable to that obtained from morphine. The mechanism proposed by Schöpf and Hirsch (13), which involves an improbable series of alternate additions and eliminations of hydrogen chloride, becomes superfluous. The essential steps in the formation of apomorphine have now been realized individually and successively. Morphine is first transformed to β-chloromorphide, through substitution of chlorine for the alcoholic hydroxyl, simultaneous with, or followed by an α,γ-shift of halogen. The cyclic ether group of β-chloromorphide, activated by the 6,7-unsaturation (14), adds a molecule of hydrogen chloride, and the resulting dichlorodihydrodesoxymorphine undergoes rearrangement. The transitory intermediate may be of the metathebainone type (a), analogous to that postulated by Schöpf, but we consider it more probable that the intermediate is formed by loss of hydrogen chloride at 8,14 (b), and that an α,γ-shift of the chain from 13 to 8 is accompanied by loss of the second molecule of hydrogen chloride (aromatization) to yield apomorphine. Dichlorodihydrodesoxymorphine

Morphine

↓

β-Chloromorphide

↓



Dichlorodihydrodesoxymorphine

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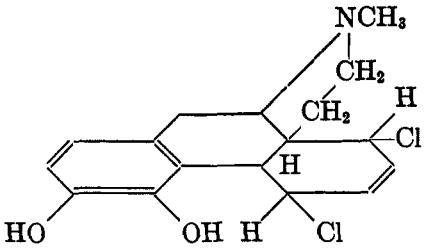
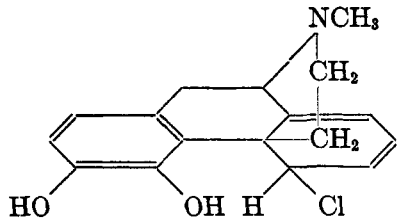


(a)



(b)

Possible intermediates

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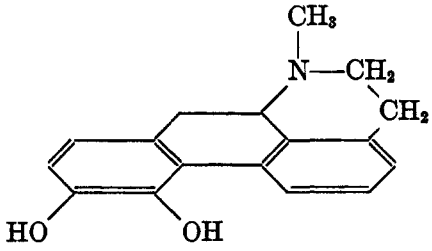

Apomorphine

carries halogen at both C-5 and C-8, and, of these positions, the former is probably the more active; this follows from the extreme ease of ether ring-closure to the 5-position, and the comparative inactivity of β-chloromorphide toward iodination or hydrolysis. That the shift of the ethanamine chain does not proceed toward C-5, an adjacent carbon atom, may be due to the relative difficulty of formation of the 7-membered ring. The only proved examples of a move of the chain to this position also involve breaking the ring structure, between C-9 and nitrogen.

It is reasonable to assume that apocodeine (apomorphine 3-methyl ether, known as pseudoapocodeine in early publications) is formed from codeine by a mechanism similar to that which we propose for apomorphine. This assumption receives some support in Knorr's observation (15) that a better yield of apocodeine is obtained from pseudocodeine (in which the first step, an α,γ-shift, has already taken place) than from codeine. The usual preparative methods have consisted in melting codeine with oxalic acid or zinc chloride. In a recent improvement on the oxalic acid method, Folkers (16) succeeded in obtaining a 12.8% yield of apocodeine. We have observed, in experiments unrelated to the subject of this paper, and in which no attempt was made to find optimum conditions, that fusion

of codeine with glacial phosphoric acid gives yields of apocodeine of about 30%.

Trichloromorphide. Morphine reacts with thionyl chloride to form principally α-chloromorphide (17). The beautifully crystalline product obtained from the reaction has, however, a specific rotation about 100° lower than that of pure α-chloromorphide. By the use of suitable purification methods, we have found that this is due chiefly to the presence of β-chloromorphide, (to the extent of about 3%), but that a second by-product, containing three chlorine atoms, can also be isolated (1.2% yield). This new compound, which we shall call trichloromorphide, is a phenolic base, and reacts with diazomethane to give a monomethyl ether, trichlorocodide, which has no phenolic properties. This result, together with the fact that trichloromorphide is regained unchanged from its solution in alkali, shows that it is not related to Warnat's dichlorodihydrodesoxymorphine. Analysis indicates clearly that the morphine alcoholic hydroxyl and two hydrogen atoms have been replaced by chlorine. The 1- and 6- (or 8-) positions for two of the halogens are therefore probable, but the location of the third is not obvious. Attempts to obtain identifiable halogen-free material by various reductions of trichlorocodide were unsuccessful.

Pentachloroxycodide. Codeine, dihydropseudocodeine, β-chlorocodide, and α-chloromorphide are converted to resinous products by cold sulfuryl chloride. Morphine, which is ordinarily more sensitive than codeine to acidic agents, is unaffected. α-Chlorocodide reacts very rapidly at 0° with sulfuryl chloride to give a good yield of crystalline base having the composition $C_{18}H_{20}Cl_5NO_3$, *i.e.*, containing one oxygen and four chlorine atoms more than the starting material. Its solubility in organic media shows that it is not perchlorinated at nitrogen. From the analytical results, it is apparent that the new constituents have been added, not substituted, but no suggestion can be offered concerning the mode of addition. Neither hydrolysis nor reduction yielded any identifiable products.

EXPERIMENTAL

Hydrogenation of α-chlorocodide. A suspension of 10.0 g. of α-chlorocodide (of m.p. 151°, $[\alpha]_D^{26}$ −383.0°) in 25 cc. of absolute ether was treated with an excess of ethereal hydrogen chloride, and the pasty mass was stirred vigorously until evolution of heat ceased. The powdery, amorphous salt was filtered, washed well with absolute ether, and dried in a vacuum; yield 11.7 g. The entire product was dissolved in 40 cc. of glacial acetic acid (distilled from chromic anhydride) and subjected to hydrogenation in the presence of 100 mg. of platinum oxide. The absorption, corrected to standard conditions, was 1282 cc., or 1.73 moles, and stopped completely in one hour. After dilution with an equal volume of water, the solution was filtered, layered with 300 cc. of ether, and made alkaline with ammonia. The

precipitate extracted readily into the ether, from which large, glassy, six-sided crystals rapidly separated. These crystals, and the residue from distillation of the ether, were treated with 5.0 g. of *d*-tartaric acid. The first crop of tartrate, which separated at room temperature, had the m.p. 191–192° (foaming). It was converted to the base, and yielded 5.2 g. of chlorodihydrocodide, m.p. after crystallization from alcohol, 172.5–174°, no depression in mixture with an authentic sample.

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; Cl, 11.10.
Found: C, 67.46; H, 7.05; Cl, 11.22, 11.23.

Chlorodihydrocodide hydrochloride melts in an evacuated tube at 203–205°, solidifies, and remelts at 226°. In water it shows $[\alpha]_D^{26}$ −129.5° (c = 1.17). The base has $[\alpha]_D^{27}$ −177.8° (chloroform, c = 1.57).

The mother liquors from the precipitation of chlorodihydrocodide tartrate gave 1.1 g. of dihydrodesoxycodeine-D acid tartrate (equivalent to 0.72 g. of base) after standing several days in the ice-box. The salt melted at 125–128° (gas evol.) and did not depress the melting point of a known sample. The separation of the tartrates is possible only because of the marked tendency of dihydrodesoxycodeine-D tartrate toward delayed crystallization. The end mother liquors from preparation of the tartrate gave 3.8 g. of tetrahydrodesoxycodeine hemihydrate when converted to base in the usual way. These products account for 9.9 g. of the 10 g. of starting material.

Hydrogenation of β-chlorocodide. Numerous attempts to reduce β-chlorocodide without dehalogenation, as described for the α-isomer, resulted only in dihydrodesoxycodeine-D and tetrahydrodesoxycodeine, accompanied by unreduced β-chlorocodide when catalyst of low activity was used. Reduction in alcoholic hydrogen chloride solution was occasionally successful; the cause of the variations could not be ascertained. Ten grams of β-chlorocodide, $[\alpha]_D$ −10°, in 120 cc. of absolute alcohol with 80 cc. of saturated alcoholic hydrogen chloride and 100 mg. of platinum oxide absorbed 1825 cc. (2.3 moles) of hydrogen rapidly. After removal of the catalyst, solvent and excess acid were taken off under diminished pressure at 40°, the salt was dissolved in water, and the base liberated by ammonia and brought into ether. The ether solution was extracted with the calculated amount of 0.2 *N* hydrochloric acid in seven fractions. The first two fractions yielded only tetrahydrodesoxycodeine; fractions 3 to 5 contained this base together with halogen-containing material. Fraction 6 gave nearly pure β-chlorodihydrocodide (fraction 7, negative). After purification from alcohol, the base melted unsharp at about 145°. In alcohol it showed $[\alpha]_D^{25}$ +37.5° (c = 1.0). Although analytical results were unsatisfactory, the *dextro* rotation value makes it probable that the product is as claimed, for all the other possible reduction-products are *levo*rotatory.

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; Cl, 11.10.
Found: C, 67.41; H, 7.83; Cl, 11.18.

Reduction of bromocodide hydrobromide in glacial acetic acid, with excess hydrogen bromide and various catalysts resulted in absorption of about 2.5 moles of hydrogen. The principal product was always tetrahydrodesoxycodeine. Some bromine-containing product could be isolated by exhaustive fractional extraction, but the basicity differences involved were too small to permit complete separation.

Iodomorphide. The halogen atom in α-chloromorphide and bromomorphide enters into exchange reactions so readily that the hydriodides cannot be prepared in the usual way. Even under the gentlest conditions, either base gives exclusively iodomorphide hydriodide. Three grams of α-chloromorphide in 24 cc. of 10% acetic acid was brought into solution by addition of 40 cc. of boiling water, and treated with 4.9 g. of potassium iodide in 5 cc. of water. The clear solution was allowed to

cool very slowly, and finally kept overnight in the ice-box. The yield of long, white crystals was nearly quantitative. A similar result was obtained by working with cold solutions, or using bromomorphide. Iodomorphide hydriodide can be recrystallized from water (70°) in an atmosphere of carbon dioxide, with addition of a trace of sodium hydrosulfite to prevent oxidation. The white crystals turn yellow unless dried in an inert atmosphere. In water, the salt shows $[\alpha]_D^{25}$ +114.5° (c = 0.23).

Anal. Calc'd for $C_{17}H_{19}I_2NO_2$: I, 48.54. Found: I, 48.74.

Iodomorphide base is a vitreous solid having $[\alpha]_D^{27}$ +123.2° (methanol, c = 1.10). The liberation of the base from the salt involved appreciable hydrolysis, as indicated by the analysis.

Anal. Calc'd for $C_{17}H_{18}INO_2$: I, 32.13. Found: I, 30.25.

The acid tartrate crystallized best from 50% alcohol. In water, $[\alpha]_D^{25}$ +120.3° (c = 0.20).

Anal. Calc'd for $C_{21}H_{24}INO_8$: I, 23.28. Found: I, 22.76.

The salicylate was prepared with alcoholic salicylic acid, and was purified from alcohol. It had the m.p. 161° (decomp.) and $[\alpha]_D^{26}$ +113.4° (alcohol, c = 0.88).

Anal. Calc'd for $C_{24}H_{24}INO_5$: I, 23.81. Found: I, 23.66.

The benzoate, prepared like the salicylate, had the m.p. 159–160° (decomp.) and $[\alpha]_D^{26}$ +115.5° (alcohol, c = 1.13).

Anal. Calc'd for $C_{24}H_{24}INO_4$: I, 24.54. Found: I, 24.35.

The methiodide was prepared by treating the amorphous base with cold methyl iodide. It could be crystallized in small portions from 50% alcohol without hydrolysis. In 50% alcohol it showed $[\alpha]_D^{26}$ +90° (c = 0.21), but after the solution stood for 36 hours the value dropped to +54°.

Anal. Calc'd for $C_{18}H_{21}I_2NO_2$: I, 47.27. Found: I, 47.35.

Iodomorphide was further identified by conversion to iodocodide. An excess of diazomethane was distilled into a suspension of iodomorphide benzoate in absolute ether containing a little methanol. After 48 hours the solution was shaken with dilute hydrochloric acid, and the ether and methyl benzoate discarded. From the acid layer, a good yield of iodocodide was obtained; identification by melting point and rotation.

On catalytic hydrogenation, iodomorphide absorbed one mole of hydrogen, giving a halogen-free, amorphous base that could not be identified. It resisted sublimation in a high vacuum at 200°, and is therefore probably dimolecular.

β-Chloromorphide hydriodide. When a hot solution of β-chloromorphide in 10% acetic acid was treated with potassium iodide, β-chloromorphide hydriodide was obtained in 92% yield. The salt crystallized from water in large white needles, and had $[\alpha]_D^{26}$ 0° (water, c = 0.2). No substitution by iodine took place, as was shown by analysis, and by the fact that β-chloromorphide could be regained from the salt.

Anal. Calc'd for $C_{17}H_{19}ClINO_2$: I, 29.41.
Found, (ionic halogen): I, 29.75.
Calc'd, mixed silver halides from 117.8 mg. sample: 102.1 mg.
Found: 103.8 mg.

Molecular compound of α- and β-chlorocodides. The alcohol mother liquors from the purification of α-chlorocodide were freed as far as possible from α- and β- chlorocodides by successive concentrations and crystallizations, and finally diluted with water. The crystalline precipitate that separated had the melting point 112–113°, and after purification from alcohol melted at 114–116°. This melting point did not change on fractional crystallization of the product. The compound sublimed in a high vacuum at 110°; the sublimate melted at 115–117°, $[\alpha]_D^{25}$ −150.4° (absolute

alcohol, $c = 1.077$). When equal amounts of α- and β- chlorocodide were crystallized together from alcohol, the product was identical in physical properties with that described above, and gave no depression in mixed melting point. In view of the fact that the main portion of the α and β isomers can be separated without difficulty, the appearance of the molecular compound in the end-fraction is remarkable.

8-Chlorodihydrocodide. Five grams of dihydropseudocodeine was added slowly to 10 g. of phosphorus pentachloride in 15 cc. of dry chloroform, and the mixture was boiled under reflux for 8 hours. The solution was poured on ice, and chloroform was removed under diminished pressure. The water solution was made ammoniacal, and the base was extracted into ether, from which 4.5 g. of dark oil was obtained. This yielded a crystalline tartrate, which was purified from water, decolorizing with Norit; the yields averaged 3 to 4 grams. The tartrate melted at 230–232° (evac. tube). The base was regenerated from the tartrate and recrystallized from 75% acetone. It had the m.p. 123–124°, $[\alpha]_D^{25}$ −42.7° (absol. alcohol, $c = 1.05$).

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.58; H, 6.94; N, 4.38; Cl, 11.10.
Found: C, 67.80, 67.79, 67.81; H, 6.30, 6.58, 6.57; N, 4.37; Cl, 11.28.

The parallel reaction of dihydroallopseudocodeine with phosphorus pentachloride gave the same product, but in somewhat lower yield.

8-Chlorodihydromorphide. 8-Chlorodihydrocodide was regained from prolonged vigorous reduction with sodium in ethanol or from drastic electrolytic reduction. The action of sodium in cyclohexanol is discussed in a following communication (Desoxycodeine-D). Sodium methoxide caused demethylation. Three grams of 8-chlorodihydrocodide in 240 cc. of methanol containing 6 g. of sodium was heated in an autoclave at 140° for 24 hours. The solution was diluted with water, and methanol was removed under diminished pressure. A crystalline precipitate (0.7 g.) of starting material separated. Carbon dioxide was passed into the alkaline solution, whereby 1.4 g. of lustrous platelike crystals was precipitated. The compound was very sparingly soluble in organic media, and was recrystallized from 850 cc. of boiling acetone. Analytical values and the strongly phenolic nature show it to be 8-chlorodihydromorphide; m.p. 257–258° (evac. tube, decomp.).

Anal. Calc'd for $C_{17}H_{20}ClNO_2$: C, 66.75; H, 6.60; N, 4.58; Cl, 11.60.
Found: C, 66.69; H, 6.40; N, 4.54; Cl, 11.50.

1,8-Dichlorodihydrocodide. The mother liquor from the preparation of 8-chlorodihydrocodide tartrate was concentrated to one-fourth its volume, and a small crop of tartrate was removed. The remaining solution yielded a new base, which was purified by several crystallizations from alcohol; the m.p. was 190.5–191.5°.

Anal. Calc'd for $C_{18}H_{21}Cl_2NO_2$: Cl, 20.08. Found: Cl, 20.29.

Dihydrocodeine isomers with thionyl chloride. Dihydrocodeine reacts with cold thionyl chloride to give a good yield of a chlorinated base of m.p. 187–190°. Its nature as 1-chlorodihydrocodeine is evident from the result of reduction with sodium in alcohol, which gave pure dihydrocodeine, m.p. 85–87°.

Dihydroisocodeine under the same conditions gave a chlorinated base that was isolated as the tartrate (Calc'd: Cl, 7.3. Found: Cl, 7.9). The base liberated from the tartrate was difficult to crystallize; m.p. 103–105°. On reduction with sodium and alcohol it gave a quantitative yield of dihydroisocodeine, m.p. 189–194°.

Dihydropseudocodeine yielded a chlorinated base of m.p. 108–112°, which gave dihydropseudocodeine, m.p. 151–152°, on sodium-alcohol reduction. The chlorination product from dihydroallopseudocodeine and thionyl chloride was isolated as the oxalate, from which chlorodihydroallopseudocodeine, m.p. 189–191° was obtained.

Bromination of the dihydrocodeine isomers. Bromination of the dihydrocodeine

isomers was attempted, using 15 cc. of phosphorus tribromide with 5 g. of alkaloid, in sealed tubes at 105–115° for 5 hours. From dihydrocodeine, phosphorus-containing products were usually obtained. In one experiment only, a phosphorus-free product was isolated, phenolic in nature, m.p. 260–262°, that appears to be 6-bromodihydromorphide; Calc'd for $C_{17}H_{20}BrNO_2$: Br, 22.8. Found: Br, 23.1. Dihydroisocodeine gave an unidentified halogen-free base, isolated only as the salicylate. Dihydroallopseudocodeine gave a small yield of desoxymorphine-D. From dihydropseudocodeine a crystalline base of m.p. 230–232° was obtained, which may be the expected 8-bromodihydrocodide.

Anal. Calc'd for $C_{18}H_{22}BrNO_2$: Br, 21.9. Found: Br, 22.2.

Trichloromorphide. The reaction of anhydrous morphine with thionyl chloride is claimed to result in a yield of 70–90% of α-chloromorphide (17). Under the most scrupulous observation of the conditions of Wieland and Kappelmeier, we were never able to attain these yields of pure product. The crystalline chloromorphide (from ether) obtained from reaction of a total of 1450 g. of anhydrous morphine weighed 1300 g. It showed the specific rotation −269°, whereas pure α-chloromorphide has $[\alpha]_D$ −375°. One hundred-gram portions were each shaken vigorously with 200 cc. of alcohol, and filtered, whereby the specific rotation was raised to −340°. A second, similar, treatment gave a product having $[\alpha]_D$ −360°; total yield 1000 g., or about 65% of the calculated. This material was sufficiently pure for most experimental purposes; one crystallization from methanol resulted in α-chloromorphide of specific rotation −372.5°, but large quantities of methanol were required.

The alcohol washings, 5800 cc., were diluted with water until no further precipitation took place. The powdery, amorphous material weighed 447 g., but contained 147 g. of water, which was subsequently found in the benzene treatment. Fifty grams of the powder was dissolved in 250 cc. of cold benzene, and a small amount of brown flocculent material was removed by filtration through paper pulp. The benzene solution was separated from water (16.5 cc.), diluted with benzene to 1.5 liters, and again filtered through pulp. The benzene solution was extracted with 0.2 *N* hydrochloric acid, the base was liberated with ammonia, and brought into ether. The ether was concentrated to about 30 cc. and decanted from a viscous oil. From the ether, β-chloromorphide crystallized, and the oil, rubbed with ethyl acetate, gave another crop. Total β-chloromorphide, 4.3 g. The ethyl acetate mother liquors, on concentration and dilution with a little benzene, gave 3.1 g. of α-chloromorphide. When the benzene filtrate was diluted with more benzene, a flocculent precipitate formed, which was removed. The total, unidentified amorphous material from the several filtrations involved was 10 g. The benzene was extracted 3 times with 33 cc. of 0.1 *N* hydrochloric acid and 9 times with 33 cc. of 0.2 *N* acid. Fractions 1 to 3 yielded 1 g. of β-chloromorphide; fractions 4 and 5, 0.7 g. of a mixture of α- and β- chloromorphides; fractions 6 and 7, 0.9 g. of α-chloromorphide. Fraction 8 solidified as the hydrochloride, and with 9, 10, and 11, gave 2.5 g. of trichloromorphide. Fraction 12 contained no alkaloid. The yield of trichloromorphide, based on morphine, was about 1.2% of the possible amount.

Trichloromorphide crystallizes best from ethyl acetate, m.p. (decomp.) about 195°. In methanol it has $[\alpha]_D^{21}$ −285° (c = 0.410).

Anal. Calc'd for $C_{17}H_{16}Cl_3NO_2$: C, 54.77; H, 4.33; Cl, 28.55.
Found: C, 54.85; H, 4.32; Cl, 28.43.

The hydrochloride crystallizes when the base is treated with 3 *N* hydrochloric acid, and may be purified from water. It has $[\alpha]_D^{20}$ −245.6° (water, c = 0.721).

Anal. Calc'd for $C_{17}H_{17}Cl_4NO_2$: Cl, 34.68. Found: Cl, 34.57.

Trichlorocodide. Methylation was accomplished in ether containing a little

methanol, with diazomethane. The ethereal solution was washed with sodium hydroxide, concentrated, and the new base was purified from ethyl acetate and from absolute ethanol; m.p. 143–143.5°. It shows in ethyl acetate $[\alpha]_D^{25}$ −302° (c = 1.11).

Anal. Calc'd for $C_{18}H_{18}Cl_3NO_2$: C, 55.88; H, 4.69; Cl, 27.52.
Found: C, 55.80; H, 4.70; Cl, 27.74.

The hydrochloride, prepared with 3 *N* hydrochloric acid and purified from water, has $[\alpha]_D^{25}$ −218° (water, c = 0.840).

Anal. Calc'd for $C_{18}H_{19}Cl_4NO_2$: Cl, 33.53. Found: Cl, 33.71.

Trichlorocodide hydrochloride in aqueous solution with palladium-barium sulfate took up two moles of hydrogen. The product was a liquid from which no crystalline salts could be obtained. Hydrogenation of the base in the presence of piperidine as hydrogen halide acceptor (absorption 3 moles) was not more successful, nor were reductions with zinc and alcohol or sodium and alcohol.

Dichlorodihydrodesoxymorphine. This compound was prepared in the form of hydrochloride, according to Example 1 of the Warnat patent (11). Thirty grams of morphine hydrate yielded 28.6 g. of dichlorodihydrodesoxymorphine hydrochloride, or 73% of the calculated amount. The melting point was 230–235° [reported m.p. 270–272° (Warnat, 18)]. We were not able to find any purification method that would raise the melting point to Warnat's value.

Anal. Calc'd for $C_{17}H_{20}Cl_3NO_2$: C, 54.17; H, 5.37; N, 3.72; Cl, 28.24.
Found: C, 53.87, H, 5.53, N, 3.79, Cl, 28.07. (By Warnat, 18).

The dichlorodihydrodesoxymorphine from our preparation showed $[\alpha]_D^{27}$ +276° (c = 0.104, 50% alcohol); Warnat's value, +263° (11).

When 0.501 g. of dichlorodihydrodesoxymorphine hydrochloride was dissolved in dilute potassium hydroxide, acidified with hydrochloric acid, and made up to 20 cc., the optical rotation, based on the calculated formation of 0.404 g. of β-chloromorphide was $[\alpha]_D$ −10.9° (experiment by K. Warnat).

Diacetyldichlorodihydrodesoxymorphine (18). The hydrochloride of dichlorodihydrodesoxymorphine was boiled for 3 hours with acetic anhydride, to complete solution. The product was precipitated by addition of ether, and the oily precipitate was dissolved in water. The solution was treated with sodium bicarbonate and extracted with ether. The residue from distillation of the ether was dissolved in methanol, and the diacetyl derivative was precipitated by addition of water.

Anal. (18) Calc'd for $C_{21}H_{23}Cl_2NO_4$: C, 59.42; H, 5.47; N, 3.30; Cl, 16.72.
Found: C, 59.89; H, 5.40; N, 3.34, Cl; 16.06.
(Experiment and analysis by K. Warnat.)

We were unable to isolate dichlorodihydrodesoxymorphine base. If the hydrochloride is brought into solution in a large volume of boiling water and treated with sodium bicarbonate, the product is β-chloromorphide. It is probable that the β-chloromorphide is already formed before addition of the precipitating agent. This is evident from the following experiment. Five grams of dichlorodihydrodesoxymorphine was suspended in 100 cc. of water, and boiled until solution was complete (8 minutes). The initially neutral solution became strongly acid. It was evaporated to dryness at 25°, and the frothy product was taken up in 6 cc. of water and seeded with β-chloromorphide hydrochloride (obtained from β-chloromorphide with 3 *N* hydrochloric acid). The first crop of crystals weighed 2.6 g. It was recrystallized twice from water; $[\alpha]_D^{25}$ 0° (c = 2.05).

Anal. Calc'd for $C_{17}H_{19}Cl_2NO_2 + H_2O$: Cl, 19.81; H_2O, 5.0.
Found: Cl, 19.63, 19.86; H_2O, 3.9.

Dichlorodihydrodesoxymorphine hydrochloride can be recrystallized in poor

yield by dissolving 1 g. in 300 cc. of 50% alcohol at room temperature and concentrating to 100 cc. at 25° under diminished pressure; yield 0.2 g. The ring-closure apparently proceeds with facility also with dichlorodihydrodesoxycodeine. Two grams of dichlorodihydrodesoxymorphine hydrochloride was suspended in ether containing methanol and treated with 1 g. of diazomethane during two days. The 4-hydroxyl evidently did not undergo methylation and must be very weakly acidic. The ether was extracted with dilute acetic acid and excess sodium bicarbonate was added. The only product was β-chlorocodide.

β-Chloromorphide as intermediate. Twenty grams of anhydrous morphine in 210 g. of conc'd hydrochloric acid was held at 60° for 42 hours, with occasional saturation of the solution with hydrochloric acid gas. The first fine crystals of dichlorodihydrodesoxymorphine hydrochloride had begun to form, and were filtered out. The acid solution was evaporated to dryness at 35° under diminished pressure, and the residue, in 15 cc. of water, was seeded with morphine hydrochloride. The crystals weighed 8.6 g., and were practically pure morphine hydrochloride, $[\alpha]_D^{21}$ −103.3°; lit. value −111.5°. The mother liquor was diluted with water, layered with a liter of ether, made ammoniacal, and extracted. A trace of morphine stayed between the layers. The ether solution was extracted with successive portions of 0.2 *N* hydrochloric acid, each portion equivalent to 2 g. of alkaloid, and each fraction was converted back to base and brought into ether. The first three fractions yielded residues that formed dark, semi-crystalline hydrochlorides with 3 *N* hydrochloric acid. Fractions 4 to 6 gave 5.9 g. of β-chloromorphide hydrochloride, $[\alpha]_D^{26}$ 0°. The extremely low solubility of dichlorodihydrodesoxymorphine hydrochloride in acid or water makes it impossible that the β-chloromorphide could have been formed from it.

β-Chloromorphide to dichlorodihydrodesoxymorphine. Nine grams of pure β-chloromorphide in 75 cc. of conc'd hydrochloric acid was held at 65° for 72 hours. At this time 2.9 g. of crystals of dichlorodihydrodesoxymorphine hydrochloride had separated, and the experiment was stopped. The salt showed $[\alpha]_D^{27}$ +272° (*c* = 0.107, 50% alcohol).

Dichlorodihydrodesoxymorphine to apomorphine. In parallel experiments, 5 g. of anhydrous morphine, and 5 g. of dichlorodihydrodesoxymorphine hydrochloride, in sealed tubes with 50 cc. of conc'd hydrochloric acid, were heated at 130–140° for 3 hours. From the morphine, (a) 1.8 g. (33.8% yield) of apomorphine hydrochloride was obtained; from the dichlorodihydrodesoxymorphine (b), 1.5 g. (37.3% yield). The products were identified by rotation, respectively $[\alpha]_D^{25}$ −47.8° (a), and −47.8° (b) (water, *c* = 1.13, 1.21). For further identification, the samples were converted to the diacetyl derivatives. Tiffeneau and Porcher (19) reported complex mixtures in their acetylation of apomorphine. The samples in question were therefore acetylated as hydrochloride, 0.5 g. in 5 cc. of anhydrous pyridine with 2 cc. of acetic anhydride at room temperature for 24 hours. We obtained: from apomorphine (a), 0.30 g. of diacetylapomorphine, m.p. 127–128°, $[\alpha]_D^{24}$ −87.5° (0.1 *N* hydrochloric acid, *c* = 1.12); from apomorphine (b), 0.37 g. of diacetylapomorphine, m.p. 127–128°, $[\alpha]_D^{25}$ −87.5° (0.1 *N* hydrochloric acid, *c* = 1.12); no depression in mixed melting point.

Apocodeine. Twenty grams of glacial phosphoric acid was heated (oil-bath) to the point where it could be stirred, and 4 g. of codeine was added. The mixture was held at 175° with stirring for 12 minutes, where a test showed complete alkali-solubility. The glassy mass was dissolved in 60 cc. of hot water, made alkaline with addition of a little sodium hydrosulfite, and filtered from a trace of amorphous material. The alkaline solution was extracted four times with benzene, from which

a yellow oil was obtained. With 3 *N* hydrochloric acid, this gave 1.3 g. (30%) of white crystalline apocodeine hydrochloride. From this 1.15 g. of apocodeine base was obtained. It crystallized from methanol in small prisms, which appeared to lose solvent at about 96°, and melted at 121–121.5°; $[\alpha]_D^{24}$ −97° (absolute alcohol, c = 0.449). The alkaline solution above, with ammonium chloride and chloroform, gave only dark oils.

Pentachloroxycodide. The action of cold sulfuryl chloride on codeine, β-chlorocodide, α-chloromorphide, or dihydropseudocodeine gave only dark resinous products; morphine was unaffected. One gram of α-chlorocodide was added slowly to 10 cc. of sulfuryl chloride cooled in ice-salt mixture. The cold, yellow solution was poured immediately on ice, and the mixture was made ammoniacal and extracted with ether. One gram of acicular crystals was obtained; they became black without melting at 180–200°. The compound was recrystallized to constant rotation from acetone; $[\alpha]_D^{25}$ −298.8° (acetone, c = 0.36).

Anal. Calc'd for $C_{18}H_{20}Cl_5NO_3$: C, 45.43; H, 4.24; Cl, 37.29.
Found: C, 45.72; H, 4.22; Cl, 37.19.

Qualitative tests for nitrogen were positive, for sulfur negative; the iodide-starch test was negative. The compound decomposed when warmed with dilute acids. Catalytic reduction in acetic acid caused absorption of 2.9 moles, in alcohol 5 moles absorption; the products were colored and resinous; aluminum amalgam reduction also caused decomposition.

SUMMARY

The halogen atom in α-chlorocodide has been proved to occupy the 6-position. New halogenated derivatives of the morphine series and of the isomeric dihydrocodeines have been prepared, but proof of structure for β-chlorocodide and bromocodide was unsuccessful. The reaction of morphine with thionyl chloride gives not only α-chloromorphide, but also β-chloromorphide, and a trichloromorphide, of unknown structure. α-Chlorocodide with sulfuryl chloride gives pentachloroxycodide.

Controlled treatment of morphine with concentrated hydrochloric acid results first in β-chloromorphide, which is then transformed to dichlorodihydrodesoxymorphine. Both of these compounds are intermediates in the conversion of morphine to apomorphine, for which a simple mechanism is offered.

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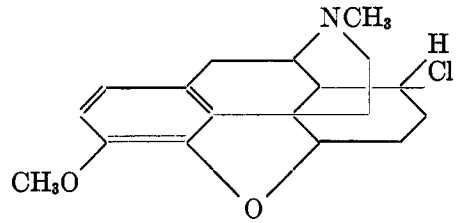
[CONTRIBUTION FROM THE NATIONAL INSTITUTE OF HEALTH AND THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA]

DESOXYCODEINE STUDIES. VI. DESOXYCODEINE-D (DESOXYNEOPINE)[1]

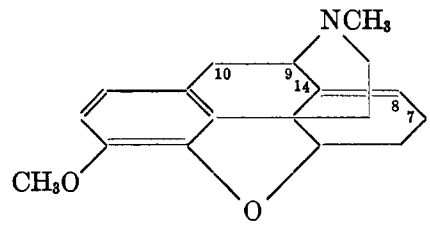
LYNDON SMALL AND JAMES E. MALLONEE[2]

Received January 6, 1940

In the preceding communication (1) it was pointed out that the action of phosphorus pentachloride on dihydropseudocodeine and on dihydroallopseudocodeine resulted in the same 8-chlorodihydrocodide (I). This chloro compound is exceedingly resistant to reduction, but we find that prolonged treatment with sodium in boiling cyclohexanol results in loss of hydrogen chloride, with formation of a new desoxycodeine that we shall designate as desoxycodeine-D. The structure II that we propose for the compound represents it also as the desoxy derivative of the rare opium alkaloid neopine (2). The new desoxycodeine might be logically named desoxyneopine, but this leads to embarrassment in selecting a name for the morphine analog.



I. 8-Chlorodihydrocodide

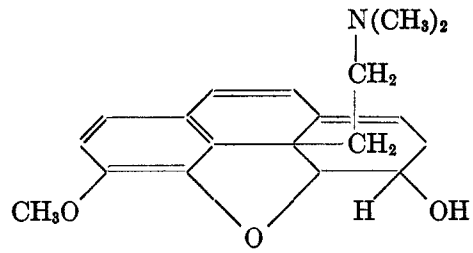


II. Desoxycodeine-D

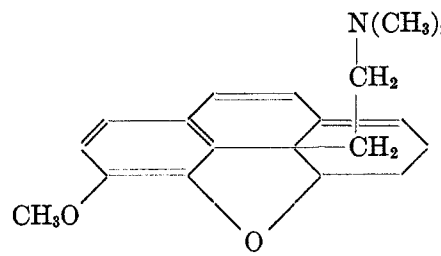
[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

[2] Mallinckrodt Fellow in Alkaloid Chemistry 1937–39.

Desoxycodeine-D adds one mole of hydrogen on catalytic reduction, to give the well-known dihydrodesoxycodeine-D in nearly quantitative yield. This simple relationship demonstrates unequivocally the desoxycodeine nature of the compound, but leaves open the alternative position of the double bond, between carbons 7 and 8. The structure II that we favor is based on negative but fairly convincing evidence. In the methylmorphimethine series, α- and γ- methylmorphimethines, derived respectively from codeine and isocodeine and having the 7,8-unsaturation, undergo with ease a rearrangement (to β- and δ- methylmorphimethines) that consists in a shift of the unsaturated linkage into the 8,14-position, *i.e.*, into conjugation with the 9,10-double bond. We find that desoxycodeine-D-methine cannot be caused to rearrange in this fashion, whence it may be concluded that the methine already has the stable β-methylmorphimethine (neopinemethine) arrangement of double linkages. We were unable to devise any method of preparing desoxy-β-methylmorphimethine for a direct comparison.



III. β-Methylmorphimethine



IV. Desoxycodeine-D-methine

Further support for our conception of the structure of desoxycodeine-D has been obtained through the von Braun cyanogen bromide degradation (3). Von Braun has shown by numerous examples that cyanogen bromide reacts with morphine derivatives having the 7,8-unsaturation, to replace methyl on nitrogen by a cyano group. When, on the other hand, an unsaturated center is located in the β,γ-position to nitrogen, *i.e.* 8,14-, the attachment of nitrogen to an adjacent carbon is so loosened that this

linkage is more easily broken than the N-methyl linkage, and addition of cyanogen bromide takes place with rupture of the cyclic nitrogen structure. We first convinced ourselves of the applicability of the first type of reaction to the desoxycodeine series by an experiment with a compound of known structure. Desoxycodeine-C (4) was converted smoothly by cyanogen bromide to the expected cyanonordesoxycodeine-C. Desoxycodeine-D, on the other hand, reacted to yield an amorphous, bromine-containing product, as would be expected from rupture of the nitrogen-containing ring through cyanogen bromide addition. The result is reminiscent of that obtained by von Braun with thebaine, and, like von Braun's product, our desoxycodeine-D degradation-product behaved as though it slowly lost hydrogen bromide (5).

We may mention, further, that desoxycodeine-D behaves pharmacologically more like thebaine than like a codeine type, a fact that is suggestive of a structural similarity, *i.e.*, the 8,14-unsaturation. We know of no other instance where morphine derivatives of this type have been tested, so that one can scarcely formulate any general connection between physiological action and the presence of the 8,14-unsaturation. Saturation of the 8,14-double bond of thebaine (to dihydrothebaine), and conversion of desoxycodeine-D to dihydrodesoxycodeine-D, results in a marked change in the pharmacological picture, specifically in a two-fold or greater increase in analgesic power, and a moderate reduction in convulsant action (6).

As a by-product in the dehalogenation of 8-chlorodihydrocodide, a small amount (11% yield) of the demethylation product, desoxymorphine-D, was obtained. This was identified by methylation with diazomethane. In one experiment, desoxymorphine-D was obtained as a by-product from heating dihydroallopseudocodeine with phosphorus tribromide. It seems probable that dihydroallopseudocodeine was first converted to 8-bromodihydrocodide, and that this compound suffered loss of hydrogen bromide and demethylation.

EXPERIMENTAL

Desoxycodeine-D. A solution of 5.0 g. of 8-chlorodihydrocodide in 500 cc. of cyclohexanol was brought to boiling, and 55 g. of sodium was added over a period of three hours, while the solution was stirred mechanically and maintained in ebullition under reflux. Addition of 600 cc. more of cyclohexanol was necessary to keep the mixture liquid. The solution was cooled, and made acid with 6 *N* hydrochloric acid. The cyclohexanol was removed by steam distillation, since the alkaloidal material could not be extracted from it with acid. The resulting aqueous solution was made strongly alkaline with sodium hydroxide and extracted thoroughly with ether. Desoxymorphine-D, described in a later paragraph, remained in the alkaline solution. Concentration of the ether solution gave 3.5 to 4.5 g. of liquid base, which was converted to the acid tartrate with saturated aqueous *d*-tartaric acid solution.

The salt was purified from water, yield 4 to 4.5 g. (59–66%). It melted at 204–206° (evac. tube, foaming) and had $[\alpha]_D^{25}$ 0° (water, c = 1.17).

Anal. Calc'd for $C_{22}H_{27}NO_8$: C, 60.9; H, 6.3.
Found: C, 60.8; H, 6.3.

The desoxycodeine-D base obtained from the tartrate was a viscous liquid, and could be purified to some extent by distillation in a high vacuum at 110°. Like most of the compounds of the series, it gave low carbon values on analysis.

Anal. Calc'd for $C_{18}H_{21}NO_2$: C, 76.3; H, 7.5.
Found: C, 75.0, 75.0; H, 7.4, 7.1.

The hydrochloride was prepared with alcoholic hydrogen chloride, and was precipitated crystalline with absolute ether. It could be purified from butanone, m.p. 234–235° (evac. tube); $[\alpha]_D^{28}$ −12.1° (water, c = 0.21).

Anal. Calc'd for $C_{18}H_{22}ClNO_2$: C, 67.6; H, 6.6.
Found: C, 66.5, 66.9; H, 6.7, 6.8.

The acid oxalate was prepared with alcoholic oxalic acid and absolute ether, and was recrystallized from 95% alcohol; m.p. 220–221° (evac. tube, decomp.).

Anal. Calc'd for $C_{20}H_{23}NO_6$: C, 64.3; H, 6.2.
Found: C, 63.5, 63.6; H, 6.4, 6.0.

Bromodesoxycodeine-D. Saturated bromine water was added to a solution of desoxycodeine-D in normal hydrochloric acid until precipitation of the insoluble yellow perbromide was complete. By addition of sulfur dioxide water, excess bromine was destroyed and the perbromide was brought back into solution. The brominated base separated in crystalline form when dilute ammonia was added; yield quantitative. The compound crystallized in six-sided plates from 60% alcohol; m.p. 125–126°. In analogy with bromocodeine (7), this compound may be assumed to be 1-bromodesoxycodeine-D.

Anal. Calc'd for $C_{18}H_{20}BrNO_2$: C, 59.6; H, 5.6; Br, 22.1.
Found: C, 59.0; H, 5.2; Br, 22.2.

After sublimation in a high vacuum, Found: C, 59.4; H, 5.1.

Hydrogenation of desoxycodeine-D. In spite of the analytical difficulty experienced with desoxycodeine-D and its derivatives, the result of hydrogenation appears to establish the empirical formula proposed. A solution of 1 g. of desoxycodeine-D acid tartrate in 35 cc. of water, with 50 mg. of platinum oxide absorbed one mole of hydrogen in 7 hours. Removal of the solvent under diminished pressure resulted in 0.8 g. of white crystals, m.p. 153–155°, which proved to be dihydrodesoxycodeine-D acid tartrate (4b). The base obtained from the salt had the melting point 102–105°, and did not depress the melting point of dihydrodesoxycodeine-D.

Desoxycodeine-D-methine. Reaction of desoxycodeine-D with methyl iodide in alcohol gave a quantitative yield of the methiodide, m.p. 204–206° (evac. tube). One and three-tenths grams of the methiodide was boiled for 10 minutes with 10 cc. of 20% sodium hydroxide solution. The partly crystalline mass was extracted into ether, from which 0.8 g. of crystals was obtained. The methine crystallized from dilute alcohol in lustrous six-sided plates of melting point 76–77°.

Anal. Calc'd for $C_{19}H_{23}NO_2$: C, 76.7; H, 7.8.
Found: C, 76.9; H, 7.6.

A solution of 0.3 g. of the methine in 2.5 cc. of alcohol with 0.35 g. of potassium hydroxide and 1.5 cc. of water was boiled under reflux for two hours. Desoxycodeine-D-methine was regained quantitatively.

Desoxycodeine-D and cyanogen bromide. Following the procedure of von Braun, we extracted into chloroform the base liberated from 1.5 g. of desoxycodeine-D acid tartrate, dried the solution over sodium carbonate, and concentrated it to 5 cc.

After addition of 0.6 g. of cyanogen bromide, the solution was boiled under reflux for two hours, and poured into 150 cc. of ether. The red precipitate that formed was identified after basification as desoxycodeine-D. The ether was concentrated in a vacuum until all odor of cyanide was gone. The reddish oily product contained much halogen, and was slowly transformed to an ether-insoluble substance, probably as a result of splitting out hydrogen bromide and formation of a hydrobromide.

Cyanonordesoxycodeine-C. Desoxycodeine-C differs in structure from the proposed desoxycodeine-D formula only in having the unsaturated linkage in a position other than β,γ- to nitrogen. A solution of 1 g. of desoxycodeine-C in 3 cc. of chloroform with 0.4 g. of cyanogen bromide was boiled under reflux for 2 hours, and then boiled to dryness. The oily product was treated with water and extracted into ether, from which 0.7 g. of crystals was obtained. After recrystallization from alcohol, the compound melted at 159.5–161°.

Anal. Calc'd for $C_{18}H_{18}N_2O_2$: C, 73.4; H, 6.2; N, 9.5.
Found: C, 72.9; H, 6.0; N, 9.7.

Desoxymorphine-D. The alkaline mother liquors from the preparation of desoxycodeine-D were acidified with hydrochloric acid and concentrated. After sodium chloride was removed, ammonia was added and the precipitate was brought into ether. The yield was 0.5 g. (11% of the calculated) of desoxymorphine-D. The base was purified from alcohol, m.p. 254–255° (evac. tube, decomp.); strongly phenolic. It sublimed in a high vacuum at 130–140°. Desoxymorphine-D was also obtained in one experiment when dihydroallopseudocodeine was heated for 7 hours at 120° with phosphorus tribromide. Desoxymorphine-D was converted easily to desoxycodeine-D by the action of diazomethane.

Anal. Calc'd for $C_{17}H_{19}NO_2$: C, 75.8; H, 7.1.
Found: C, 74.7, 75.0; H, 6.9, 7.0.

SUMMARY

The preparation of desoxycodeine-D and desoxymorphine-D from 8-chlorodihydrocodide is described. Desoxycodeine-D appears to have its unsaturation at the 8,14-position and hence represents the desoxy derivative of neopine. Desoxycodeine-D-methine behaves like β-methylmorphimethine in resisting rearrangement.

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[CONTRIBUTION FROM THE INSTITUTE OF PHARMACEUTICAL CHEMISTRY]

A STUDY OF THE INTERMEDIATES IN THE PREPARATION OF SYMPATHOL

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One of the most valuable substitutes for epinephrine is sympathol (synephrine), *p*-hydroxyphenyl-N-methylaminoethanol, $HOC_6H_4CHOHCH_2NHCH_3$. The substance is prepared commercially in several countries, under patents (1). Its preparation in the laboratory is extremely difficult. The classical epinephrine synthesis of Stolz, when applied to the preparation of sympathol, is quite inadequate, because of negligible yields. In seeking a satisfactory method, we accumulated much interesting material, some of which we consider sufficiently important to be published.

As an illustration of the poor yields obtained in the sympathol synthesis, we may cite the fact, that whereas Stolz (2) obtained a 61% yield of the methylamino ketone (adrenalone) by condensing 3,4-dihydroxy-α-chloroacetophenone with methylamine, Legerlotz (3) reported a yield of only 12% of *p*-hydroxy-α-methylaminoacetophenone when he treated *p*-hydroxy-α-chloroacetophenone with methylamine. The yield was appreciably increased when the phenolic group was benzoylated. The compound, *p*-benzoyloxy-α-bromoacetophenone, is frequently mentioned by Legerlotz, but we were unable to find any statement regarding its preparation in any of the Legerlotz patents which were available to us. Slotta (4), and Kindler and Peschke (5),[2] however, quote Legerlotz as having prepared *p*-benzoyloxy-α-bromoacetophenone by the condensation of phenyl benzoate with bromoacetyl bromide in the presence of aluminum chloride:

$$C_6H_5OCOC_6H_5 + BrCH_2COBr = BrCH_2COC_6H_5OCOC_6H_5 + HBr.$$

Working with phenyl benzoate and chloroacetyl chloride, we obtained, however, not the expected *p*-benzoyloxy-α-chloroacetophenone, but *p*-(chloroacetoxy)benzophenone:

$$C_6H_5OCOC_6H_5 + ClCH_2COCl = C_6H_5COC_6H_4OCOCH_2Cl + HCl.$$

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[2] Kindler and Peschke claim to have a convenient synthesis of sympathol from anisaldehyde.

p-Benzoyloxy-α-chloroacetophenone we prepared by benzoylating *p*-hydroxy-α-chloroacetophenone.

After repeating practically all the work embodied in the patents by Legerlotz, we found that one of the best methods of preparing sympathol was through the use of methylbenzylamine (6). Satisfactory yields were obtained by condensing *p*-benzoyloxy-α-chloroacetophenone with methylbenzylamine, hydrolyzing the *p*-benzoyloxy-α-methylbenzylaminoacetophenone with alcoholic hydrogen chloride, and reducing catalytically the *p*-hydroxy-α-methylbenzylaminoacetophenone to sympathol. Since *p*-benzoyloxy-α-chloroacetophenone was difficultly accessible, we attempted to replace it by *p*-benzyloxy-α-bromoacetophenone. We prepared this compound by the bromination of the benzyl ether of *p*-hydroxyacetophenone. Due, however, to the simultaneous formation of *p*-benzyloxy-α,α-dibromoacetophenone, $C_6H_5CH_2OC_6H_4COCHBr_2$, the isolation of the pure monobromo compound could be effected only with great difficulty, and with a poor yield. Far more easy to prepare, and with better yield, was the dibromo compound, which was readily formed from *p*-benzyloxyacetophenone and two moles of bromine. Treatment of *p*-benzyloxy-α-bromoacetophenone with methylbenzylamine yielded *p*-benzyloxy-α-methylbenzylaminoacetophenone.

While working on the bromination of the benzyl ether of *p*-hydroxyacetophenone, we became interested in studying the bromination of *p*-hydroxyacetophenone itself. We found that Nencki and Stoeber (7) had brominated *p*-hydroxyacetophenone and had obtained a dibromide, $C_8H_6Br_2O_2$, of unknown constitution. We have proved that the structure of this compound is 3,5-dibromo-4-hydroxyacetophenone, since oxidation of the methyl ether gave 3,5-dibromoanisic acid. By appropriate treatment with bromine, 3,5-dibromo-4-hydroxyacetophenone yielded 3,5-dibromo-4-hydroxy-α-bromoacetophenone and 3,5-dibromo-4-hydroxy-α,α-dibromoacetophenone, respectively. Similarly, the benzyl ether of 3,5-dibromo-4-hydroxyacetophenone could be converted into 3,5-dibromo-4-benzyloxy-α-bromoacetophenone and 3,5-dibromo-4-benzyloxy-α,α-dibromoacetophenone.

p-Benzyloxy-α-isonitrosoacetophenone was obtained in good yield by the Claisen condensation of *p*-benzyloxyacetophenone with two moles of sodium ethoxide and an excess of butyl nitrite. When hydrogen chloride was used as the catalyst, the only reaction-product isolated was a small amount of *p*-benzyloxybenzoic acid. This same product was also obtained by treatment of *p*-benzyloxy-α,α-dibromoacetophenone with alkali. A small amount of dibenzyloxybenzoic acid as a by-product was obtained by the action of sodium ethoxide and butyl nitrite on 3,4-dibenzyloxyacetophenone and 3,4-dibenzyloxypropiophenone. Catalytic reduction of

p-benzyloxy-α-isonitrosoacetophenone by Hartung's method (8) gave *p*-benzyloxy-α-aminoacetophenone.

EXPERIMENTAL

Condensation of phenyl benzoate with chloroacetyl chloride. When 10 g. of phenyl benzoate, 5.6 g. of chloroacetyl chloride, and 0.8 g. of phosphorus oxychloride were refluxed with 15 cc. of benzene for 45 hours, the phenyl benzoate was isolated from the mixture in practically quantitative yield. A similar full recovery of the phenyl benzoate was obtained by heating for 6 hours 19.8 g. of phenyl benzoate, 11.2 g. of chloroacetyl chloride, and 20 g. of aluminum chloride, in 50 cc. of carbon disulfide. Repeating the latter experiment, but without the carbon disulfide, a slight evolution of hydrogen chloride was observed at 80–95°. After about an hour, the temperature was raised to 120°, and the reaction was allowed to proceed at this temperature for another two hours. The contents could be removed only by breaking the flask. The reaction-mass was powdered in a mortar and gradually introduced into 300 cc. of a water-ice mixture. On the addition of ether, about a gram of crystalline substance, m.p. 120–123°, separated. The ether extract was dried over anhydrous sodium sulfate, and the ether evaporated. A gum was obtained, which, when seeded with the crystalline substance, crystallized. The mass was stirred up with 75 cc. of alcohol, filtered, and crystallized from 75 cc. of alcohol, with the addition of 3 g. of activated charcoal. The yield of *p*-(chloroacetoxy)benzophenone was 4.0 g., m.p. 123°.

Anal. Calc'd for $C_{15}H_{11}ClO_3$: Cl, 12.93. Found: Cl, 12.92.

For hydrolysis, 10 cc. of fuming hydrochloric acid and 0.8 g. of the substance were kept together at room temperature for several days. Sixty cubic centimeters of water was added, and the mixture distilled with steam until a liter of distillate was collected. No benzoic acid was found in the distillate. The contents of the distilling-flask (about 250 cc.) was twice filtered hot from the tar. On cooling, 0.08 g. of needles, m.p. 128–130°, separated. The filtrate was evaporated to about 50 cc., and a second crop of crystals, 0.08 g., m.p. 130–132°, was obtained. The melting point of *p*-hydroxybenzophenone is recorded in the literature (9) as 134°. The two crops of crystals were mixed and analyzed.

Anal. Calc'd for $C_{13}H_{10}O_2$: C, 78.70; H, 5.05.
Found: C, 78.53; H, 5.06.

p-Benzoyloxy-α-chloroacetophenone (obtained from *p*-hydroxy-α-chloroacetophenone, benzoic acid, and phosphorus oxychloride in benzene solution) melted at 115°.

p-*Benzyloxyacetophenone* (I). Metallic sodium, 2.3 g., was dissolved in 45 cc. of absolute alcohol, and 13.6 g. of *p*-hydroxyacetophenone and 15.0 g. of benzyl chloride were added. The mixture was boiled under reflux for 5 hours. The alcohol was then distilled off, the sodium chloride dissolved in hot water, and the solid residue crystallized from 100 cc. of 95% alcohol. The yield was 19 g. of substance, m.p. 93°.

Anal. Calc'd for $C_{15}H_{14}O_2$: C, 79.64; H, 6.19.
Found: C, 79.82; H, 6.50.

The *o*-benzyloxyacetophenone was prepared in the same manner, and melted at 40°.

p-*Benzyloxy-α-bromoacetophenone* (II). One gram of (I) in 10 cc. of chloroform was treated with 0.7 g. of bromine dissolved in 5 cc. of chloroform. After about 15 minutes, the reaction was complete. An intermediate insoluble addition-product with hydrogen bromide appeared, which redissolved upon shaking the solution. The

chloroform was removed under reduced pressure. The solid residue was washed with a little alcohol and recrystallized several times from 95% alcohol. The substance, 0.10 g., melted at 91°.

Anal. Calc'd for $C_{15}H_{13}BrO_2$: Br, 26.2. Found: Br, 26.8.

p-*Benzyloxy-α, α-dibromoacetophenone* (III). One gram of (I) in 15 cc. of chloroform was treated with 1.5 g. of bromine dissolved in 5 cc. of chloroform. After an hour, the chloroform was removed under reduced pressure. The solid residue (1.07 g., m.p. 82°) was washed with a little alcohol and crystallized from 95% alcohol. The yield was 0.25 g., m.p. 84°.

Anal. Calc'd for $C_{15}H_{12}Br_2O_2$: Br, 41.6. Found: Br, 41.6.

p-*Benzyloxy-α-methylbenzylaminoacetophenone* (IV). A solution of 10.5 g. of (II) in 25 cc. of absolute alcohol was treated with 8.6 g. of methylbenzylamine. The solution became hot. It was cooled and set aside. After 3 hours, a precipitate had separated. The next day, the alcohol was removed under reduced pressure. To the residue was added 150 cc. of water and 150 cc. of ether, and the two solutions were separated. On evaporation of the water solution, pure methylbenzylamine hydrobromide was obtained.

Anal. Calc'd for $C_8H_{12}BrN$: N, 6.93; Br, 39.56.
Found: N, 7.00; Br, 39.52.

The ethereal solution containing the *p*-benzyloxy-α-methylbenzylaminoacetophenone was shaken up in a separatory funnel with 100 cc. of 3% hydrochloric acid. The hydrochloride of the base precipitated out in the form of an oil. It was dissolved in chloroform, the solution dried over anhydrous sodium sulfate, and the chloroform distilled under reduced pressure. The *p*-benzyloxy-α-methylbenzylaminoacetophenone hydrochloride left behind was dried *in vacuo* but did not crystallize. It was obtained in the form of a glassy mass, which immediately liquefied on exposure to air. For conversion into the base, the hydrochloride was dissolved in a little acetone and treated with a concentrated solution of potassium carbonate. The free base was extracted with ether, the ethereal solution dried with anhydrous sodium sulfate, and the ether distilled. The *p*-benzyloxy-α-methylbenzylaminoacetophenone was obtained in the form of a gum.

Anal. Calc'd for $C_{23}H_{23}NO_2$: N, 4.07. Found: N, 4.02.

That this compound was actually *p*-benzyloxy-α-methylbenzylaminoacetophenone was proved by the formation of sympathol on catalytic reduction and by the fact that it closely resembled in physical properties *p*-benzoyloxy-α-methylbenzylaminoacetophenone, which we had previously prepared a number of times, but which we likewise could not obtain in crystalline form, although Legerlotz (6) claims the substance melts at 96°.

3,5-Dibromo-4-hydroxyacetophenone (V). To a solution of 6.0 g. of *p*-hydroxyacetophenone in 30 cc. of glacial acetic acid, 85 cc. of water was added. A solution of 14.0 g. of bromine in 30 cc. of 80% acetic acid was then gradually added, with efficient stirring. After standing for several hours, the precipitate was filtered and dried on the steam-bath. The yield was 12.2 g., m.p. 178°. The substance, after two recrystallizations from benzene, melted at 181°.

Anal. Calc'd for $C_8H_6Br_2O_2$: Br, 54.3. Found: Br, 54.6.

The *phenylhydrazone* melted at 147°.

Anal. Calc'd for $C_{14}H_{12}Br_2N_2O$: N, 7.3. Found: N, 7.3.

3,5-Dibromo-4-methoxyacetophenone (VI). This compound, which melted at 78°, was prepared from (V) by treatment with dimethyl sulfate and sodium hydroxide. For oxidation to 3,5-dibromo-4-methoxybenzoic acid, 3.0 g. of the ether was suspended in 200 cc. of concentrated nitric acid diluted with 300 cc. of water, and the

mixture warmed on the water-bath for 14 hours. The solid was filtered from the cold solution, then dissolved in sodium carbonate, and the filtered solution acidified with hydrochloric acid. After crystallization from 50% alcohol, the 3,5-dibromo-4-methoxybenzoic acid melted at 213°. The melting point was not depressed by the addition of a pure sample of 3,5-dibromo-4-methoxybenzoic acid, m.p. 213°, obtained by bromination of anisic acid.

3,5-Dibromo-4-benzyloxyacetophenone (VII), m.p. 79°, was prepared from (V) and benzyl bromide, in a manner similar to that described for (I).

Anal. Calc'd for $C_{15}H_{12}Br_2O_2$: Br, 41.6. Found: Br, 42.3.

3,5-Dibromo-4-benzyloxy-α-bromoacetophenone (VIII). To a solution of 0.5 g. of (VII) in 5 cc. of chloroform was added 0.208 g. of bromine in 5 cc. of chloroform. Decolorization took place in about an hour. The chloroform solution precipitated some crystals, apparently a molecular addition-compound with hydrogen bromide. On spontaneous evaporation of the chloroform solution, large plates were obtained. After 3 recrystallizations from alcohol, the compound was obtained in the form of needles, m.p. 119°.

Anal. Calc'd for $C_{15}H_{11}Br_3O_2$: Br, 51.8. Found: Br, 52.6.

3,5-Dibromo-4-benzyloxy-α,α-dibromoacetophenone (IX), m.p. 104°, was prepared as was (VIII), using double the amount of bromine. The substance was very prone to form supersaturated solutions, so that scratching with a glass rod was necessary to cause precipitation from solution. This behavior is exactly like that of *p*-benzyloxy-α,α-dibromoacetophenone.

Anal. Calc'd for $C_{15}H_{10}Br_4O_2$: Br, 59.09. Found: Br, 59.06.

3,5-Dibromo-4-hydroxy-α-bromoacetophenone (X). To one gram of (V) in 30 cc. of warm chloroform was added 0.5 g. of bromine in 5 cc. of chloroform. After 30 minutes, the chloroform was allowed to evaporate spontaneously. The residue was washed with a little benzene and crystallized from 10 cc. of benzene. The substance melted at 128°. The bromination was also carried out in glacial acetic acid, and the same product was obtained.

Anal. Calc'd for $C_8H_5Br_3O_2$: Br, 64.0. Found: Br, 64.13.

3,5-Dibromo-4-hydroxy-α,α-dibromoacetophenone, (XI), m.p. 105°, was prepared as was (X), using twice the amount of bromine.

Anal. Calc'd for $C_8H_4Br_4O_2$: Br, 70.8. Found: Br, 70.16.

p-Benzyloxy-α-isonitrosoacetophenone (XII). In preparing the isonitroso ketones, care is taken to employ exactly one mole of sodium ethoxide and one mole of butyl nitrite for one mole of ketone. We have found, however, that the reaction was much quicker, and a better yield was obtained by using twice the amount of sodium ethoxide recommended. An excess of butyl nitrite likewise did not hurt the reaction. The sodium salt was not subjected to further action of the butyl nitrite because it was removed from the reaction by precipitation.

Sodium, 0.8 g., was dissolved in 20 cc. of absolute alcohol. To this was added 30 cc. of benzene, and then 4.0 g. of *p*-benzyloxyacetophenone. A clear solution resulted. Four grams of butyl nitrite was added, the bottle was tightly stoppered, and set aside for 48 hours. The sodium salt was filtered, washed with a little alcohol, then with benzene, and dried. It weighed 3.7 g. The sodium salt was suspended in water and decomposed with dilute hydrochloric acid, by rubbing the salt in a mortar until no pink particles remained. The isonitroso ketone, after crystallization from alcohol or benzene, melted at 149°.

Anal. Calc'd for $C_{15}H_{13}NO_3$: C, 70.58; H, 5.13; N, 5.49.
Found: C, 70.46; H, 5.20; N, 5.49.

p-*Benzyloxy-α-aminoacetophenone* (XIII). To a suspension of 1.0 g. of (XII) in

10 cc. of absolute alcohol was added 4.3 cc. of a solution of 10% hydrogen chloride in absolute alcohol, and 0.5 g. of 5% palladium-charcoal catalyst. In 20 minutes, two moles of hydrogen had been absorbed (190 cc.), and further shaking with hydrogen resulted in no additional reduction. The solution was filtered, and since from the filtrate only a very small amount (10 mg.) of reduced product was recovered, it was evident that the substance had precipitated from the solution, and was mixed with the catalyst. The charcoal was therefore extracted three times with 75 cc. of hot water. After concentrating the aqueous solution under reduced pressure to a volume of 30 cc., 0.75 g. of *p*-benzyloxy-α-aminoacetophenone hydrochloride, m.p. 226°, was obtained.

Anal. Calc'd for $C_{15}H_{16}ClNO_2$: N, 5.04. Found: N, 5.05.

p-*Benzyloxybenzoic acid from* p-*benzyloxyacetophenone.* A solution of 5.0 g. of *p*-benzyloxyacetophenone in 40 cc. of benzene was treated with 2.3 g. of freshly distilled butyl nitrite dissolved in 12 cc. of benzene. A current of dry hydrogen chloride was passed into the solution for 30 minutes. The solution was then set aside until the next day. After removal of the benzene under reduced pressure, a gum was obtained. Dilute alkali was added, and the resulting crystalline mass was filtered. The material on the filter was identified as unchanged *p*-benzyloxyacetophenone. The filtrate was acidified with dilute hydrochloric acid. The crude material weighed 0.65 g. It was crystallized from 25 cc. of 95% alcohol, and then melted at 187°.

Anal. Calc'd for $C_{14}H_{12}O_3$: C, 73.68; H, 5.30.
Found: C, 73.59; H, 5.42.

The substance was therefore *p*-benzyloxybenzoic acid (10). On treatment of (III) with alcoholic potassium hydroxide, a small amount of *p*-benzyloxybenzoic acid was also obtained.

3,4-Dibenzyloxybenzoic acid from 3,4-dibenzyloxypropiophenone and 3,4-dibenzyloxyacetophenone. In this experiment, one mole of sodium ethoxide and one mole of butyl nitrite were used for every mole of 3,4-dibenzyloxypropiophenone. To a sodium ethoxide solution prepared by dissolving 0.17 g. of sodium in 10 cc. of absolute alcohol, was added 1.3 g. of 3,4-dibenzyloxypropiophenone, and a solution of 0.4 g. of butyl nitrite in 5 cc. of benzene. The flask was stoppered and set aside for 24 hours. The precipitate was filtered, washed with benzene, and decomposed with dilute acetic acid. Only 0.04 g. of substance, m.p. 177°, was obtained by decomposing the precipitated sodium salt. This represented crude 3,4-dibenzyloxybenzoic acid, the sodium salt of which was rather soluble in the alcohol-benzene mixture. The solvent was allowed to evaporate spontaneously from the filtrate. The residue was taken up in water and ether. On acidifying the aqueous solution, 0.25 g. of a solid, m.p. 165°, was obtained. This was crystallized from 10 cc. of 95% alcohol, and yielded 0.11 g. of substance, m.p. 182°.

Anal. Calc'd for $C_{21}H_{18}O_4$: C, 75.5; H, 5.42.
Found: C, 75.5; H, 5.35.

3,4-Dibenzyloxyacetophenone, m.p. 98°, when treated with butyl nitrite and sodium ethoxide as condensing agent, also gave a small amount of 3,4-dibenzyloxybenzoic acid, m.p. 182°.

SUMMARY

The condensation reaction between phenyl benzoate and chloroacetyl chloride, in the presence of aluminum chloride, was studied. A number of new intermediates, useful in the synthesis of sympathol and related amino alcohols, have been prepared.

Moscow, U. S. S. R.

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(8) HARTUNG, *J. Am. Chem. Soc.*, **53,** 2248 (1931).
(9) BEILSTEIN, 4th Ed., Vol. VIII, p. 158.
(10) BEILSTEIN, 4th Ed., Supplement, Vol. X, p. 70.

[CONTRIBUTION FROM THE GEORGE HERBERT JONES LABORATORY, THE UNIVERSITY OF CHICAGO]

THE REACTION OF SODIUM IN LIQUID AMMONIA WITH ESTERS[1]

M. S. KHARASCH, E. STERNFELD, AND F. R. MAYO

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INTRODUCTION

The first thorough work on the reactions of sodium with organic esters was done by Bouveault and Locquin (1). They reported that two molecules of an aliphatic ester in benzene or ether solution at temperatures below 10° condensed to form the corresponding acyloins. Small amounts of diketones were also found as products, and these were assumed to have been formed by atmospheric oxidation of the acyloins. These investigators reported that they encountered difficulty in obtaining a good yield of acetoin from ethyl acetate, though the higher esters all gave better than 50% yields of the acyloins. This apparently anomalous behavior of ethyl acetate was ascribed to the reactivity of acetoin and its destruction during hydrolysis and subsequent operations. As a matter of fact, when the sodium compound first formed with ethyl acetate was acetylated, and then the ordinary procedures carried out, acetoin mono- and di- acetates were obtained without any difficulty. The schematic representation of the reaction was written as follows:

$$2\mathrm{RC(=O)OEt} + 4\mathrm{Na} \longrightarrow \underset{\mathrm{RCONa}}{\overset{\mathrm{RCONa}}{\|}} + 2\mathrm{NaOEt}$$

VI

Wahl (2) obtained a small yield of benzoin by allowing two moles of sodium to react for three days with one mole of ethyl benzoate in ether solution. If the reaction-mixture stood for three months the yield of benzoin was increased to 14%. Of the other products of the reaction, only benzoic acid was identified.

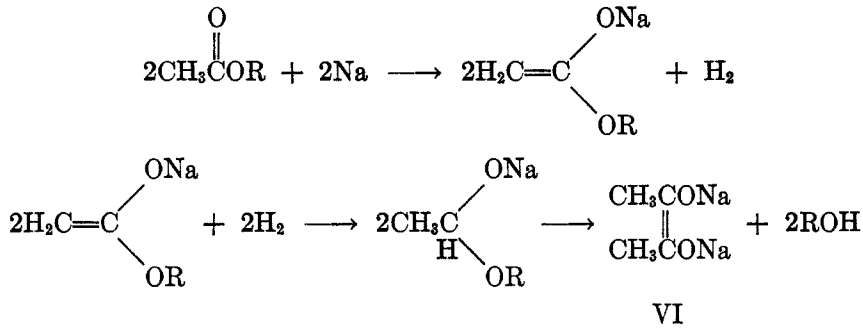
Tingle and Gorsline (3) in the same year carried out a series of experi-

[1] Presented at a Symposium on the Chemistry of Liquid Ammonia Solutions at the Milwaukee Meeting of the American Chemical Society, September, 1938. A preliminary note appeared in the *J. Am. Chem. Soc.*, **61**, 215 (1939).

ments with ethyl benzoate and sodium in ether and in petroleum ether. They found large amounts of benzoic acid and only traces of benzoin.

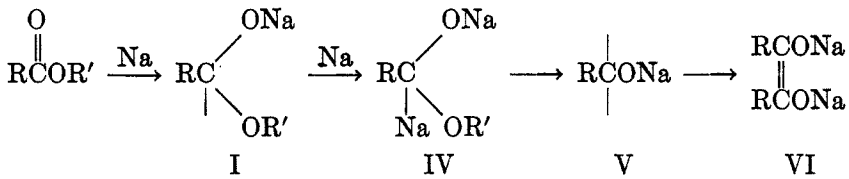
Chablay (4) treated acetic, butyric, isovaleric, and caproic esters in liquid ammonia with sodium, expecting either the acetoacetic ester or acyloin condensation to take place. He states that ethyl acetate gave acetoacetic ester, whereas the other esters yielded only the corresponding alcohols and amides.

Scheibler and Voss (5) proposed a mechanism for the acyloin condensation which involves the formation of an ester enolate and its subsequent reduction by the hydrogen liberated in the reaction. The reactions were written as follows:



VI

The difficulty with this mechanism lies in its inability to include in the reaction scheme non-enolizable esters such as ethyl trimethylacetate. This was recognized by Scheibler, and he proposed a special mechanism for non-enolizable esters (6).

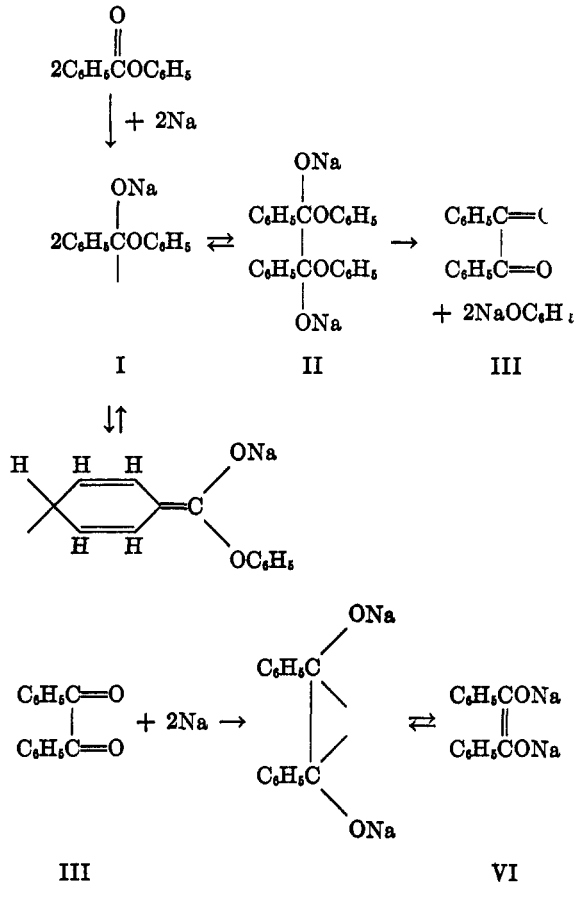


I IV V VI

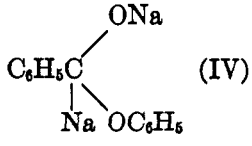
There is little evidence to support Scheibler's formulation of the reactions of the enolizable esters. If hydrogen is formed in the reaction, at least a portion would be expected to escape, and this is contrary to observation. The second mechanism in some aspects is similar to the one favored by us and described in this paper.

Blicke (7) observed the formation of a red color and a flocculent precipitate when either one or two atoms of sodium were used with one mole of phenyl benzoate in ether. He isolated phenol and benzoic acid and deduced the presence of benzoin by qualitative tests, but did not isolate

either benzil or benzoin. The following equations were proposed for the reaction:

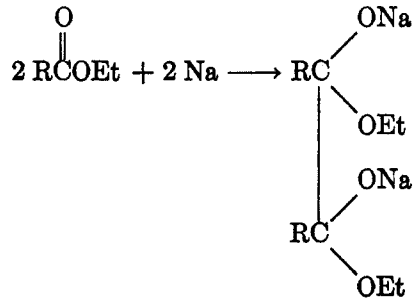


The existence of a free radical was postulated from the color of the products for either free radical could be written with a quinoid form. Blicke recognized that benzil was not necessarily an intermediate in the reduction of esters to acyloins, but that phenyl benzoate and two equivalents of sodium might give



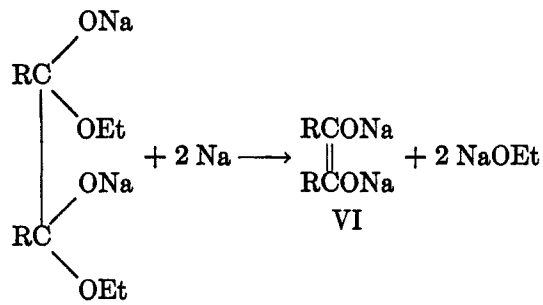
directly, and that this compound would then give the sodium derivative of benzoin.

More recent work by Snell and McElvain (8) on aliphatic esters has shown that the reaction-mixtures in ether or benzene need not be kept below 10° during the reaction as recommended by Bouveault and Locquin. Thus, by heating the mixtures to the boiling point of the solvent throughout the reaction, they were able to isolate over 50% yields of the acyloins, except with ethyl acetate, where the yield was only 23%. Trimethylacetic ester gave 32% of the diketone, the other esters yielding less than 10%. The reaction was thought to take place in two steps: (A) The ester reacts with one mole of sodium to form the diketone-sodium ethoxide addition-product:



II

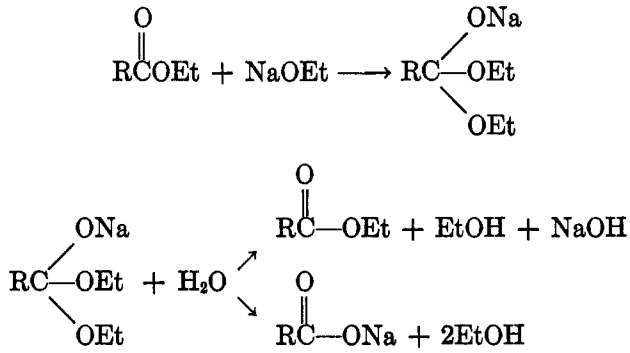
(B) The diketone-sodium ethoxide addition-product is then converted by two atoms of sodium to the acyloin:



II

The authors suggested that the diketone-sodium ethoxide addition-product might result from the union of two free radicals as postulated by Blicke

(7). They explain the formation of acids by the reactions previously proposed by Scheibler and Marhenkel (9).



Evidence for this mechanism was obtained by treating ethyl butyrate with sodium ethoxide. Upon hydrolysis, the mixture yielded nearly 50% butyric acid.

DISCUSSION

It seemed that further work on the reactions of liquid ammonia sodium solutions with esters would prove profitable, in that such a solution gives the ester an opportunity to react rapidly and completely with the sodium. Furthermore, the primary reaction is known to be over upon the disappearance of the characteristic blue color of the solution. Ethyl acetate, propionate, isobutyrate, trimethylacetate, phenylacetate, diphenylacetate, and benzoate were allowed to react with either one or two moles of sodium in liquid ammonia. The following general observations were made during the course of the reactions: (a) Only half a mole of ester was required to discharge the color of one mole of sodium if the ester was added to the liquid ammonia solution of sodium. (b) No hydrogen gas was evolved when any of the esters reacted with either one or two moles of sodium nor was there any evolution of hydrogen gas when the reaction-mixtures were treated with ammonium bromide, regardless of the presence or absence of benzene as solvent for the ester. These facts imply that the carbonyl group of the ester is directly attacked, without a preliminary enolization. The products of the various reactions are summarized in Table I. The Table shows that in some instances reduction of ester to alcohol takes place to a considerable extent. In these experiments, however, roughly equivalent quantities of acid and amide are also formed. This is in agreement with our statement that only 0.50 ($\pm$ .05) mole of ester per mole of sodium is required to discharge the color of a sodium solution. If direct reduction of ester to alcohol were possible, only one-fourth mole of ester would be

TABLE I

REACTION OF SODIUM WITH ESTERS

ESTER	ATOMS SODIUM/MOLE ESTER	OTHER REAGENTS	YIELDS[a] OF IDENTIFIED PRODUCTS			
			Acyloin	Diketone	Aldehyde	Other products
Acetic	2		25%			8% β-Aminocrotonic ester 25% Acetic acid
Acetic	2	Acetyl chloride				83% Acetoin diacetate
Acetic	1			Trace		
Propionic	2		22%			24% Propyl alcohol 10% Propionamide 30% Propionic acid
Propionic	1			18%		46% Propionic acid 12% Propionamide
Isobutyric	2		12%		30%	10% Isobutyl alcohol 25% Isobutyric acid 8% Isobutyramide
Isobutyric	2	Ethyl bromide	28%			32% Ethyl isopropyl ketone
Trimethylacetic	2		29%		35%	15% t-Butyl carbinol 6% Trimethylacetic acid 10% Trimethylacetamide
Trimethylacetic	2	Ethyl bromide	22%			33% Ethyl t-butyl ketone
Phenylacetic	2				7%	27% Phenylethyl alcohol 31% Phenylacetamide
Diphenylacetic	2		11%			36% Diphenylethyl alcohol 18% Benzophenone 32% Diphenylacetic acid
Benzoic	2		14%		50%	9% Benzamide 12% Benzoic acid
Benzoic	2	Benzyl chloride	15%		30%	5% Desoxybenzoin 10% Isobenzamarone 8% Dibenzyl 15% Benzoic acid
Benzoic	2	Ethyl bromide	27%			34% Propiophenone
Benzoic	2	n-Butyl bromide	20%			30% Valerophenone
Benzoic	1			30%		28% Benzilic acid 25% Benzoic acid

[a] Based on ester used. In all cases there were unidentified substances, some of them tars.

required to react with one mole of sodium. Experiments with esters in the absence of sodium, but in the presence and absence of sodamide, show that the formation of amide is not due to ammonolysis of the ester. The formations of alcohol and amide are apparently related, and an obvious possibility is that both come from the disproportionation of an intermediate.

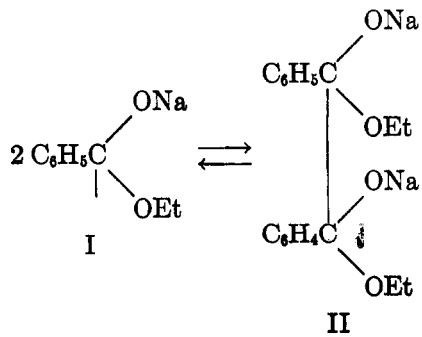
Reaction of esters with one equivalent of sodium. An attempt to obtain diacetyl by reacting ethyl acetate with one equivalent of sodium was partially successful in that a product was obtained which boiled at 78–95° and gave the characteristic green ring test with thiophene-containing benzene and concentrated sulfuric acid. The diketone itself, however, was not isolated. In one experiment a few milligrams of yellow needles which resembled dimethylquinone (from the condensation of two molecules of diacetyl) were obtained, but these were contaminated with a nitrogenous impurity which rendered their analysis worthless.

Experiments with ethyl propionate were more successful in yielding diketones. Dipropionyl was distilled with steam and identified by means of its 2,4-dinitrophenylhydrazone.

When ethyl benzoate was treated with one equivalent of sodium in liquid ammonia a deep red-purple color developed. Hydrolysis of the mixture yielded either benzil or a mixture of benzil and benzilic acid, depending upon the treatment of the reaction-mixture.

It seemed probable that the monosodium ethyl benzoate compound can exist as a free radical in equilibrium with its dimer, similar to the metal ketyls. Some evidence for this hypothesis was obtained when oxygen was passed through the ammonia solution of monosodium ethyl benzoate. The color of the solution was black at first, then brown. Benzoic acid was the only product that was isolated, although an effort was made to obtain other products. The non-crystallizable material was a tar which exploded upon heating, indicating that peroxides may have been formed from free radicals in solution.

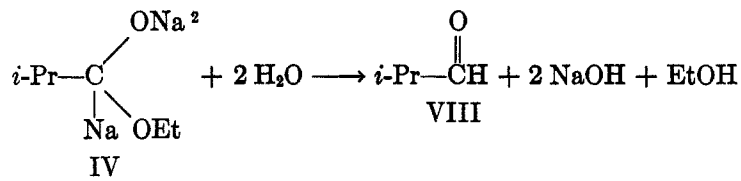
Benzil was added to two equivalents of sodium ethoxide in liquid ammonia to test the reversibility of the reaction:



A purple color developed which could be instantly discharged by neutralizing the solution with ammonium bromide. This suggests that the sodium ethoxide addition-product of benzil may dissociate into free radicals in much the same way as the sodium salt of benzpinacol, although the concentration of free radicals is probably small.

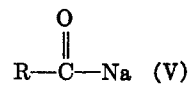
Reaction of esters with two equivalents of sodium. In accordance with previous investigations, it was found difficult to obtain clear-cut results from the reduction of ethyl acetate with two atoms of sodium. Attempts to isolate pure acetoin resulted in low yields, but acetoin diacetate was formed in good yield if, upon evaporation of the ammonia, but before hydrolysis, the sodium compound was treated with acetyl chloride. The formation of pure acetoacetic ester claimed by Chablay as a result of the reaction of ethyl acetate with sodium in liquid ammonia has not been substantiated. We obtained, instead, a small amount of β-aminocrotonic ester. This product was formed by a Claisen condensation of two molecules of ethyl acetate and subsequent ammonolysis of the product by the solvent, as shown by the fact that acetoacetic ester, when dissolved in liquid ammonia, gave better than an 80% yield of the amino ester. Ethyl propionate behaved like ethyl acetate except that it gave no evidence of a Claisen condensation under the conditions used; the same was true of the other esters investigated by us.

Ethyl isobutyrate differed from ethyl acetate and ethyl propionate in that its sodium derivative was spontaneously inflammable in air; this suggested that the compound had a structure involving a sodium-to-carbon linkage according to the classical formulation (IV).[2] Further support for this formula was obtained by hydrolysis of the inflammable substance to isobutyraldehyde.



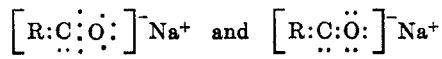
IV VIII

[2] Throughout this paper, as in this case, such formulas will be written as though the sodium ethoxide were an integral part of the molecule, though there is no evidence to show whether the sodium ethoxide is free or associated with the reduced ester. If the sodium ethoxide is not an integral part of the molecule then the structure

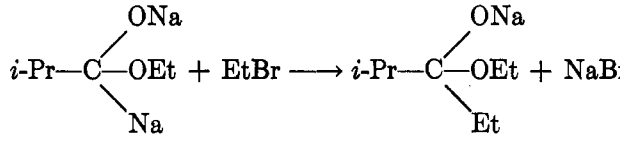


(V)

is more elegantly represented as a resonance hybrid of the following forms



Formulation of the reaction of esters and sodium to give compounds of types IV or V has been postulated previously. Additional evidence of the existence of such compounds was obtained by treating the intermediate with ethyl bromide, and isolating ethyl isopropyl ketone from the reaction-mixture:



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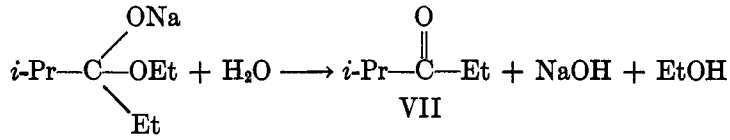
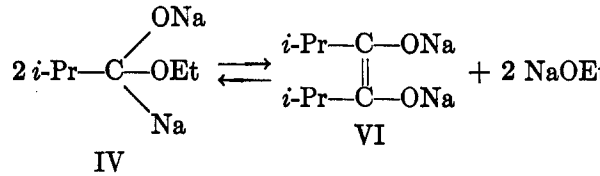


VII

The simultaneous presence of isobutyraldehyde and isobutyroin, obtained as such and as the diacetate upon hydrolysis, suggests an equilibrium of the type given below:



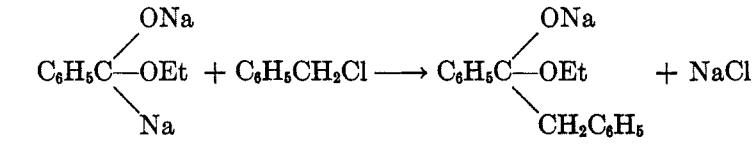
IV VI

Similar observations were made with trimethylacetic ester. Some aldehyde was obtained from ethyl phenylacetate by treatment with sodium in liquid ammonia. The corresponding acyloin, however, could not be isolated, though the high-boiling fraction, obtained as a syrup, reduced Fehling's solution in the cold. This reaction, however, may have been due to an aldehyde polymer.

Diphenylacetic ester with two equivalents of sodium gave a strong yellow color, deeper than the yellow from ethyl isobutyrate or phenylacetate. Instead of yielding diphenylacetaldehyde it gave benzophenone and a greater proportion of alcohol (diphenylethanol in this case) than any of the other esters. Further work would be necessary to determine the mode of formation of benzophenone.

Striking results were obtained with ethyl benzoate and sodium in liquid ammonia. When the ester was treated with two equivalents of sodium a deep red solution resulted which resembled in color a solution of triphenylmethylsodium in liquid ammonia. Upon evaporation of the ammonia and hydrolysis of the red solid, benzaldehyde was obtained in good yield. Treatment of the red solution with benzyl chloride gave desoxybenzoin

and isobenzamarone. This indicates a sodium-to-carbon linkage analogous to that in triphenylmethylsodium.



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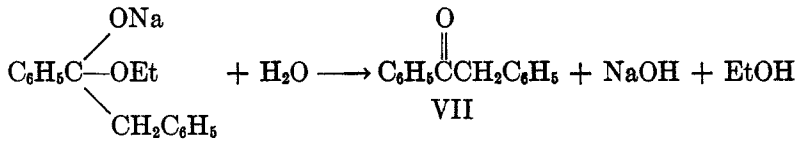
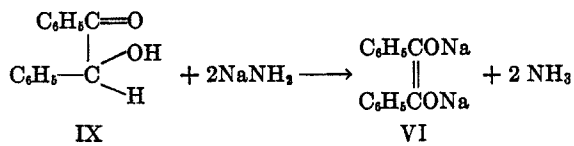


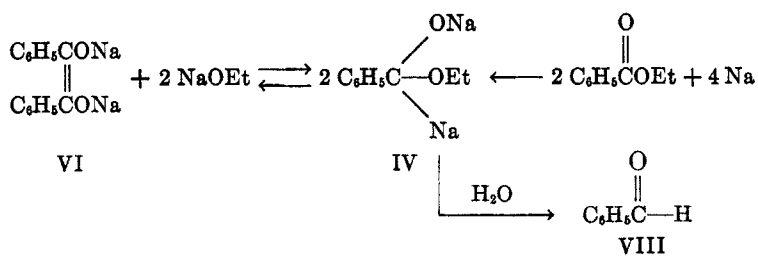
VII

Isobenzamarone is formed by the reaction of benzaldehyde and desoxybenzoin (10). Further indication of the structure of the sodium ethyl benzoate compound is furnished by the formation of propiophenone and valerophenone by treatment of the red solution with ethyl bromide and *n*-butyl bromide respectively. The reactions are similar to the one in which benzyl chloride is involved.

That the sodium compound (IV or V) is presumably in equilibrium with the sodium salt of benzoin (VI) and sodium ethoxide is indicated by the following reactions. A red solution resulted when benzoin, suspended in liquid ammonia, was treated with sodium ethoxide and sodamide. The color was similar to that obtained from sodium and ethyl benzoate in liquid ammonia, but less intense. Upon hydrolysis of the reaction-mixture, benzaldehyde was obtained, and upon addition of ethyl bromide and subsequent hydrolysis, propiophenone. These reactions indicate the identity of this red solution with that obtained from two moles of sodium and ethyl benzoate. The lower yield of aldehyde and less intense color when starting with benzoin may be due in part to differences in the state of suspension or solution of the reactants.

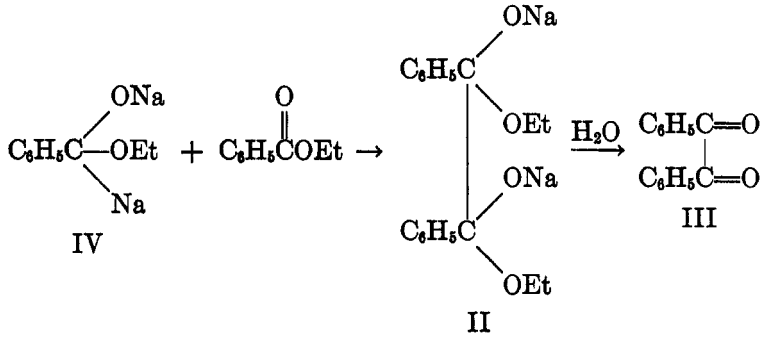


IX VI



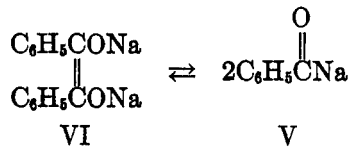
VI IV VIII

We have been unable to secure evidence that diketones can be formed by the following sequence of reactions since the disodium ethyl benzoate compound in liquid ammonia did not yield a diketone when treated with ethyl benzoate[2]:



When the reaction-mixtures were allowed to stand for a short time little reaction took place. On longer standing, tars were obtained.

It seems appropriate at this point to discuss what relation the compounds formed by the action of sodium on ethyl benzoate bear to those obtained from benzil and sodium or potassium. Staudinger and Binkert (11) claim that the red compound from benzil and two atoms of potassium is the dipotassium salt of stilbenediol, in spite of the fact that the esters and ethers of stilbenediol are colorless. Their reason is that the ultraviolet absorption of salts of phenols and enols is much stronger and of a different type than that of the ethers and esters. These investigators did not consider the possibility of an equilibrium of the salts of the stilbenediol with benzoylsodium:



That such an equilibrium actually exists has been demonstrated by treating the reaction-product of benzil and sodium (the so-called stilbenediol salt) with ethyl bromide. Propiophenone in good yield was isolated from the reaction-mixture. It is conceivable, therefore, that the color of the compound is not due to the salts of the stilbenediol *per se* but rather to its equilibrium partners.

The series of reactions which occurs when sodium reacts with esters is, in our opinion, best summarized by the scheme depicted in Figure I. As

indicated in the literature review, all of the compounds in Figure I have been isolated or suggested by previous workers. Our work presents better evidence for the existence of the free radical (I) and the "sodium-to-carbon" compound (IV) or (V). It indicates strongly the existence of

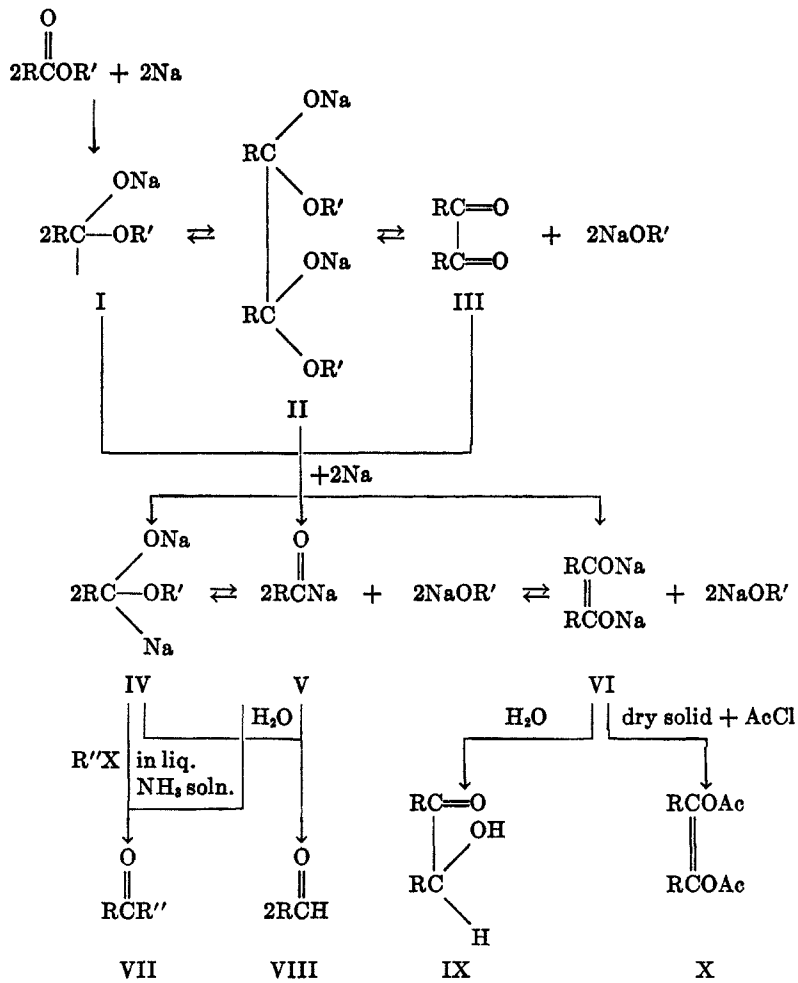


FIGURE I.—The reaction of sodium with esters

one equilibrium between (I), (II), and (III) and another between (IV), (V), and (VI). We have also shown that liquid ammonia is a convenient solvent for study of the indicated reactions because they take place very rapidly in a homogeneous solution at low temperature.

EXPERIMENTAL PART

Procedure I. Reaction of esters with two equivalents of sodium. The sodium was dissolved in 100–500 g. of liquid ammonia contained in a clear glass Dewar flask equipped with a stirrer, dropping-funnel, and escape valve. The ester, in pure form or in dry benzene solution, was then added to the ammonia solution drop by drop until the blue color of the sodium was entirely discharged. The reaction was very vigorous at first, more so with ethyl isobutyrate, trimethylacetate, and benzoate than with ethyl acetate or propionate, but abated in violence as the sodium was consumed. The mixture was then forced over into a filter flask under its own pressure and the liquid ammonia evaporated by suction. Ice and water were added along with an organic solvent, either benzene or ether. The hydrolyzed mixture was separated into aqueous and organic portions, the aqueous solution extracted rapidly with three or four successive portions of benzene or ether, acidified, and again extracted thoroughly. In a number of experiments this procedure was reversed, the original mixture being hydrolyzed with sulfuric or acetic acid and then made basic for the extraction of nitrogenous compounds. No significant difference in the results was noted. The basic and acidic organic solutions were washed twice with a saturated salt solution, then dried over anhydrous sodium sulfate and distilled.

Procedure II. Reaction of esters with one equivalent of sodium. The liquid ammonia solution of sodium prepared as above was forced under its own pressure into a previously cooled round-bottomed flask containing the ester and equipped with an escape valve and stirrer. The ester could not be added to the sodium solution directly, as all the sodium would react when only half the ester had been added. The reaction-mixture was then evaporated and treated as above.

Reaction of ethyl acetate with sodium. When treated according to Procedure I (2 equivalents of sodium), 9 g. of ethyl acetate gave 1.2 g. of acetoin, b.p. 147–153°, identified as the phenylhydrazone, m.p. 82–84° (12).

Anal. Calc'd for $C_{10}H_{14}N_2O$: N, 15.73. Found: N, 15.51.

β-Aminocrotonic ester, b.p. 103° at 15 mm., was identified as the copper salt, m.p. 182°. Evaporation of the basic water solution and acidification yielded 1.5 g. of acetic acid, b.p. 118°.

To obtain the acetoin diacetate, the dry solid left from the sodium-ester reaction after evaporation of the ammonia *in vacuo*, was treated with a slight excess of acetyl chloride in benzene with strong cooling. The sodium chloride was collected and washed several times with benzene. The filtrate and washings were combined and distilled. Nineteen grams of ethyl acetate yielded 14 g. of acetoin diacetate which boiled at 203°, and 3 g. of a liquid which boiled at 203–214°. A distinct odor of acetic acid suggested that some of the ester had decomposed, and treatment of a small portion of the lower-boiling liquid with semicarbazide gave the semicarbazone of acetoin monoacetate, m.p. 163–164°. The liquid was therefore redistilled *in vacuo*. Almost all of the product boiled at 103–105° at 20 mm.

Anal. Calc'd for $C_8H_{12}O_4$: C, 51.72; H, 6.89.
Found: C, 51.54; H, 6.63.

Acetyl determinations on this substance gave no conclusive results: short periods of hydrolysis with aqueous sodium hydroxide gave one acetyl group per molecule, whereas long periods of refluxing gave more than two, due to the decomposition of acetoin into acid products.

When ethyl acetate was treated with one equivalent of sodium as outlined in Procedure II, it gave mostly unidentified high-boiling products and tar. A portion

was subjected to distillation and the fraction of b.p. 78–95°, when mixed with thiophene-containing benzene and treated with concentrated sulfuric acid, gave the green ring test characteristic of diacetyl. Semicarbazide, phenylhydrazine, and 2,4-dinitrophenylhydrazine, however, all failed to yield any identifiable derivative. The lack of yellow color in the fraction itself showed that it was at most a very dilute solution of the diketone. Approximately 0.1 g. of yellow needles melting at 123–125° separated from the portion of the product not subjected to distillation. The color and melting point suggested that they might be 2,5-dimethylquinone (m.p. 124–125°) from condensation of diacetyl, but analysis showed that they contained 1–4% of nitrogen.

Reaction of ethyl propionate with sodium. Twenty grams of ethyl propionate was added to 9.2 g. (2 equivalents) of sodium in liquid ammonia as in Procedure I. The following products were isolated: 1.3 g. of propionamide, m.p. 76–78°, 3 g. of propyl alcohol, b.p. 97–100°; 4.5 g. of propionic acid, b.p. 129–135°; and 2.6 g. of propioin, b.p. 67–72° at 18 mm. This yielded a 2,4-dinitrophenylhydrazone which melted at 154°.

Anal. Calc'd for $C_{12}H_{16}N_4O_6$: N, 18.92. Found: N, 18.96.

Ten grams of ethyl propionate treated with one equivalent of sodium as in Procedure II yielded 8.5 g. of light yellow liquid, b.p. 85–110°. This wide fraction was collected because the yellow color began to appear when the temperature of the distilling vapors was as low as 85°. The distillate gave the green ring test for 1,2-diketones and precipitated the 2,4-dinitrophenylhydrazone of dipropionyl, m.p. 145–145.5°.

Anal. Calc'd for $C_{12}H_{14}N_4O_6$: N, 19.06. Found: N, 19.20.

The quantity of hydrazone which was isolated corresponded to a weight of 1.3 g. of dipropionyl in the original mixture.

Reaction of ethyl isobutyrate with sodium. Twelve grams of ethyl isobutyrate was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia as in Procedure I. Two grams of a liquid, b.p. 110–112°, was identified as isobutyl alcohol by its 3,5-dinitrobenzoate, m.p. 63–64°.

Anal. Calc'd for $C_{11}H_9N_2O_6$: N, 10.56. Found: N, 10.63.

From the acidified aqueous solution were extracted 3.7 g. of isobutyramide m.p. 128°, and 0.8 g. of isobutyric acid, identified as the ammonium salt, m.p. 118°.

Twelve grams of ethyl isobutyrate in 50 cc. of benzene was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia and treated as in Procedure I. The fraction boiling at 58–67° gave 2 g. of isobutyraldehyde, calculated from the weight of its 2,4-dinitrophenylhydrazone, m.p. 181°. One gram of isobutyl alcohol was collected at 109–112° and 1 g. of isobutyroin distilled at 80° (20 mm.). It was identified as the oxime, m.p. 109°.

Anal. Calc'd for $C_8H_{17}NO_2$: N, 8.50. Found: N, 8.63.

Twelve grams of ethyl isobutyrate was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia. To the resulting mixture was added 11 g. of ethyl bromide, and the reaction-mixture was worked up as in Procedure I. The fraction boiling at 116–118° (3 g.) was pure ethyl isopropyl ketone as indicated by the quantitative isolation of its 2,4-dinitrophenylhydrazone, which melted at 168–169°.

Anal. Calc'd for $C_{12}H_{18}N_4O_4$: N, 20.00. Found: N, 20.04.

Reaction of ethyl trimethylacetate with sodium. Thirteen grams of ethyl trimethylacetate was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia. After treatment as in Procedure I, the fraction of the distillate boiling up to 80° was treated with 2,4-dinitrophenylhydrazine, whereupon the 2,4-dinitrophenylhydra-

zone of trimethylacetaldehyde separated. The melting point after crystallization from ethyl alcohol was 210° (12).

Anal. Calc'd for $C_{11}H_{14}N_4O_4$: N, 21.13. Found: N, 20.96.

Of the remaining liquid, which had a marked camphor-like odor, 1.3 g. boiled at 110–114°, solidifying when cooled, and melting at 47°. It was identified as *t*-butyl carbinol. Two and one-half grams of pivaloin was obtained. It boiled at 92–103° (30 mm.), m.p. 77–80°. Approximately 1 g. of trimethylacetamide, m.p. 178°, remained in the distilling flask. From the aqueous layer upon acidification was obtained about 0.5 g. of trimethylacetic acid, m.p. 32–35°.

Eight grams of ethyl trimethylacetate was added to 3 g. (2 equivalents) of sodium in liquid ammonia, and 8 g. of ethyl bromide was added to the mixture. The mixture, upon hydrolysis, yielded 2.5 g. of ethyl *t*-butyl ketone, b.p. 120–126°. Further confirmation was obtained by the preparation of the 2,4-dinitrophenylhydrazone, m.p. 175°.

Anal. Calc'd for $C_{12}H_{18}N_4O_4$: N, 19.05. Found: N, 18.90.

Reaction of ethyl phenylacetate with sodium. Sixteen grams of ethyl phenylacetate was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia. The following products were isolated: 3 g. of β-phenylethyl alcohol b.p. 115–120° (25 mm.), identified as the phenylurethane, m.p. 80°; 4 g. of phenylacetamide, m.p. 155°, identified by its mercury salt, m.p. 205–207°; 0.8 g. of phenylacetaldehyde, identified as the 2,4-dinitrophenylhydrazone, m.p. 240° (13).

Anal. Calc'd for $C_{14}H_{12}N_4O_4$: N, 18.68. Found: N, 18.41.

Reaction of ethyl diphenylacetate with sodium. Seventeen grams of ethyl diphenylacetate was added to 3 g. (2 equivalents) of sodium in liquid ammonia. The mixture, upon hydrolysis, yielded 5.1 g. of 2,2-diphenylethanol, m.p. 64–65°, and 2.3 g. of benzophenone, b.p. 275–280°. The alcohol, upon analysis, gave the following results:

Anal. Calc'd for $C_{14}H_{14}O$: C, 84.85; H, 7.07.
Found: C, 84.92; H, 6.94.

It was further identified as the oxalate, m.p. 159.5–160° (14). The benzophenone was identified as the 2,4-dinitrophenylhydrazone, m.p. 238°.

Anal. Calc'd for $C_{19}H_{14}N_4O_4$: N, 15.47. Found: N, 15.48.

That portion of the organic layer which did not distill up to 310° was crystallized from methyl alcohol. A solid was obtained which melted at 100°. It reduced Fehling's solution upon heating for five minutes in boiling water, but failed to yield a hydrazone. Analysis suggests that the compound is tetraphenylacetoin. This compound is not described in the literature and no effort was made to characterize it further.

Anal. Calc'd for $C_{28}H_{24}O_2$: C, 85.74; H, 6.12.
Found: C, 86.02; H, 6.40.

From the basic water solution, upon acidification, 4.4 g. of diphenylacetic acid, m.p. 146°, was obtained.

Reaction of ethyl benzoate with sodium. Fifteen grams of ethyl benzoate in 50 cc. of dry benzene was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia. After treatment as in Procedure I, the following products were isolated: 5 g. of benzaldehyde, b.p. 174–180°, identified as the 2,4-dinitrophenylhydrazone, m.p. 236°, and 1.2 g. of impure benzoin, m.p. 128–130°, b.p. 220–230° (40 mm.). The pure 2,4-dinitrophenylhydrazone of benzoin was obtained after several crystallizations from methyl alcohol. It melted sharply at 234° (12).

The yield of benzoin was increased to 50% by the following procedure: to 14 g. (0.1 mole) of ethyl benzoate in liquid ammonia was added 4.6 g. (0.2 atom) of sodium

in small slices. A violent reaction occurred with the addition of each slice. After the usual treatment (in this case the mixture was acidified immediately after evaporation of the ammonia), 5 g. of benzoin, m.p. 129–130°, crystallized from ether solution.

Fifteen grams of ethyl benzoate was added to 4.6 g. (2 equivalents) of sodium in liquid ammonia. The mixture was stirred for a short time and 12.6 g. of benzyl chloride was added slowly. After treating as in Procedure I, 7.5 g. of material which boiled at 195–280° (8 mm.) was collected. On repeated crystallizations of the distillate from ether and petroleum ether, two products were obtained: 1.5 g. of dibenzyl, m.p. 50°, and 0.3 g. of isobenzamarone, m.p. 179°.

Anal. Calc'd for $C_{35}H_{27}O_2$: C, 87.67; H, 5.63.
Found: C, 87.58; H, 5.69.

The mother liquors were evaporated to dryness and the residue was extracted with cold methanol. Upon refluxing the methanol extract with 2,4-dinitrophenylhydrazine, the hydrazone of desoxybenzoin was obtained, contaminated with some of the 2,4-dinitrophenylhydrazone of benzoin. After three crystallizations from methyl alcohol the pure hydrazone of desoxybenzoin was obtained. It melted at 181° and its melting point was not depressed by the addition of a known sample. The methanol-insoluble residue was dissolved in hot ethyl alcohol and yielded, upon addition of 2,4-dinitrophenylhydrazine, the hydrazone of benzoin, m.p. 232–234°. Extraction of the residue which was insoluble in cold methanol with very dilute alkali, and acidification, yielded 2.6 g. of benzoic acid, m.p. 121°.

To the red mixture from 15 g. of ethyl benzoate and 4.6 g. (2 equivalents) of sodium in liquid ammonia was added 11 g. of ethyl bromide. The red color faded to light brown. The material was hydrolyzed in the usual manner, and upon distillation gave 4.4 g. of propiophenone, b.p. 198–218°. Three grams of benzoin was obtained by crystallization of the residue. Other high-boiling compounds not identified may represent mono- or di- ethyl ethers of benzoin. The propiophenone was identified as the 2,4-dinitrophenylhydrazone, which was found not to depress the melting point of an authentic sample.

To the red mixture from 15 g. of ethyl benzoate and 4.6 g. (2 equivalents) of sodium in liquid ammonia was added 13 g. of *n*-butyl bromide. After the usual treatment, the mixture upon distillation yielded 4.7 g. of valerophenone, b.p. 135–152° (30 mm.). The valerophenone was further characterized by the preparation of its 2,4-dinitrophenylhydrazone, m.p. 154°, and by analysis.

Anal. Calc'd for $C_{17}H_{18}N_4O_4$: N, 16.87. Found: N, 17.02.

Of the remaining organic material, 7.5 g. boiled at 185–320° at 30 mm., partly solidifying in the receiver. Two grams was identified as benzoin (the 2,4-dinitrophenylhydrazone melted at 234°). The remainder, unidentified, may represent mono- or di- butyl ethers of benzoin or their decomposition-products.

Two and one-half grams (0.8 equivalent) of sodium in liquid ammonia was added to 20 g. of ethyl benzoate according to Procedure II. Four grams of benzil distilled at 120–130° at 3 mm. and was characterized by the preparation of the 2,4-dinitrophenylhydrazone, m.p. 184–185° (13), and analysis.

Anal. Calc'd for $C_{26}H_{14}N_4O_8$: N, 14.30. Found: N, 14.21.

In a similar experiment, the alkaline water layer was shaken several times with the organic layer and allowed to stand for some period before separation. Under these conditions 2 g. of benzil was isolated and identified as the 2,4-dinitrophenylhydrazone. Three grams of benzilic acid, identified by its deep red color in concentrated sulfuric acid solution and its neutralization equivalent, was obtained upon acidification of the aqueous solution.

Reaction of benzoin with sodium ethoxide and sodamide in liquid ammonia. To 2.3 g. of sodium dissolved in liquid ammonia were added a few crystals of anhydrous ferric nitrate. After the sodium had reacted completely, 2.3 g. of absolute alcohol was added dropwise. Five grams (0.024 mole) of benzoin was then added in small portions. A red color developed, lighter in shade than that from ethyl benzoate and sodium. Subsequent treatment as in Procedure I gave 1.2 g. of benzaldehyde 2,4-dinitrophenylhydrazone, m.p. 236°. Four grams of benzoin, m.p. 135–137°, was recovered. A few drops of a viscous liquid distilled above 340°, and a little tar remained in the distilling-flask.

Five grams of benzoin was added to a mixture of sodium ethoxide and sodamide prepared as above. The red mixture was then treated with 11 g. of ethyl bromide, the red color becoming light brown. When hydrolyzed, the mixture upon distillation yielded 1.6 g. of propiophenone, b.p. 198–220° (2,4-dinitrophenylhydrazone, m.p. 190°). One and one-half grams of benzoin was recovered; the remainder of the material (3 g.) was a tar which decomposed upon attempted distillation.

Reaction of benzil with sodium in liquid ammonia. Ten grams of benzil in 100 cc. of dry ether was added to 2 g. (2 equivalents) of sodium in liquid ammonia and the red solution treated with 15 g. of ethyl bromide. The usual procedures of hydrolysis and distillation yielded 1.5 g. of propiophenone, b.p. 190–206°, 2,4-dinitrophenylhydrazone, m.p. 188–190°. The melting point of the hydrazone was not lowered by the addition of an authentic sample. The water solution, upon acidification, yielded 2 g. of benzoic acid, m.p. 119–120°.

SUMMARY

1. Equilibria and intermediate products in the acyloin condensation have been investigated in liquid ammonia, an excellent solvent for this purpose.

2. New evidence is presented that the action of one and two equivalents of sodium with an ester gives respectively a free radical and a very reactive organo-sodium compound.

3. It is shown that similar compounds can be obtained by the combined action of sodamide and sodium ethoxide on a diketone or an acyloin.

CHICAGO, ILL.

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[CONTRIBUTION FROM THE BUREAU OF ANIMAL INDUSTRY, UNITED STATES DEPARTMENT OF AGRICULTURE][1]

THE SYNTHESIS OF CONDENSED RING COMPOUNDS. III. A HEXAHYDRONAPHTHALENE DERIVATIVE FROM A DIENEYNE

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In the preceding paper (1) it was shown that 1,3,5-hexatriene might serve as the basis of a general synthetic method for condensed ring compounds of angular construction, such as steroids, since it was possible to secure, as the principal product of its addition to a cyclohexene, a derivative of 1-vinyloctahydronaphthalene with the annular double bond probably in the 2,3-position. The utility of this intermediate in the synthesis of angular polycyclic compounds would depend on its ability to isomerize to a 1-vinyl-1-octalin which could then add a dienophile. Before the feasibility of this procedure could be tested, we had observed that a 1,5-diene-3-yne can add two molecules of dienophile to give a crystalline product and it has now been found that this addition proceeds in the manner required for the synthesis of compounds of the type sought.

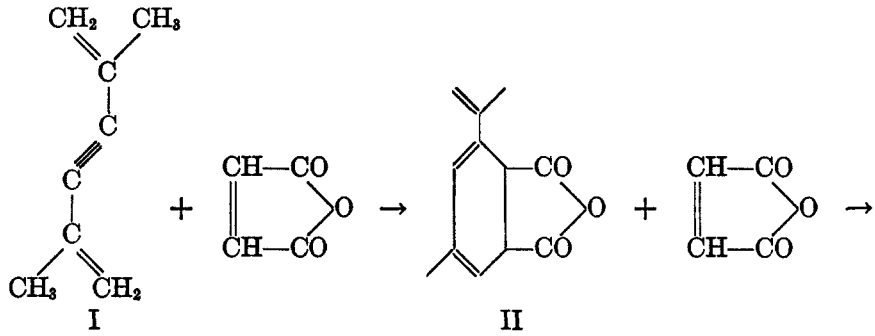
In 1933 Blomquist and Marvel (2) found that both 4,7-di-*n*-propyl-3,7-decadiene-5-yne and 6,9-dimethyl-5,9-tetradecadiene-7-yne added two moles of maleic anhydride in boiling xylene. Since the products of reaction did not crystallize, the solution in xylene was heated with aqueous alkali. Neutralization of the alkaline extract gave products with the composition $R_4C_{14}H_{10}O_8$ but, as these were amorphous, no attempt was made to characterize them further.

We have now heated 2,5-dimethyl-1,5-hexadiene-3-yne (I) with maleic anhydride at 130°. From the reaction-mixture a crystalline product, $C_{16}H_{14}O_6$, was isolated. If the two moles of maleic anhydride added one after the other in the manner of a Diels-Alder reaction, then III and IV would be the expected structures.[2] The intermediate II has not been

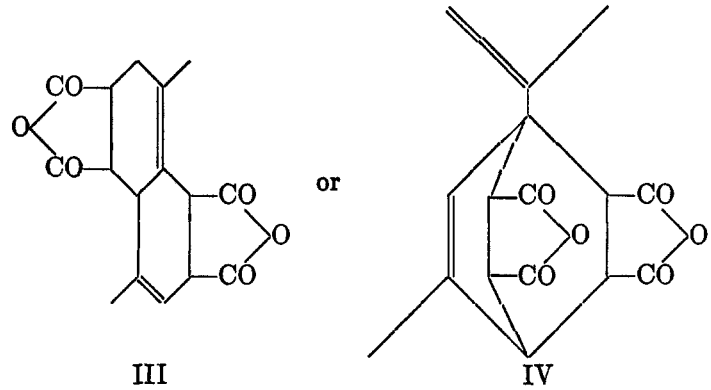
[1] This work was supported by an appropriation from Bankhead-Jones funds (Bankhead-Jones Act of June 29, 1935), and is part of an investigation of the animal metabolism of substances related to the steroid hormones being carried out under the Physiology of Reproduction Project, a cooperative project of the Bureau of Animal Industry and the Bureau of Dairy Industry.

[2] Providing that any 1-isopropenyl-3-methyl-1,2-cyclohexadiene-5,6-anhydride, formed as a primary adduct, rearranges before a second mole of maleic anhydride adds.

isolated. This is not surprising since II at 130° should add maleic anhydride readily, or it might polymerize.



I II



III or IV

The new compound, $C_{16}H_{14}O_6$, melts at 262–263° and is a dianhydride. It dissolves slowly in boiling water and the solution is acid. A barium salt may be precipitated from the solution in aqueous sodium hydroxide. The adduct dissolves slowly in cold ethanol. A tetraethyl ester, $C_{24}H_{34}O_8$, was formed by heating with ethanol. The presence of olefin linkages was indicated by reduction of permanganate, addition of bromine, and catalytic hydrogenation with palladium.

Structure IV was eliminated as a possibility, since after heating the dianhydride with palladium-charcoal an easily sublimable hydrocarbon, $C_{12}H_{12}$, with a naphthalene-like odor was obtained. The melting points of the hydrocarbon (77°) and its picrate agree closely with those reported in the literature (12, 13) for 1,5-dimethylnaphthalene. The hydrocarbon has been shown to be 1,5-dimethylnaphthalene by a mixed melting point determination with a specimen prepared from *o*-bromotoluene.[3] The

[3] This method, not hitherto used for the synthesis of 1,5-dimethylnaphthalene, and the intermediate compounds will be described elsewhere.

crystalline adduct is therefore a 1,5-dimethylhexahydronaphthalene-3,4, 7,8-dianhydride. Structure III, however, is probably not correct. Spectroscopic examination of the solutions obtained by dissolving the dianhydride in boiling water or cold ethanol indicate the presence of two con-

TABLE I

COMPARISON OF ABSORPTION SPECTRA WITH THOSE OF KNOWN COMPOUNDS (3)

COMPOUNDS	SOLVENT	λ MAX (Å)	ε
2,4-Cholestadiene		2,670, 2,750	5,500
3,5-Cholestadiene		2,400	14,000
4,6-Cholestadiene		2,380	24,000
Maleic acid	Ethanol	2,100	13,000
Ethylene		1,800	10,000
1,5-Hexadiene	Ethanol	<1,850	20,000
Tetracarboxylic acid, $C_{16}H_{18}O_8$	Water	2,450	21,000
Tetraethyl ester, $C_{24}H_{34}O_8$	Ethanol	2,470	22,000

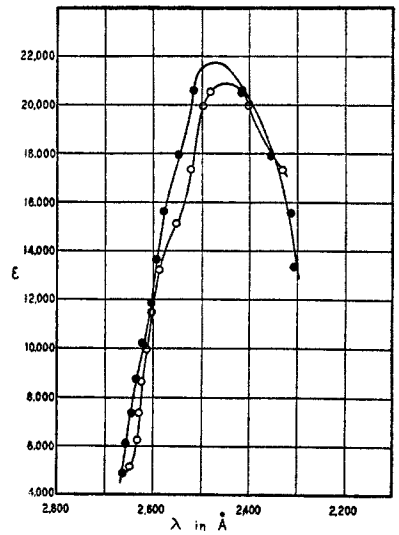
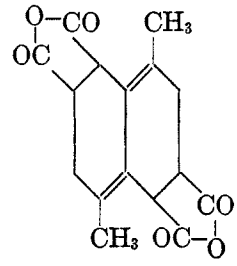


FIGURE I. ABSORPTION CURVES OF THE TETRACARBOXYLIC ACID (○) AND TETRAETHYL ESTER (●)

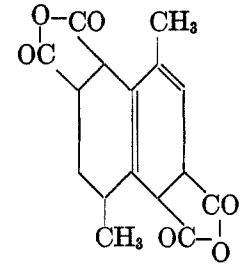
jugated double bonds distributed over two rings as shown in Figure I and Table I. It is unlikely that conjugation of one of the carbon-carbon double bonds with one or two carboxyl groups could explain the observed maxima, although data (3) for comparison are available only for acyclic compounds. It is more probable that the two carbon-to-carbon double bonds are in

conjugation. By migration of a single hydrogen atom in III, structures V and VI could be formed. A comparison with data (3) for 2,4-, 3,5-, and 4,6-cholestadienes indicates V as the more probable structure, but this cannot be taken as final because V represents a derivative of 4,8-hexalin whereas the known data relate to 3,5- and 4,6-cholestadienes, derivatives of 1,8-hexalin. Of the twenty-one isomeric hexahydronaphthalenes, only two, the 1,2,6,7,8,8a- and the 1,2,3,5,6,7-hexahydro- isomers contain heteronuclear conjugated double bonds. V is derived from the latter hydrocarbon and there is no reason to expect a derivative of the former from this reaction.

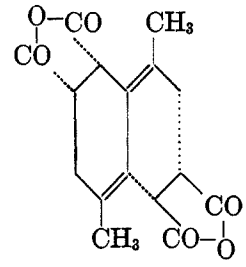
The crystalline compound from the dieneyne and maleic anhydride is therefore probably one of the stereoisomers of *1,5-dimethyl-2,3,4,6,7,8-hexahydronaphthalene-3,4,7,8-tetracarboxylic acid* (*dianhydride*) Va or Vb with *cis* attachment to the ring of the carbonyls within each of the anhydride groups.



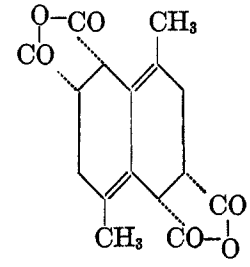
V



VI



Va

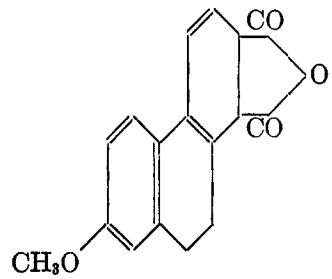


Vb

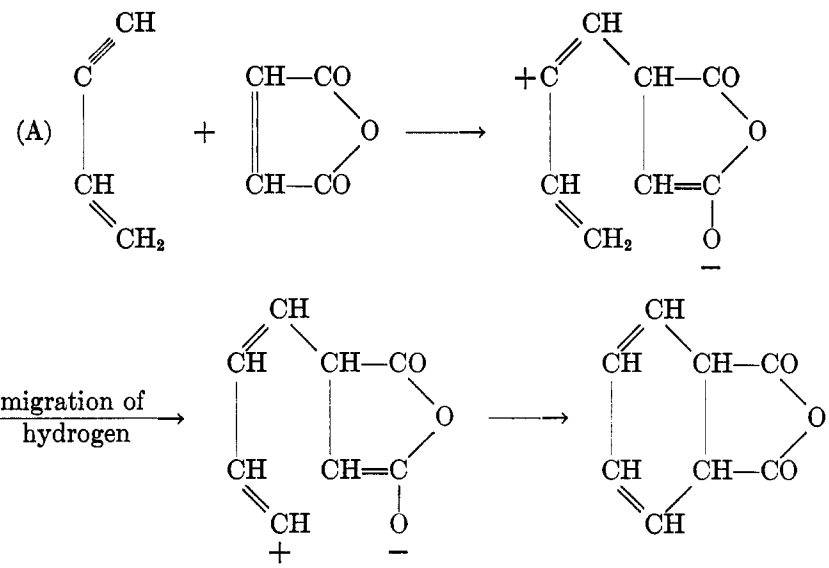
It is unlikely that the *cis*-anhydride formed primarily in the Diels-Alder reaction would be transformed by heat into a *trans*-anhydride, since Baeyer (4) found that *trans*-1,2,3,6-tetrahydrophthalic anhydride is converted to the *cis*-isomer at 210°. A decision between the two structures Va and Vb would be of great interest in further defining the stereochemical

course of the Diels-Alder reaction (5) and experiments directed towards this end are in progress.[4]

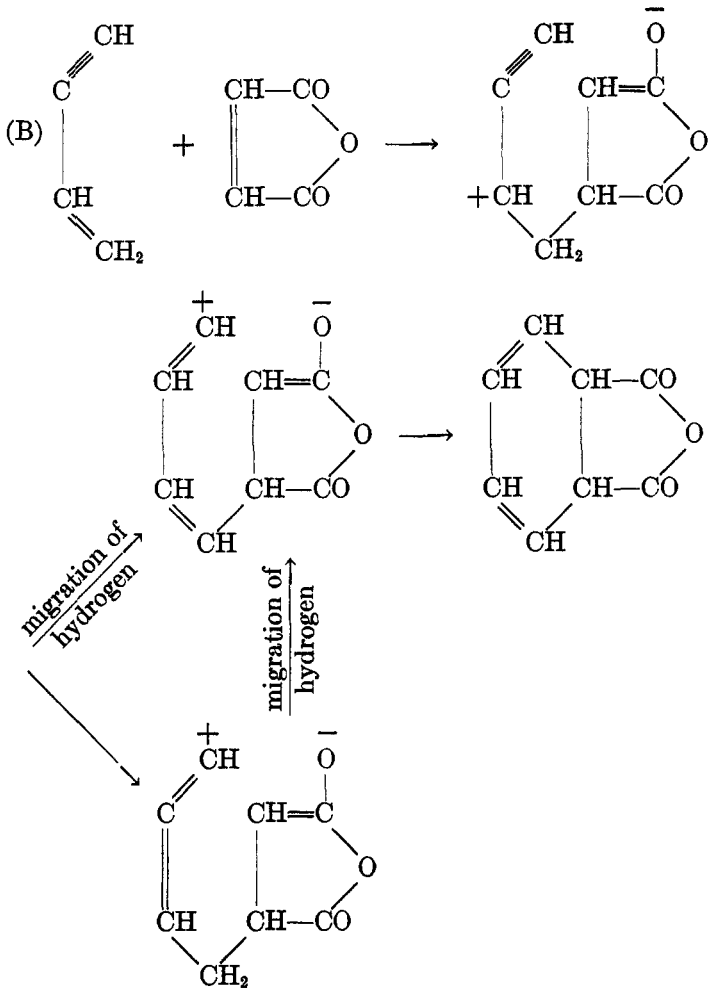
The mechanism of the addition of a dienophile to a 1,3-eneyne must differ in some respect from the addition to a 1,3-diene, since in the latter process a new ring can form without migration of a hydrogen atom. Dane and co-workers (6) have added maleic anhydride to 1-ethynyl-6-methoxy-3,4-dihydronaphthalene and have formulated their product as VII. Thus the original 1,3-eneyne system appears in the adduct as a 1,3-diene system made up of the same carbon atoms. Migration of a hydrogen atom must have occurred during the formation of the new ring. The same would hold for their second case (7) in which methyl propiolate was the dienophile and a new benzene ring was formed during addition.



VII



[4] It is proposed that Va be referred to as the 3x, 4x, 7y, 8y- or simply xxyy-isomer, and Vb as the racemic xxxx-isomer. This system will be subsequently employed in



If the mechanism of the Diels-Alder addition proposed by Robinson (8) is extended to eneynes, processes A and B are conceivable. It will be seen that the hydrogen attached to the triply bonded carbon does not migrate in any of these hypothetical processes and hence it might be inferred that the eneyne need not contain such hydrogen in order to add a dienophile. This is borne out by the addition to 2,5-dimethyl-1,5-hexadiene-3-yne

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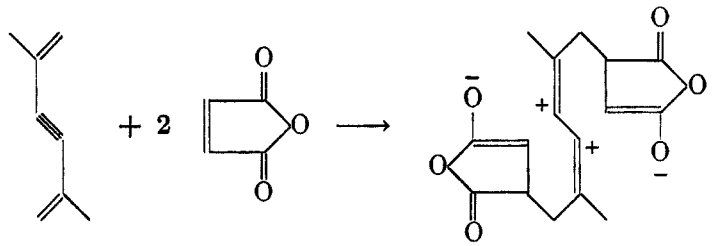
designating the various stereoisomers of more complicated types. Thus for the unsymmetrical molecule III, four stereoisomers would come up for consideration. These are the *r*-xxxxx-, *r*-xxyxx-, *r*-xxxyy- and *r*-xxyyy-isomers. The third prefix (x or y) refers to the configuration of the hydrogen at the 4a position.

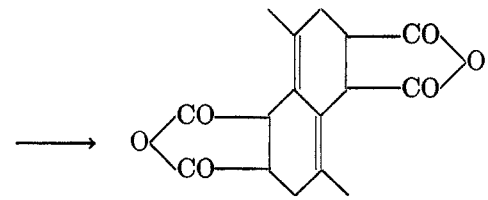
reported in this paper. One would predict on the same basis that a compound like 1,1-dimethyl-1-butene-3-yne would not add, since the 1-carbon has no hydrogen to supply during ring formation. It will be of interest to investigate the intermediate case of an eneyne in which the 1-carbon has but one hydrogen. The compounds studied by Blomquist and Marvel (2) are of this type, but these may have presented difficulty for other reasons.

Until a compound II has been found, another mechanism for the formation of V must be considered. It is conceivable that V is not formed from III and that II is not an intermediate at all. Using again Robinson's conception (8) of the general mechanism of diene additions, the dimethylhexadieneyne, being a perfectly symmetrical molecule, might add two molecules of maleic anhydride at the same instant to give VIII, which then could cyclize directly to V. No migration of hydrogen occurs according to this scheme. A formal analogy to this mode of addition is presented by the addition of two moles of hydrogen chloride to divinylacetylene observed by Coffman *et al.* (9). Here no intermediate allene was isolated. Could it be that an unsymmetrical dienophile would add in the same manner as hydrogen chloride?

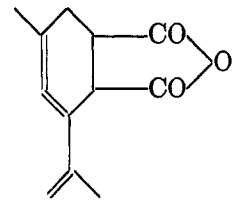
Still another possibility, quite aside from ionic mechanisms, is perhaps worth considering. The primary adduct from I and maleic anhydride may be the allene IX. This may exist long enough to add another mole of maleic anhydride, which addition would result in the direct formation of V. Such a mechanism involves no migration of hydrogen. Some support for the idea of IX as an intermediate is furnished by the discovery of Favorskii (14) that 1,2-cycloheptadiene is sufficiently stable to be isolated.



VIII



V



IX

EXPERIMENTAL

2,5-Dimethyl-3-hexyne-2,5-diol and 2,5-dimethyl-1,5-hexadiene-3-yne. The glycol, m.p. 95°, was prepared by the method of Kazar'yan (10), modified by taking the theoretical proportion of acetone, instead of half that quantity as stated in the original paper. The dieneyne, b.p. 38–43° (22 mm.), n_D^{21} 1.4854, was prepared from the glycol by the procedure of Mitchell and Marvel (11).

Addition of maleic anhydride to 2,5-dimethyl-1,5-hexadiene-3-yne. All the experiments were done at 130° in sealed tubes in which the air was replaced by carbon dioxide. The dieneyne was taken in excess and usually no other solvent was added. In one experiment where benzene was employed as solvent the dianhydride V was not found among the products. These have not yet been fully investigated. One is a substance much less stable toward heat than V. The yield of V was improved by using maleic anhydride which had been twice distilled. This precaution also prevented the formation during the reaction of a benzene-insoluble amorphous product which made difficult the separation of products. Analysis of the old undistilled sample of maleic anhydride used in some of these experiments indicated a content of about 10% of maleic acid.

In a typical run, 3 g. of twice distilled maleic anhydride and 4.7 g. (1.5 moles) of 2,5-dimethyl-1,5-hexadiene-3-yne were heated together for 2 hours. After cooling, the oil (about 3 g. consisting apparently of unchanged and dimerized dieneyne) was separated from the crystals, which were quite pure after one recrystallization from acetone, 1.1 g. (representing 24% of the maleic anhydride taken), m.p. 256–258°. Recrystallization from ethyl acetate or acetone-benzene gave V, m.p. 262–263° (uncorr.; tubes placed in bath previously heated to 220°).

Anal.[5] Calc'd for $C_{16}H_{14}O_6$: C, 63.55; H, 4.67.
Found: C, 63.55; H, 4.79.

When undistilled maleic anhydride was taken, the crystalline product did not separate readily and it was necessary to resort to continuous extraction for several days with benzene in order to separate it from amorphous material.

The mother liquors, which contain three-fourths of the maleic anhydride taken, or products therefrom, remain to be investigated. Saponification with sodium hydroxide followed by neutralization with hydrochloric acid gave a product melting indefinitely around 250°, which appears to be an acid related to III or V.

Anal. Calc'd for $C_{16}H_{18}O_8$: C, 56.78; H, 5.36.
Found: C, 56.45; H, 6.07.

No compound corresponding to structure II has been found; and, indeed, it is questionable whether such a substance would be stable alone at 130°. Certainly it would add maleic anhydride very rapidly.

The crystalline product $C_{16}H_{14}O_6$ is insoluble in cold water, but dissolves slowly in

[5] All analyses by Arlington Laboratories, Arlington, Virginia.

hot water to give an acid solution. A few mg. in acetone decolorized potassium permanganate slowly (15 minutes) and a suspension in acetic acid reacted with bromine at 25° somewhat more slowly than cholesteryl acetate. The bromide (?) which was obtained by precipitation with water melted above 310°. A single experiment indicated that 1.5 moles of hydrogen are absorbed in ethanol in the presence of palladium; 77.5 mg. dianhydride, 9.8 cc. hydrogen, 747 mm., 27°, 2 hours.

Preparation of a tetraethyl ester from the dianhydride $C_{16}H_{14}O_6$. The dianhydride dissolved slowly in ethanol at 25°. Twenty-three cubic centimeters of ethanol was added to 101 mg., let stand 20 hours, warmed on the steam-bath 5 minutes to complete solution, and cooled. No solid separated. Evaporation of the ethanol (steam-bath, 50 minutes) in a stream of nitrogen gave an oil which crystallized on addition of benzene. Twenty cubic centimeters of benzene was added, the mixture boiled for a few minutes, filtered, and the insoluble part recrystallized from benzene-acetone (30:1); colorless crystals, m.p. 163–165° (corr.).

Anal. Calc'd for $C_{24}H_{34}O_8$: C, 63.98; H, 7.16.
Found: C, 63.95; H, 6.99.

Dehydrogenation to 1,5-dimethylnaphthalene. The dianhydride (841 mg.) was heated at 230–325° for 30 minutes with 244 mg. of palladium (12%) on charcoal. Rapid production of gas and water occurred at 285–325°. The temperature was then maintained at 325–355° for one hour. During the reaction some colorless solid appeared in the receiver as a result of steam distillation. The solid products of reaction were extracted successively with ether and sodium hydroxide solution. Partition between ether and aqueous sodium hydroxide gave 50 mg. of material soluble in ether. Evaporation of the ether gave a crystalline residue which formed a picrate, m.p. 130–131° (corr.); 1,5-dimethylnaphthalene picrate (12), m.p. 137–138°.

Anal. Calc'd for $C_{12}H_{12}\cdot C_6H_3O_7N_3$: N, 10.90. Found: N, 10.49, 10.50.

More 1,5-dimethylnaphthalene was obtained by acidification of the alkaline solution, distillation of the precipitated acids with calcium hydroxide, steam distillation of the condensate thus obtained, and recrystallization of the steam distilled products from methanol. The hydrocarbon thus obtained had the m.p. 76° (corr.); literature, Veselý and Štursa (12), 77–78°, Anderson and Short (13), 80–80.5°. It did not depress the m.p. (77–78°) of 1,5-dimethylnaphthalene prepared from *o*-bromotoluene.

Anal. Calc'd for $C_{12}H_{12}$: C, 92.31; H, 7.69.
Found: C, 92.25; H, 7.65.

The same hydrocarbon was obtained by another procedure. The dianhydride was dissolved in aqueous sodium hydroxide, the solution precipitated with barium hydroxide, and the dried barium salt heated at 450–500° with palladium-charcoal and two moles of barium hydroxide octahydrate.

SUMMARY

1. 2,5-Dimethyl-1,5-hexadiene-3-yne adds two molecules of maleic anhydride to give a crystalline substance, $C_{16}H_{14}O_6$, which can be converted to 1,5-dimethylnaphthalene by heating with palladium-charcoal.

2. The new compound is probably 1,5-dimethyl-2,3,4,6,7,8-hexahydronaphthalene-xxyy-3,4,7,8-tetracarboxylic acid (dianhydride) or *r*-1,5-dimethyl-2,3,4,6,7,8-hexahydronaphthalene-xxxx-3,4,7,8-tetracarboxylic acid (dianhydride).

3. This dianhydride forms the tetraethyl ester with great ease by merely heating with ethanol.

4. The mechanism of the addition of dienophiles to eneynes and di-eneynes is discussed.

BELTSVILLE, MD.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF HARVARD UNIVERSITY]

SOLVENT AND PEROXIDE EFFECT IN THE ADDITION OF HYDROGEN BROMIDE TO UNSATURATED COMPOUNDS. IV. ISOPROPYLETHYLENE (1)[1]

ARTHUR MICHAEL AND NATHAN WEINER

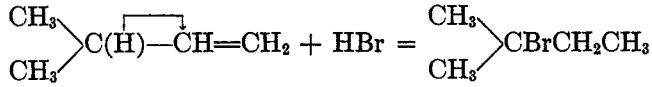
Received February 13, 1940

Wishnegradski (2) first examined the action of concentrated aqueous hydrogen bromide on isopropylethylene and, in agreement with the so-called Markownikoff rule (3), obtained pure secondary isoamyl bromide. Later, Ipatieff (4) confirmed that the secondary derivative appeared in an almost pure state in the reaction, but found that the primary bromide, mainly, was formed when the addition was carried out in acetic acid solution. On the other hand, hydrogen iodide gave practically the secondary derivative under both conditions. Michael and Leupold (5) analyzed

[1] In a preliminary notice in the May issue of the *J. Org. Chem.*, **4**, 132, footnote 13 (1939), and **3**, 379, footnote (1938), it was announced that we had proved the course of addition of hydrogen bromide to isopentene-2 to be susceptible to solvent and also to peroxide influence, although Kharasch [*J. Org. Chem.*, **2**, 288 (1937)] had concluded that only alkenes with terminal unsaturation show the latter property. The report of the completed research was sent to this Journal on May 24, 1939, and appeared in the November issue, p. 532. On August 3, 1939, Kharasch and co-workers submitted a paper to the *J. Am. Chem. Soc.*, **61**, 2694 (1939) in which peroxide effect on isopentene-2 is now admitted, but no reference is made to our announcement in September 1938 or in May 1939. We are now engaged in an investigation on tertiary butylethylene, in a manner similar to that here presented on isopropylethylene. Ipatieff and Dechanoff (*Chem. Zentr.*, **1904**, II, 901) found that trimethylethylene in acetic acid yielded 10–15%, not 10–25% as stated by Kharasch, of the secondary bromide and 85–90% of the tertiary bromide. Michael and Zeidler, *Ann.*, **385**, 245 (1911), showed that the appearance of the secondary derivative in the solvent-free reaction was due to a slight impurity in the hydrocarbon and that with pure hydrocarbon, tertiary bromide alone is formed. Kharasch and co-workers (*loc. cit.*) consider these results "similar." These chemists state the secondary bromide easily undergoes isomerization in the addition, since "methyl isopropyl carbinol or isopropylethylene with hydrogen bromide" yield more or less of the isomeric tertiary bromide. This carbinol is dehydrated by strong acids into trimethylethylene [Wishnegradski (2)], which yields solely the tertiary bromide, and which is therefore formed by addition, not by rearrangement. Its formation from isopropylethylene is explained in this paper and is not connected with Kharasch's assumption. There is no support for the statement that the secondary bromides are rearranged to the tertiary isomers under the conditions used in the hydrogen bromide additions.

the addition-products semi-quantitatively and found that with concentrated aqueous hydrobromic acid, the addition-product consisted of a mixture of 52% of the secondary and 48% of the tertiary isoamyl bromide. The investigation was continued by Michael and Zeidler (6), who confirmed the latter result and found, contrary to Wishnegradski (2), that the addition of hydriodic acid, in concentrated solution, gave a mixture of secondary and tertiary iodides in about the same proportion as the bromides in the above experiment. Nor did the results of hydrogen bromide addition in acetic acid coincide fully with Ipatieff's (4); instead of mainly the primary bromide, a mixture of the isomeric isoamyl bromides was formed, containing the primary, secondary, and tertiary bromides in about the proportion of 65.5:28:5.6.

The experiments with isopropylethylene were carried out before the influence of oxidants on the addition of hydrogen bromide to alkenes was known. The appearance of the primary bromide could possibly be ascribed to the presence of peroxide in the hydrocarbon or solvent. However, the appearance of the tertiary amyl halides in the reaction with the hydrogen halides involves a novel course of organic addition, since it can occur only with simultaneous intramolecular migration of the tertiary hydrogen atom; the reaction may, therefore, be called an intramolecular rearrangement-addition:



The formation of the tertiary halide is obviously opposed to the so-called Markownikoff rule (3), which has long since been shown to be untenable for other groups of unsaturated compounds (7)[2] and is not even applicable to all hydrocarbons of the alkene-1 type. There can be no doubt that alkenes of the type $(Alk)_2CHCH{=}CH_2$ will yield with hydrogen bromide considerable tertiary halide and that the relative amount will increase with the combined relative positivity of the alkyl groups. The affinity and energy relations of those atoms in the system, which mainly activate the rearrangement-addition are: (a) the chemical hindrance, *i.e.*, the energy required to separate the tertiary hydrogen from the attached carbon atom is relatively slight, owing to the direct positive influence of the two

[2] The primitive Markownikoff rule is repeatedly mentioned in "Organic Chemistry" (edited by Gilman); only in one place (p. 549), do Allen and Blatt note its limitations and inadequacies. They then state that "no wholly satisfactory explanation" why "addition follows this rule has been advanced." This remark illustrates how the theoretical foundation of organic addition phenomena upon the law of degradation of energy, and the principle of partition, with the experimental confirmations (7), have been entirely overlooked in the above treatise. (A. M.)

alkyl groups upon the attached carbon (8); (b) the heat of formation of the tertiary bromide is considerably greater than that of the secondary, which correspondingly increases the energy degradation of the reaction in that direction; (c) isopropylethylene itself adds hydrogen bromide with relative difficulty, doubtlessly due to the greater reduction of the affinity of the unsaturated methylene carbon for the additive hydrogen, by the influence of the six methyl hydrogens in the spatially near 5-positions, over that of the carbon of the unsaturated methinyl group, which is in the spatially, relatively distant 4-position. The different spatial relations bring the relative polarities of the unsaturated carbons nearer together and thus reduce the differences in their relative additivity,[3] as indicated in the structural formulas and tends, therefore, to the formation of a mixture of isomeric bromides. The above affinity-energy factors mainly determine the energy degradation in the addition to the isoalkene and so favor the maximum energy degradation through a rearrangement-addition, that it approximates that occurring by direct union of hydrogen bromide at the unsaturated carbons. From the above viewpoint, the changes in the proportion of tertiary and secondary halide produced by addition of hydrogen bromide to $(Alk)_2CHCH{=}CH_2$, with change in alkyl, may be predicted. The more positively the alkyls act upon the attached methinyl group, the greater will be the proportion of tertiary to secondary halide. Less definite is the effect of replacing a hydrogen of the unsaturated methylene group by alkyl since, while the relative value of (a) would be increased, that of (b) would be lessened. Probably, however, the relative proportion of isomeric halides obtained would not be greatly changed from that appearing with isopropylethylene.

The influence of peroxides and solvents upon the course of the addition of hydrogen bromide to isopropylethylene is of considerable theoretical interest. In contrast to trimethylethylene (1c), in the absence of solvent and peroxide, the addition of hydrogen bromide to isopropylethylene takes place quite slowly at $-78°$ and even at $0°$; for this reason the additions were carried out in sealed tubes at room temperature. Under these conditions, it was found that isopropylethylene and dry hydrogen bromide (see Table I) yielded *ca.* 61% of the tertiary and 39% of the secondary derivative; the primary bromide could not be detected. A comparison of this result with that obtained with a saturated aqueous solution of hydrobromic acid under comparable conditions, which gave 48% and 52% of the respective bromides, shows that even water may exert a noticeable effect as a solvent; the proportion of the tertiary bromide decreased about 12%. Hence, in the future, the solvent effect of water in additions upon an

[3] See Michael and Brunel, *Am. Chem. J.*, **41**, 128 (1909), for an explanation of the relative additivities of other alkenes from this viewpoint.

addendum should be taken into consideration. The active agent is undoubtedly the hydrated acid, $HBr \cdot H_2O$.[4] There is no indication in our results that halogen hydrides function, either in normal or abnormal additions, in the ionic state.[4] We next examined the effect of ascaridole upon the action of fuming hydrobromic acid. Addition of 0.012 mole of ascaridole scarcely changed the percentage of tertiary bromide (49.3%), but 37% of the primary bromide now appeared, formed at the expense of the secondary bromide; this relationship underwent only a slight change when the amount of ascaridole was increased four-fold. In the presence of water, therefore, ascaridole exerted a very slight, if any, action upon the tertiary hydrogen of the hydrocarbon, but functioned characteristically

TABLE I

REACTIONS BETWEEN ISOPROPYLETHYLENE AND HYDROGEN BROMIDE, WITHOUT SOLVENT, AT ROOM TEMPERATURE

EXPT.	RATIO $\frac{\text{MOLES ASCARIDOLE}}{\text{MOLES } (CH_3)_2CHCH{=}CH_2}$	PER CENT PRIMARY	PER CENT SECONDARY	PER CENT TERTIARY
1	0.0006	36.5	11.0	52.5
2	0.0009	36.4	10.4	53.2
3	0.002	45.9	20.6	33.5
4	0.003	44.4	20.0	35.6
5	0.003	43.4	23.3	33.3
6	0.009	66.3	14.8	18.9
7	0.02	80.0	13.6	6.4
8	0.02	75.8	18.6	5.6
9	None		39.3	60.7
10	None		38.8	61.2
11	0.2 g. hydroquinone		41.5	58.5
12	0.2 g. hydroquinone		40.7	59.3
13	0.1 g. ferric chloride		18.5	81.5

upon the addition relationship between the primary and secondary derivatives (Table II), causing the appearance of the former.

Under the same experimental conditions, addition of antioxidant hydroquinone to a mixture of dry hydrogen bromide and pure isopropylethylene did not materially affect the proportion of tertiary to secondary bromide. On the other hand, ferric chloride showed a marked influence, increasing the percentage of tertiary bromide from 61% to 81.5% and decreasing

[4] Michael and Brunel, *Am. Chem. J.*, **48**, 267 (1912), showed that the system, isopentene-2·HBr·$8H_2O$, yielded directly an addition-product containing an equal number of molecules of the saturated bromide and carbinol and that any system containing the acid in greater or lesser concentration leads to the formation of the halide in a greater or lesser proportion. Other strong acids showed a similar relationship.

the percentage of secondary bromide correspondingly.[5] On the other hand, the presence of ascaridole diminished the proportion not only of tertiary bromide, in opposition to its influence in the hydrobromic acid system, but that of the secondary as well, with the appearance of a corresponding amount of the abnormal primary bromide. The abnormal reaction is remarkably sensitive to the influence of the peroxide. The addition of 0.0006 mole of ascaridole caused the appearance of 36.5% of the primary bromide, by reduction in the yields of the tertiary and secondary bromides by *ca.* 8% and 28.5%, respectively (Table I). With an ascaridole molar concentration of 0.003, the percentage of the abnormal primary bromide increased to 44%, this time mainly at the expense of the tertiary bromide, since the percentage of the secondary bromide was only slightly greater than the initial low amount formed at the lowest concentration investigated. The effect of further increase in ascaridole concentration proceeded

TABLE II

REACTIONS BETWEEN FUMING HYDROBROMIC ACID, SATURATED AT 0°, AND ISOPROPYLETHYLENE

The reactions were carried out at 25°.

EXPT.	RATIO $\frac{\text{MOLES ASCARIDOLE}}{\text{MOLES } (CH_3)_2CHCH{=}CH_2}$	PER CENT PRIMARY	PER CENT SECONDARY	PER CENT TERTIARY
14	None		49.7	50.3
15	None		48.1	51.9
16	0.012	37.0	13.7	49.3
17	0.05	36.0	15.4	48.6

in the same direction, *i.e.*, with increased formation of the primary derivative and corresponding decrease in the tertiary bromide. Thus, over the range of ascaridole concentrations investigated (0.0006–0.08 molar), the net change in the secondary bromide was only 13% (10.4–23.3%), whereas the primary bromide increased by 43.5% and the tertiary bromide decreased by 47.3%. The experimental data are collected in Table I.

We next turned to the influence of organic solvents upon the course of the addition, using those we had found effective in producing addition reversals with trimethylethylene (1c). In opposition to the result with that hydrocarbon in methanol solution, we found that no reaction took place at −78° and 0° (Table III), even after twenty-four hours, a period which sufficed, in the absence of solvent, to cause addition with excellent

[5] Kharasch, *J. Org. Chem.*, **2**, 288 (1937), and previous papers, contrariwise, found that the chloride, with the compounds he examined, caused a decided increase in the normal addition.

yields. Even in the presence of ascaridole, under conditions where addition took place in methanol solution at −78°, no reaction took place at 0°. However, at −78°, addition occurred when a certain minimum ratio of ascaridole to methanol (0.2 g. to 10 g.) was used. Contrary to the influence of water, a large increase in the proportion of primary bromide (78–83%) took place at the expense of the secondary bromide, which was reduced to 14–19% and of the tertiary bromide, which was formed only to the extent of 3–6%. Beyond the minimum concentration of ascaridole, a change in concentration exerted practically no influence on the proportions of the isomeric bromides formed.

Ether is the most effective solvent in reversing the normal addition of hydrogen bromide to trimethylethylene (1c). The use of this solvent with isopropylethylene involved difficulties. At −78°, conforming with the

TABLE III

REACTIONS BETWEEN ISOPROPYLETHYLENE AND HYDROGEN BROMIDE IN METHANOL SOLUTION

There was no reaction when the reagents were allowed to stand in methanol solution at 0° under otherwise duplicated experiments of the tabulated successful experiments at −78°.

EXPT.	$(CH_3)_2CHCH{=}CH_2$, G.	ASCARIDOLE, G.	CH_3OH, G.	TEMP.	PER CENT PRIMARY	PER CENT SECONDARY	PER CENT TERTIARY
18	5		20	0°	No reaction in two weeks		
19	5		10	−78°	No reaction in 24 hours		
20	6.5	0.1	10	−78°	No reaction in 24 hours		
21	4.5	0.2	20	−78°	No reaction in 24 hours		
22	7.0	0.2	10	−78°	82.9	14.0	3.1
23	7.0	0.4	20	−78°	80.6	13.2	6.2
24	6.0	0.4	10	−78°	77.9	18.7	3.4

relatively slight additivity of isopropylethylene, no reaction had taken place after five days, and at room temperature the cleavage of ether by hydrogen bromide, to ethyl bromide and alcohol, was so extensive that the results could not be considered wholly as due to an ether effect. However, by allowing the reaction to proceed for only eighteen hours at 0°, reproducible results and fair yields (50–60%) of bromides were realized. In the presence of antioxidants the yields were about half the above, but were also reproducible. Corresponding to the results with trimethylethylene, ether caused considerable abnormal addition (53–54% primary bromide); even in the presence of the antioxidants appreciable amounts of the abnormal primary bromide were formed. The usually more effective inhibitor of abnormal addition, hydroquinone, was less effective than diphenylamine (about 28% and 14%, respectively). This abnormal be-

havior is significant; the solvent effect of ether may be even more effective than the above figures indicate, for Kharasch (9) has recently shown that ethyl bromide, one of the products of ether cleavage, is an effective inhibitor of the abnormal addition. The results are tabulated in Table IV.

Hydrogen bromide added to trimethylethylene in acetic acid solution to give, besides the normal tertiary bromide, about 16% of the abnormal secondary derivative; the proportion was not changed when ascaridole was added to the mixture. The solvent in this addition neutralized the oxidant influence, as it did also, to a very large extent, the antioxidant influence of diphenylamine. When this solvent was used with isopropylethylene the formation of 44–48% of the abnormal, primary, 30–34% of the secondary, and 18–22% of the tertiary bromide was observed. The result was not due to "undetectable traces of peroxide," since about the same yields were obtained by Kharasch's vacuum technique and, anomalously, in the pres-

TABLE IV

ADDITION OF HYDROGEN BROMIDE TO ISOPROPYLETHYLENE IN ETHER AT 0°, 3.5 G. OF HYDROCARBON IN 5 CC. OF ETHER

EXPT.	ANTI-OXIDANT	PER CENT PRIMARY	PER CENT SECONDARY	PER CENT TERTIARY
25	None	54.0	29.6	16.4
26	None	53.4	32.3	14.3
27	0.2 g. hydroquinone	30.2	43.6	26.2
28	0.2 g. hydroquinone	26.0	49.7	24.3
29	0.2 g. diphenylamine	14.7	62.9	22.4
30	0.2 g. diphenylamine	13.0	57.0	20.0

ence of hydroquinone and diphenylamine, in a concentration of 0.2 g. to 10 cc. of glacial acetic acid. In contrast to comparable experiments with trimethylethylene, the addition of 0.0025 mole of ascaridole increased the formation of the primary bromide by about 30%, but a ten-fold increase in its concentration (0.025 mole) made very little, if any, difference in the proportions of the products formed; *i.e.*, 71–79% primary, 15–19% secondary, and 6–10% tertiary bromide. In acetic acid solution ascaridole increased the proportion of primary bromide, with an equal reduction in the percentages of the tertiary and secondary bromides.

In view of this solvent effect of acetic acid, it was of interest to attempt to determine the underlying factor in its influence. For this purpose the effect of dichloro- and trichloro- acetic acids ($K = 5 \times 10^{-2}$ and 3×10^{-1}, respectively) was examined. With the first acid, a reduction in the percentage of the abnormal primary bromide occurred, to 18–22%, along with 20–25% secondary, and 57–58% tertiary bromides. Therefore, this

acid, with a much higher K value than acetic acid (1.8×10^{-5}), was far less effective in inducing abnormal addition; the lessened influence appeared also in the ascaridole catalyzed reaction. Using ascaridole in a ten-fold increase in concentration (0.005–0.05 molar) a nearly constant proportion of addition-products was obtained, *viz.*, 55–58% primary, 15–22% secondary, 22–26% tertiary bromide. In agreement with the decreased abnormal

TABLE V

ADDITION OF HYDROGEN BROMIDE TO ISOPROPYLETHYLENE IN ACETIC, DI- AND TRI-CHLOROACETIC ACIDS

6.5 g. of hydrocarbon in 10 cc. of the liquid acids; 6.5 g. of hydrocarbon with 10 g. of Cl_3CCOOH. The reactions were all carried out at room temperature.

EXPT.	CATALYST, WEIGHT, G.	PER CENT PRIMARY	PER CENT SECONDARY	PER CENT TERTIARY
	Acetic acid			
31	Vacuum technique	46.8	29.9	23.3
32	None	43.9	34.7	21.4
33	0.2 diphenylamine	47.6	34.4	18.0
34	0.2 hydroquinone	45.9	32.1	22.0
35	0.04 ascaridole	78.8	15.3	5.9
36	0.04 ascaridole	78.0	15.7	6.3
37	0.04 ascaridole	77.6	14.7	7.7
38	0.1 ascaridole	73.8	17.5	8.7
39	0.2 ascaridole	71.5	19.3	9.2
40	0.2 ascaridole	72.7	18.4	8.9
41	0.4 ascaridole	71.3	18.9	9.8
	Dichloroacetic acid			
42	None	18.2	24.7	57.2
43	0.2 g. hydroquinone	21.7	20.4	57.9
44	0.08 g. ascaridole	58.6	15.3	26.1
45	0.8 g. ascaridole	55.4	22.5	22.1
	Trichloroacetic acid			
46	None	None	25.7	74.3
47	0.2 g. hydroquinone	None	25.7	74.3

addition induced by dichloroacetic acid, it was found that no irregular addition could be detected in a saturated solution of trichloroacetic acid in isopropylethylene; over 74% of the tertiary bromide was produced. The results with these acids are tabulated in Table V.

According to Kharasch and Potts (10), acetic acid functioned as an antioxidant in alkene-1 additions; on the other hand, with isopentene-2 it acted mildly as an oxidant (1c). This acid functioned likewise with iso-

propylethylene, causing the appearance of the abnormal primary bromide. From the viewpoint (1c), that the primary phase leading to abnormal additions is the formation of a polymolecule of hydrogen bromide with the added reagent, followed by its union, in accordance with the principle of partition (7), at the relatively positive unsaturated carbon, it is evident that the stability of the double molecule of fatty acid and hydrogen bromide should decrease with increase in its negativity, as represented by that of the organic acid. In agreement, the abnormal effect of dichloroacetic acid was much less than that of acetic acid and it entirely disappeared with the use of the far more acidic trichloroacetic acid. Probably a similar relationship would appear in corresponding experiments with other alkenes.

EXPERIMENTAL

Materials. Isopropylethylene was prepared by the dehydration of isoamyl alcohol over activated alumina (4–8 mesh) at 410°, according to the directions of Norris and Joubert (11). The product was separated from the water formed, distilled, and the fraction of b.p. 20–24° was collected separately. This was shaken with sulfuric acid(6) (2 vols. conc'd H_2SO_4 and one vol. water) at 5°, until a fresh portion of acid no longer decreased the volume of hydrocarbon. The hydrocarbon was then shaken with ice-water and once with 20% caustic soda. It was dried over calcium chloride and distilled in a 3-foot partial reflux column, packed with glass helices, and the fraction of b.p. 20.1–20.5°/757 mm. collected. This was dried over sodium wire and redistilled, b.p. 20.3°/757 mm. The hydrocarbon was stored in a tightly stoppered flask, over sodium wire.

The solvents were purified as previously described (1 c). Dichloroacetic and trichloroacetic acids were freshly distilled *in vacuo* and used immediately. The former boiled at 88°/14 mm., and the latter at 88°/3 mm.

Hydrogen bromide was prepared by the method of Ruhoff and Reid (12), and dried by passage over phosphorus pentoxide.

Apparatus and technique. The reaction-vessels consisted of two chambers of approximately 5 cc. and 25 cc. capacities, connected by an inverted U-tube of 8 mm. tubing. The larger chamber was calibrated to show 5, 10, 15, and 20 cc. The openings to both chambers were 8 mm. tubing ending in standard taper 10/30 female joints, which permitted a direct connection with the hydrogen bromide generator, or the condenser through which the hydrocarbon was distilled.

The experiments were carried out as follows: either 5 or 10 cc. of isopropylethylene (sp. gr. 0.66) was distilled into the larger chamber, cooled to −20°, directly from the storage flask through an 18-inch column. The other opening was connected with a calcium chloride tube. When catalysts were used, the specified amount was already present. The solvent was added with a pipet, and then both chambers were cooled to −78° in a transparent Dewar cylinder. Between 2 and 3 cc. of hydrogen bromide was condensed in the smaller bulb and then the entire apparatus was sealed off. The bulb containing the hydrogen bromide was brought to room temperature and the hydrogen bromide allowed to distill into the larger chamber, still at −78°. When all the acid had volatilized, the larger chamber was placed in a bath at the specified temperature. At the end of the reaction-period the apparatus was again cooled to −78° and opened. The products were worked up in the same manner as those from trimethylethylene, except that the products from the water-miscible

solvents were first distilled *in vacuo* at room temperature before final drying over phosphorus pentoxide. The reagents, in the reaction with hydrobromic acid (Table II) were mixed at 0° in glass-stoppered flasks and shaken mechanically at room temperature for two hours. The organic layer was separated, washed once with ice-water, dried over potassium carbonate, distilled *in vacuo* at room temperature and finally dried over phosphorus pentoxide.

Analytical method. The products were analyzed for tertiary bromide by the method previously described (1 c). Secondary bromide was determined by the 0.1 *N* silver nitrate method of Michael and Leupold (5). The products were shown to consist of the isomeric amyl bromides by giving 97–100% of silver bromide after two hours heating with 0.1 *N* alcoholic silver nitrate at the boiling point.

SUMMARY

1. The appearance of a rearrangement-product in the addition of concentrated aqueous hydrobromic acid to isopropylethylene (4, 5, 6) has been confirmed. In the presence of air, the yield of the secondary bromide amounted to 49% and that of the tertiary bromide to about 51% of the theory.

2. Ascaridole induced the formation of the abnormal, primary isoamyl bromide, formed at the expense of the secondary bromide.

3. In the absence of a solvent, dry hydrogen bromide adds to isopropylethylene to yield more of the tertiary and less of the secondary bromide; water, therefore, showed a solvent effect, and the long-accepted conclusion that dry hydrogen bromide and aqueous hydrobromic acid yield identical addition-products in the same proportion can no longer be upheld. It is probable that hydrobromic acid functions in addition-reactions as the hydrated form. The change in the course of the addition may be explained by an approach in the relative positivities of the unsaturated carbons in isopropylethylene, due to the polymolecular union of the hydrated acid to a greater extent at the relatively positive methinyl carbon.

4. In the dry hydrogen bromide system, ascaridole induced the formation of primary isoamyl bromide. Up to 0.009 molar concentration, it was formed mainly at the expense of the secondary bromide, but a further increase involved the tertiary bromide, which at 0.02 molar concentration almost disappeared.

5. The unusual fall in reaction velocity with rise in temperature, previously observed with trimethylethylene in methanol solution, was likewise encountered with isopropylethylene. Its slight reactivity manifested itself in no addition at −78° and at 0° in methanol alone, or at the higher temperature in the presence of ascaridole. However, at −78°, a certain critical concentration of ascaridole induced the addition and then over 80% of the abnormal primary product appeared; further increase in concentration was ineffective in altering the relative proportion of the products.

6. Ether exerted a marked solvent effect; it led to the formation of *ca.* 53% of the primary bromide, at the expense of the tertiary and secondary isomers. With isopropylethylene, contrary to the general results with other alkenes, the antioxidant diphenylamine was more effective in reducing the extent of abnormal addition than hydroquinone. The influence of these antioxidants is far less with isopropylethylene than with normal alkenes-1.

7. Acetic acid also showed a remarkable solvent effect, inducing in vacuum, or in the presence of antioxidants, the appearance of 44–47% of the abnormal primary bromide. Small amounts of ascaridole decidedly augmented the proportion of the primary bromide, which decreased slightly in amount with increasing concentration of ascaridole.

8. With dichloroacetic acid a much smaller percentage of the abnormal primary bromide was obtained. Compared with the result of solvent-free hydrogen bromide addition to the hydrocarbon, the amount of the tertiary bromide was only slightly lower, while that of the secondary bromide fell off considerably. In comparison with the influence of acetic acid, drastic changes occurred; the percentage of the secondary bromide decreased slightly but that of the primary bromide decreased by more than half, while the relative amount of the tertiary product was more than double. This result was independent of the presence of hydroquinone. Ascaridole (0.05–0.005 molar) reduced the yield of tertiary bromide and increased that of the primary derivative, but comparatively far less than in acetic acid.

9. In the presence of trichloroacetic acid, addition became normal, in the sense that only the secondary and tertiary bromides were formed. The presence of this strong acid increased the formation of the tertiary bromide at the expense of the secondary product. Exactly the same result was obtained in the presence of hydroquinone.

10. The formation of tertiary amyl bromide by the action of hydrogen bromide on isopropylethylene should not be considered an abnormal addition. It is a normal consequence of the affinity and energy relationships existing in the chemical system. The chemical behavior of this system manifests itself, alone and in the presence of solvents, oxidants and antioxidants, by changes peculiar to the hydrocarbon.

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[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

STUDIES IN THE MORPHIMETHINE SERIES[1]

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The effect of changes in the structure of the morphine molecule on pharmacological action has been studied extensively in our laboratories during recent years (1). With the exception of morphine and codeine methochlorides, however, no compounds derived from morphine by alterations of the nitrogen group have been investigated by us. The morphimethine bases, which are in principle morphines in which the nitrogen-containing ring has been opened to an ethylamine side-chain, appeared to be particularly suited to fill out this gap.

These methine bases are known only in the form of their (phenolic) methyl ethers (2), the so-called methylmorphimethines. Previous investigators were unable to obtain a phenolic methine base in the customary manner, namely by the Hofmann degradation, because the expected intermediate compound, morphine methohydroxide, is spontaneously converted into a phenol-betaine compound, which is resistant toward hot alkali (3). Another possibility of obtaining the morphimethines lies in the demethylation of their methyl ethers, which are readily prepared by the Hofmann degradation of codeine and its isomers.

On account of the presence of two alicyclic double bonds in α-methylmorphimethine (I) and β-methylmorphimethine (II), it was not expected that these compounds would be stable enough to stand a demethylation in acidic or alkaline medium at elevated temperatures. Both isomers, indeed, when boiled in hydrogen bromide-glacial acetic acid solution, turn quickly red and then deep purple, and it was not possible to isolate from the reaction-mixture anything except amorphous red and brown reaction-products. We believed that hydrogenated methylmorphimethines would be more resistant and might be demethylated at the methoxyl group in position 3 without suffering any further destruction. When dihydro-α-methylmorphimethine (III) was allowed to stand at room temperature or

[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, The University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General, U. S. P. H. S.

slightly elevated temperatures in hydrochloric or hydrobromic acid solution, a crystalline, light yellow, alkali-insoluble compound was formed, whose solutions were fluorescent. The conditions for obtaining this product in sufficient quantity and purity have not been found yet, and a further study of this reaction, which very probably involves a rearrangement, is postponed. Dihydro-β-methylmorphimethine has been described in the literature as an oil, and has been characterized only in the form of its crystalline methiodide (4). An improvement in yield and purity of this dihydro base was realized by modifying the method of preparation by using sodium amalgam instead of sodium and alcohol in the reduction of β-methylmorphimethine. The base was purified through a crystalline benzoate and a crystalline hydrochloride; the constancy of the rotatory power of the hydrochloride was taken as a criterion for the homogeneity of the base. A sample of base that had been distilled *in vacuo* became partly crystalline after being stored for about a year. Subsequently, every purified fraction of the dihydro base crystallized readily on seeding. Dihydro-β-methylmorphimethine has been given the structural formula IV by previous investigators, with the isolated double bond located at position 8,14. We consider, however, that formula IVa, with the double bond at 9,14 is equally probable, thus taking into account a 1,4-addition to the conjugated system that has been assumed to be present in β-methylmorphimethine. It may be recorded that the latter base was not attacked by aluminum amalgam and alcohol.

When dihydro-β-methylmorphimethine (IV) was boiled in a solution of 16% hydrogen bromide in glacial acetic acid, a monoacetyl derivative (V) of a dihydromorphimethine was obtained in satisfactory yield. Since this acetyl product is alkali-soluble, the alcoholic hydroxyl group must be the one that is acetylated. This acetoxy group is readily saponified with dilute alkali. When the resulting dihydromorphimethine (VI) was remethylated with diazomethane, a dihydromethylmorphimethine (VII) was obtained, which was not identical, however, with the dihydro-β-methylmorphimethine (IV) that we had subjected to demethylation. Both dihydro bases, IV and VII, can be reduced catalytically to tetrahydro-α-methylmorphimethine, and can therefore be dissimilar only in the location of the isolated double bond. In other words, a shift of the double bond must have taken place during the demethylation, under the influence of the medium (hydrogen bromide in glacial acetic acid). Since the location of the double bond in dihydro-β-methylmorphimethine appears to us uncertain, we refrain from speculations as to where the double bond migrated during demethylation[2].

[2] Since the dihydromorphimethine VI is at present the only one known in the "dihydro series," it is unnecessary to designate this base or its acetyl derivative (V)

Tetrahydro-α-methylmorphimethine (IX) was readily demethylated by 16% hydrogen bromide in glacial acetic acid. The demethylated base was obtained in good yields in the form of a monoacetyl derivative (VIII). Since VIII was also obtained by catalytic hydrogenation of the corresponding alkali-soluble dihydro product V, it must be the alcoholic hydroxyl group of VIII that is acetylated. Surprisingly enough, although the compound has a free phenolic hydroxyl group, it is insoluble in alkali[3]. Only saponification of the alcoholic acetoxy group renders the product alkali-soluble. The fact that tetrahydro-α-morphimethine (X) could be remethylated with diazomethane to tetrahydro-α-methylmorphimethine (IX) showed that no other structural change had taken place during the demethylation process. In addition to these transformations, dihydromorphimethine (VI) was catalytically reduced to tetrahydro-α-morphimethine. By this and the analogous reduction of V to VIII, mentioned above, the postulated nature of the isomerism of IV and VII finds additional support.

We wish to point out the importance of the medium in which the demethylation of dihydro-β-methylmorphimethine and tetrahydro-α-methylmorphimethine was carried out. In the attempts to demethylate these bases in boiling aqueous hydrogen bromide solutions (48%), the solutions turned quickly purple and dark violet and only tarry reaction-products could be obtained. Obviously, in glacial acetic acid solutions, acetylation preceded demethylation, whereby further destruction was prevented.

Vongerichten (5) described a "β-morphimethine", which he had obtained as a by-product by heating the reaction-product of diacetylmorphine methiodide and silver acetate in acetic anhydride at 180°. This procedure led chiefly to 3,4-diacetoxyphenanthrene. Vongerichten characterized his base as a hydrochloride, and converted it by complete

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or its methyl ether (VII) in a way that would indicate a location of the olefinic double bond different from that in dihydro-β-methylmorphimethine (IV or IVa). Designation will become necessary only if analogous bases in the γ, δ, ε, or ζ series should be prepared.

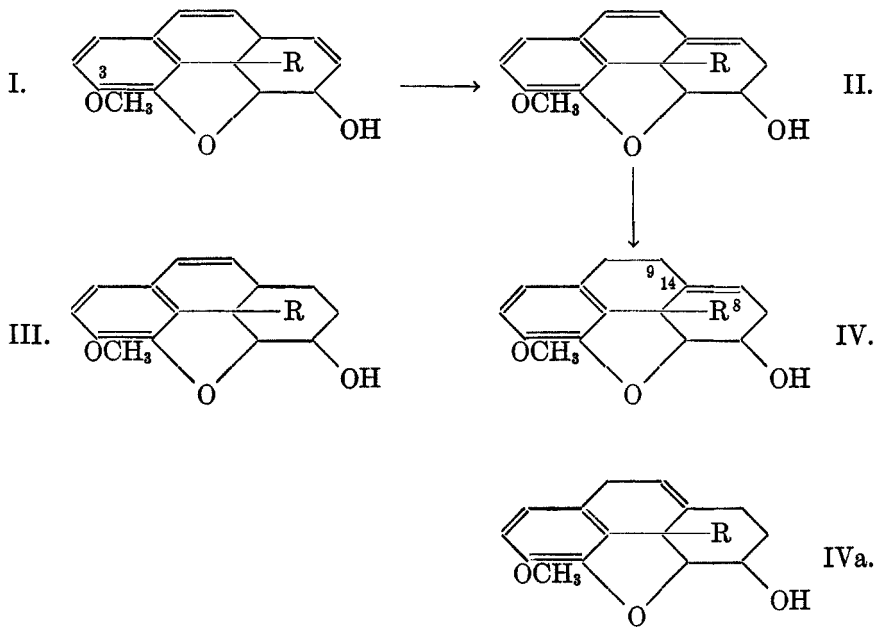
[3] This behavior of acetyldihydromorphimethine and acetyltetrahydro-α-morphimethine, *i.e.* the unsaturated phenolic base being readily soluble in alkali and the saturated base being insoluble in alkali, recalls similar relations in the desoxycodeine series. Small and Cohen, *J. Am. Chem. Soc.*, **53**, 2214, 2227 (1931); **54**, 802 (1932), observed that *e.g.* desoxycodeine-B, dihydrodesoxycodeine-B, and dihydrodesoxycodeine-C are soluble in alkali, while tetrahydrodesoxycodeine (which has no isolated double bond) is practically insoluble in alkali. It should be noted, however, that in these bases the phenolic hydroxyl group is located in position 4. There is no previous example of an alkali-insoluble morphine derivative with a free hydroxyl at the 3 position.

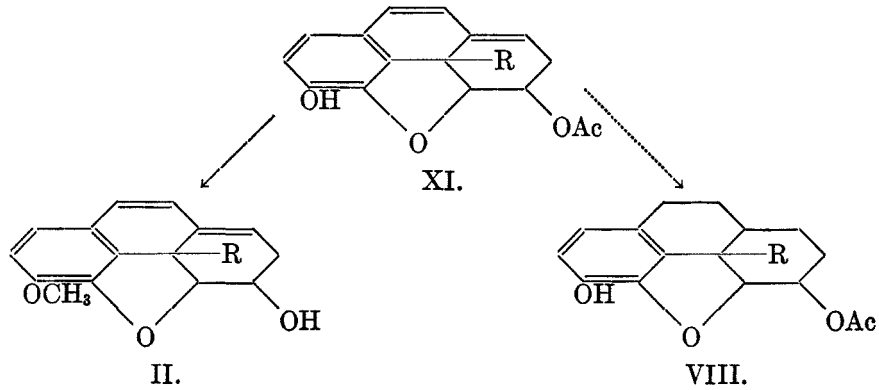
methylation (methyl iodide and sodium methylate) to a methiodide which had approximately the melting point reported for β-methylmorphimethine methiodide. He therefore assigned to his degradation base the structure of a β-morphimethine. Since it appeared to us theoretically important, we repeated Vongerichten's experiment and obtained a hydrochloride in a yield of about one per cent. It was apparently identical with Vongerichten's hydrochloride. The corresponding base, however, proved to be a monoacetyl derivative of a morphimethine, since it gave, when hydrogenated catalytically, a monoacetyltetrahydro-α-morphimethine identical with the base VIII which was obtained by demethylation of tetrahydro-α-methylmorphimethine (in glacial acetic acid). Moreover we treated our reaction-product with diazomethane, and obtained β-methylmorphimethine (II). Thus we have established that in this drastic degradation method a morphimethine derivative is obtained, if only in very small amounts.

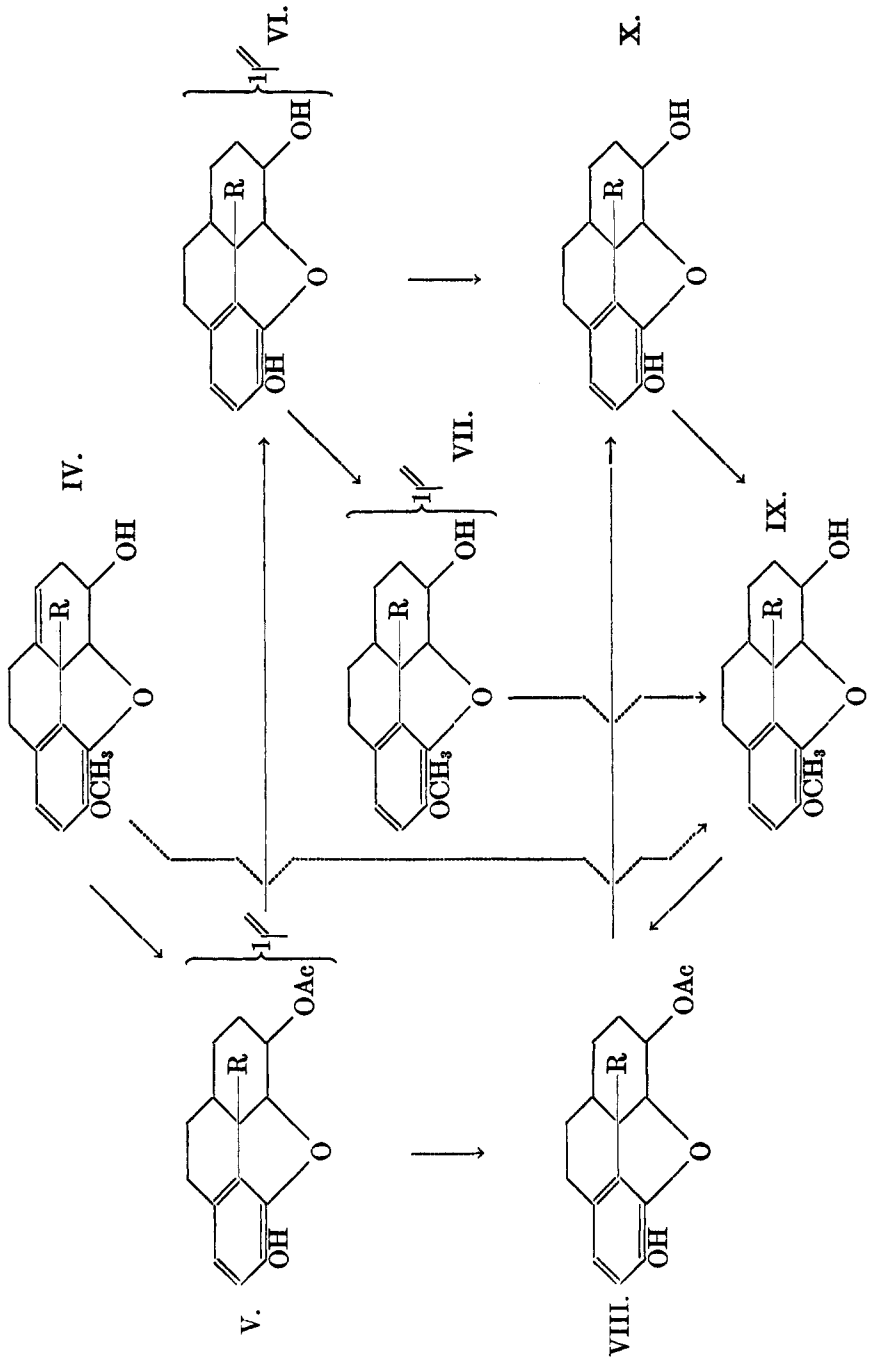
All the morphimethine derivatives discussed in this paper, with the exception of β-acetylmorphimethine, were investigated pharmacologically by Dr. N. B. Eddy at the University of Michigan (6). Three of them (dihydro-α-methylmorphimethine, dihydromorphimethine, and tetrahydro-α-morphimethine) caused no analgesia at all at doses of 100 mg. per kg., while the others (α- and β- methylmorphimethines, dihydro-β-methylmorphimethine, acetyldihydromorphimethine, tetrahydro-α-methylmorphimethine, and acetyltetrahydro-α-morphimethine) showed only a slight analgesic effect at doses of 100–150 mg., and were also in other respects pharmacologically rather inert substances. Considering the great structural similarity between morphine and the morphimethine bases, and between their corresponding derivatives, such lack of activity in the methine bases could not be expected *a priori*. Furthermore, these bases are, very obviously, more closely related to morphine in their structure than the relatively simple phenanthryl amino alcohols (7) of various types, whose analgesic action, as a whole class, is considerably higher (in the average, 25–75 mg./kg.). Thus it must be concluded that the opening of the nitrogen-containing ring in morphine and codeine, even though it leaves intact the major structural features of the morphine molecule, has a most decided and detrimental influence on analgesia and other effects except toxicity.

We wish to acknowledge the assistance of Mr. Ulysse Cormier in the preparation of α- and β- methylmorphimethine and in some of the reduction and demethylation experiments.

In the accompanying formulas R = $-CH_2CH_2N(CH_3)_2$; $\dashrightarrow$ = catalytic reduction.


I.
II.
III.
IV.
IVa.
R
OCH3
OH
O
3
9
14
8


XI.
II.
VIII.
R
OH
OAc
OCH3
O


IV.
VI.
X.
VII.
IX.
V.
VIII.
R
OH
OAc
O
OCH3

EXPERIMENTAL

All melting points are corrected.

β-Methylmorphimethine (II). This base was prepared according to Knorr and Smiles (8) from α-methylmorphimethine (9). The base crystallized from alcohol in large colorless crystals and melted at 136–137.5°.

The *hydrochloride* was prepared by adding ethereal hydrogen chloride to the solution of the base in absolute alcohol. It crystallized from absolute alcohol in colorless prisms, and melted in an evacuated tube at 265–268° (softening at 260°). Under ordinary conditions the compound decomposes gradually between 250–270°; $[\alpha]_D^{24}$ +323.6° (water, c = 1.06).

Anal. Calc'd for $C_{19}H_{24}ClNO_3$: Cl, 10.14. Found: Cl, 10.08.

The *benzoate* was prepared by combining concentrated alcoholic solutions of the base and of benzoic acid and adding ether to the mixture. It crystallized from an alcohol-ether mixture in flat, white needles and melted at 145–147°. The salt turns gradually light brown if not protected from light; $[\alpha]_D^{24}$ +260.1° (water, c = 1.09)[4].

Anal. Calc'd for $C_{26}H_{29}NO_5$: C, 71.68; H, 6.72.
Found: C, 71.62; H, 6.84.

Dihydro-β-methylmorphimethine (IV). Reduction of β-methylmorphimethine with sodium and alcohol gave yields of 40–50% of pure dihydro-β-methylmorphimethine. The reduction must be tested for completeness, either by the rotation of the hydrochloride, or by boiling the salt with 16% solution of hydrogen bromide in glacial acetic acid. Unreduced methine gives a purple color. Reduction with sodium amalgam was more satisfactory.

To a solution of 50 g. of β-methylmorphimethine in 250 cc. of absolute alcohol was added 200 g. of 5% sodium amalgam, and the mixture was kept boiling on a steam-bath for seventy-two hours. The alcoholic solution was poured off and evaporated to dryness in a vacuum. The resulting brown, oily base was converted into the benzoate, from this the base was liberated and reconverted into the hydrochloride, which was finally recrystallized from absolute alcohol. The average yield of reduced base was from 70–80%. An increase of reduction time has no effect on the yield. The sodium amalgam appeared but little changed. Occasionally a sodium amalgam was employed, which at the end of the reduction was almost entirely used up. In these instances the reduction proved to be incomplete. The values of the rotatory power of *hydrochlorides* obtained in a series of reduction experiments were between $[\alpha]_D^{24}$ −84.8° and $[\alpha]_D^{24}$ −87.2°. All fractions were finally combined and recrystallized from absolute alcohol, and gave the value of $[\alpha]_D^{24}$ −86.3° (water, c = 1.08); colorless, needle-like prisms, m.p. 235–236° (evac. tube, sintering at 233°).

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: C, 64.84; H, 7.45; Cl, 10.08.
Found: C, 64.87; H, 7.68; Cl, 9.99.

The *benzoate* crystallized from an alcohol-ether mixture in glittering, rectangular plates. It is somewhat sensitive to light; m.p. 162–164.5°.

Anal. Calc'd for $C_{26}H_{31}NO_5$: C, 71.36; H, 7.15.
Found: C, 71.36; H, 7.28.

The *base* was a colorless oil that could be readily distilled in an oil-pump vacuum. Even when crystalline it is easily soluble in the ordinary organic solvents. It may be further purified by vacuum sublimation or recrystallization from petroleum ether; colorless, sturdy prisms, m.p. 86–88.5°.

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[4] Knorr and Smiles (8) observed m.p. 157°, and $[\alpha]_D^{17}$ +254° (water, c = 1).

Anal. Calc'd for $C_{19}H_{25}NO_3$: C, 72.33; H, 7.99.
Found: C, 72.48; H, 8.09.

The hydrochloride obtained from the crystalline base showed the melting point 235–237° (evac. tube, sintering at 232°) and the rotation value $[\alpha]_D^{25}$ −85.8° (water, c = 1.12).

The *methiodide* was prepared by combining methanolic solutions of the base and methyl iodide. The precipitate was dissolved in 90% alcohol. The salt crystallizes in colorless needles or short rectangular prisms and melts with decomposition at 253–258°. Seventy-five hundredths of a gram of the finely divided methiodide was suspended in 6 cc. of acetic anhydride and boiled until a clear solution resulted (15 minutes). The *acetyl derivative* of the methiodide precipitated from the cooled solution in fine felted needles. The precipitation was completed by the addition of ether. The compound crystallized from an alcohol-ether mixture in glittering broad needles which melted at 265–270° with decomposition; $[\alpha]_D^{26}$ −71.7° (water, c = 1.11)[5].

Anal. Calc'd for $C_{22}H_{30}INO_4$: C, 52.90; H, 6.06.
Found: C, 52.40; H, 6.63.

In the catalytic hydrogenation (platinum oxide, absolute alcohol) dihydro-β-methylmorphimethine hydrochloride absorbed one molecular equivalent of hydrogen, yielding tetrahydro-α-methylmorphimethine hydrochloride, m.p. 230.5–232°; $[\alpha]_D^{22}$ −35.6° (water, c = 0.97).

Dihydromorphimethine

Acetyldihydromorphimethine (V). Forty grams of dihydro-β-methylmorphimethine hydrochloride was suspended in 240 cc. of glacial acetic acid containing 16% hydrogen bromide. The salt dissolved gradually when the mixture was heated, and the solution was kept gently boiling for two hours, after which it had turned but slightly brown. Reducing the time of heating to one hour has apparently no effect on final results. The solution was evaporated to dryness in an oil-pump vacuum, whereby a clear, slightly colored oil remained. The oil was dissolved in a small volume of water (50–100 cc.) and ether (200–300 cc.) was added to the solution. The base was precipitated with concentrated aqueous ammonia, avoiding an excess, and the mixture was allowed to stand for a few hours. The crystalline precipitate was filtered and dried in a desiccator, triturated with cold water, and dried again. Finally it was recrystallized from a benzene-petroleum ether mixture; yield 21 g., m.p. 198–200° (sintering at 195°). A further purification, either by recrystallization from benzene-petroleum ether or by sublimation in an oil-pump vacuum does not change the melting point appreciably. The base crystallizes from the solvent in fine felted needles or sublimes in broad, feather-like needles; m.p. 200–202.5° (sintering at 196°); $[\alpha]_D^{24}$ +118.4° (chloroform, c = 1.07).

Anal. Calc'd for $C_{20}H_{25}NO_4$: C, 69.93; H, 7.34.
Found: C, 69.88; H, 7.47.

Hydrochloride. The base is moderately soluble in absolute alcohol. Therefore alcoholic hydrogen chloride must be added to the warm solution of the base; no saponification takes place, as we determined by the melting point of the reliberated base. To complete the precipitation of the hydrochloride, ether may be added.

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[5] Von Braun and Cahn (4b) observed for this compound m.p. 265°, $[\alpha]_D^{22}$ +76° (c = 0.34). The fact that their rotation value is opposite in sign may be due to a misprint.

The salt crystallizes from alcohol-ether in broad, shiny needles, and melts with decomposition from 270° to 280°; $[\alpha]_D^{24}$ +39.9° (water, c = 0.102).

Anal. Calc'd for $C_{20}H_{26}ClNO_4$: C, 63.21; H, 6.90.
Found: C, 63.12; H, 7.08.

On standing for some time, some of various samples lost their transparent appearance. This change could not be brought about by drying the salt in a vacuum at 100°, and no loss of weight was observed. The change is probably a transition of one crystal-form into another. The hydrochloride dissolves readily in a small amount of water, but precipitates immediately as less soluble, short prisms.

The free base is conveniently obtained by precipitation with ammonia from the aqueous solution of the hydrochloride. The base is readily soluble in 5% alkali, and can be recovered unchanged when immediately precipitated with ammonium chloride.

When the time of demethylation of dihydro-β-methylmorphimethine hydrochloride with 16% hydrogen bromide in glacial acetic acid was extended to 7 hours, the base (m.p. 200–203°) and the hydrochloride obtained differed somewhat in their rotation values ($[\alpha]_D^{22}$ +124.8° ($CHCl_3$, c = 1.10), $[\alpha]_D^{22}$ +51.5° (water, c = 1.03) respectively) from the corresponding compounds in the first experiment. Even under entirely analogous experimental conditions, it was difficult to obtain bases and hydrochlorides of various runs, which agreed closely in their rotation values, although the melting points of the bases were practically identical. When the bases of the two experiments outlined above were reduced catalytically (platinum oxide, alcohol), the resulting samples of acetyl-α-tetrahydromorphimethines had identical melting points [240–243° (evac. tube, sintering at 238°)] and practically identical values of rotation of the respective hydrochlorides: $[\alpha]_D^{21}$ −38.0° (water, c = 1.08), and $[\alpha]_D^{21}$ −38.6° (water, c = 1.06).

Dihydromorphimethine (VI). Three and four-tenths grams of base V was dissolved in 22 cc. of 1 *N* sodium hydroxide, and the solution was kept gently boiling for 10 minutes, whereby more than half of the water was allowed to evaporate. Concentrated ammonium chloride solution was added dropwise until the solution remained slightly turbid. After a short time, a heavy crystalline precipitate began to settle. For completion, more ammonium chloride was added dropwise until no precipitate was formed. The crude product was recrystallized from ethyl acetate, sublimed in an oil-pump vacuum at 130–140°, and again recrystallized from ethyl acetate; short prisms of m.p. 171–173°, average yield 55–60%. By repeating the sublimation, the melting point can be raised to 174–176°. The compound is readily soluble in alcohol and chloroform; $[\alpha]_D^{26}$ +92.8° ($CHCl_3$, c = 1.03).

Anal. Calc'd for $C_{18}H_{23}NO_3$: C, 71.72; H, 7.70.
Found: C, 71.81; H, 8.04.

The hydrochloride was prepared in the usual manner, by addition of alcoholic hydrogen chloride to the alcoholic solution of the base. Ether was added to complete the precipitation. The salt crystallized from an alcohol-ether mixture in prismatic needles, which melted unsharply in the evacuated tube at 250-266°, and after drying at 100°, at 260-271°. The compound contains water or alcohol of crystallization, but neither carbon-hydrogen analyses nor determinations of loss of weight by drying at different temperatures gave satisfactory values. Eventually it was found, accidentally, that the salt could be sublimed in an oil-pump vacuum at 190°. It melts at 275–278° (evac. tube, sintering at 272°).

Anal. Calc'd for $C_{18}H_{24}ClNO_3$: C, 63.97; H, 7.16.
Found: C, 64.03; H, 7.11.

When the base was liberated from its hydrochloride in aqueous solution by am-

monia, the precipitate contained varying amounts of the hydrochloride. Therefore it is more satisfactory to prepare the base by precipitating it from the hydrochloride with alkali, dissolving it in an excess, and finally reprecipitating with ammonium chloride.

Diacetyldihydromorphimethine. A solution of acetyldihydromorphimethine (7 g.) in a mixture of pyridine (50 cc.) and acetic anhydride (21 cc.) was allowed to stand at room temperature for three days and worked up in the usual way. The product was a colorless oil that gave no crystalline picrate or salicylate. The hydrochloride, prepared in the usual manner (alcoholic hydrogen chloride and alcohol-ether mixture), precipitated as an oil, which on standing gradually turned into a crystalline mass. These crystals, however, proved to be the hydrochloride of the monoacetyl derivative. Likewise, when ammonia was added to the solution of the diacetyl product in aqueous dilute hydrochloric acid, an oil precipitated that gradually turned into the crystalline monoacetyl product.

The methyl ether of dihydromorphimethine (VII) was prepared by adding to the solution of 1 g. of dihydromorphimethine in 10 cc. of methanol an ethereal diazomethane solution (from 5 cc. of nitrosomethylurethane), and allowing the mixture to stand for two days. On isolation of the non-phenolic product in the usual manner, an oily base (yield nearly quantitative) was obtained that resisted all attempts at crystallization. Its *hydrochloride* crystallized from an alcohol-ether mixture in elongated prisms, and melted at 227–230° (evac. tube, sintering at 224°); $[\alpha]_D^{24}$ +47.0° (water, c = 1.00).

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: C, 64.84; H, 7.45; OCH_3, 8.82.
Found: C, 64.92; H, 7.36; OCH_3, 9.05.

Reduction to tetrahydro-α-methylmorphimethine. A mixture of 0.5 g. of the above hydrochloride and 0.05 g. of platinum oxide in 30 cc. of absolute alcohol absorbed one mole of hydrogen within a few minutes. The hydrochloride obtained from the reaction-mixture crystallized from an alcohol-ether mixture in the characteristic form of fine felted needles or rosettes. It melted at 229–231° (evac. tube, sintering at 228°). When mixed with an authentic sample of tetrahydro-α-methylmorphimethine, it melted at the same point; $[\alpha]_D^{20}$ −32.8° (water, c = 1.00).

The non-phenolic by-products in the demethylation of dihydro-β-methylmorphimethine. After the separation of the crude crystalline acetyldihydromorphimethine, an aqueous and an ethereal solution remained, both of which were red-brown in color. The aqueous solution was saturated with salt and exhaustively extracted with ether. These two ethereal solutions were combined and evaporated to dryness. The oily residue, which contained some crystalline material (obviously acetyldihydromorphimethine), was suspended in 2 *N* potassium hydroxide and boiled for 10 minutes. The remaining oil was taken up in ether. The solution left on evaporation a light brown oil from which a crystalline hydrochloride could be obtained; average yield 15–20%, calculated on the amount of dihydro-β-methylmorphimethine subjected to demethylation. The rotation values of fractions from different experiments approximated $[\alpha]_D$ +10°. It was possible to remove a small amount of less soluble material in one or two crystallizations from an alcohol-ether mixture, while the bulk of the hydrochloride retained stubbornly a light brown tinge. After repeated recrystallization, the hydrochloride was obtained eventually in practically colorless prismatic needles, m.p. 229–230° (evac. tube, softening at 224°); $[\alpha]_D^{25}$ +13.56° (water, c = 1.07).

Anal. Calc'd for $C_{19}H_{26}ClNO_3$: C, 64.84; H, 7.45; OCH_3, 8.82.
Found: C, 64.50; H, 7.27; OCH_3, 8.87.

The mixture melting point with the hydrochloride of the methyl ether of dihydro-

morphimethine was 226–229° (evac. tube, sintering at 222°). Similarly the mixture melting point with the hydrochloride of dihydro-β-methylmorphimethine was indecisive.

The hydrochloride gave, when catalytically reduced (absolute alcohol, platinum oxide), a compound that proved to be tetrahydro-α-methylmorphimethine hydrochloride. It melted at 228–230° (evac. tube, sintering at 227°) and gave no melting point depression when mixed with an authentic sample; $[\alpha]_D^{25}$ −35.2° (water, c = 1.14).

Attempted demethylation of this "by-product" under the conditions described for dihydro-β-methylmorphimethine gave decomposition-products.

Tetrahydro-α-morphimethine

Acetyltetrahydro-α-morphimethine (VIII). Fifteen grams of α-tetrahydromethylmorphimethine hydrochloride[6] was suspended in 90 cc. of 16% hydrogen bromide in glacial acetic acid. The salt dissolved gradually on warming, and the solution was kept boiling for two and one-half hours and then diluted with three parts of water. The solution, when evaporated in a water-pump vacuum to dryness, left a nearly colorless, clear oil. This was dissolved in about 50 cc. of water and 150 cc. of ether was added. By dropwise addition of ammonia, a white crystalline compound was precipitated immediately. The precipitate was filtered after five hours and washed with water and a little cold ether. It melted at 226–232° and weighed 12.4 g. The compound was sublimed at 170–175° in an oil-pump vacuum, whereby at first a small amount of oil distilled over. The acetyltetrahydro-α-methylmorphimethine sublimes in beautiful broad needles. The oil could be removed with alcohol, in which the crystals are only moderately soluble. After resublimation they melt at 240–242° (evac. tube, sintering at 237°).

Anal. Calc'd for $C_{20}H_{27}NO_4$: C, 69.53; H, 7.88; $COCH_3$, 12.46.
Found: C, 69.85; H, 8.03; $COCH_3$, 11.35.

The base does not dissolve in cold 5% potassium hydroxide. When this suspension of base in alkali is allowed to stand at room temperature, a clear solution results after about 2 hours. The base, precipitable from this solution with ammonium chloride, is pure tetrahydro-α-morphimethine.

Hydrochloride. The acetylated base is less soluble in alcohol than the corresponding dihydro compound. No saponification takes place in the preparation of the hydrochloride. The base was precipitated from this hydrochloride and reconverted to the hydrochloride. There was no difference in the rotation values of the two samples of hydrochloride. It crystallized from alcohol-ether in transparent leaflets or in elongated prisms, m.p. 253–262° (evac. tube, sintering at 245°); $[\alpha]_D^{25}$ −42.8° (water, c = 0.99).

Anal. Calc'd for $C_{20}H_{28}ClNO_4$: C, 62.88; H, 7.39.
Found. C, 62.50; H, 7.38.

As mentioned above, acetyltetrahydro-α-morphimethine was also obtained by catalytic reduction of the corresponding dihydro compound. A suspension of finely divided acetyldihydromorphimethine (1.7 g.) and platinum oxide (0.1 g.) in absolute alcohol absorbed the calculated amount of hydrogen within five hours. In the course of the reduction, the dihydro base dissolves gradually, and when the solution

[6] This salt is conveniently prepared by catalytic reduction (absolute alcohol, platinum oxide) of α-methylmorphimethine hydrochloride. It crystallizes from an alcohol-ether mixture in felted needles, m.p. 229–231° (evac. tube, sintering at 227°), $[\alpha]_D^{26}$ −35.0° (water, c = 1.13).

is clear the tetrahydro base begins to precipitate. It was filtered off together with the catalyst, redissolved in acetic acid, precipitated with ammonia, and sublimed; m.p. 240–243° (evac. tube, sintering at 238°; no depression of the melting point when this sample was mixed with that obtained above by demethylation). The values of rotation of the hydrochlorides obtained in several reduction experiments were between $[\alpha]_D$ −38.0° and −39.0°.

Tetrahydro-α-morphimethine (X). A suspension of 4.4 g. of acetyltetrahydro-α-morphimethine in 35 cc. of 1 *N* sodium hydroxide was heated to boiling. Within one or two minutes the precipitate went into solution, and boiling was continued for five minutes. On addition of concentrated ammonium chloride solution, the deacetylated product precipitated in white heavy crystals (3.7 g.). For further purification the compound was sublimed in an oil-pump vacuum at 150°. Crystallization from alcohol or ethyl acetate (the base is sparingly soluble in the latter solvent) does not change the melting point appreciably; diamond-shaped prisms, m.p. 206–208° (evac. tube, sintering at 204°).

Anal. Calc'd for $C_{18}H_{25}NO_3$: C, 71.24; H, 8.31.
Found: C, 71.35; H, 8.21.

This compound was also obtained by catalytic reduction (platinum oxide, absolute alcohol) of dihydromorphimethine. After sublimation, the reduction-product melted at 207–208° (evac. tube, sintering at 204°) and showed no melting point depression when mixed with the compound described above.

The *hydrochloride* was prepared in the customary way and crystallized from absolute alcohol in fine felted needles, m.p. 243–249° (evac. tube, sintering at 240°); $[\alpha]_D^{23}$ −29.6° (water, c = 1.03).

Anal. Calc'd for $C_{18}H_{26}ClNO_3$: C, 63.59; H, 7.71.
Found: C, 63.71; H, 7.85.

Diacetyltetrahydro-α-morphimethine was obtained (pyridine, acetic anhydride) only as an oil, which was very readily distillable in an oil-pump vacuum. Only an oily hydrochloride, picrate, and perchlorate could be prepared from the base.

When tetrahydromorphimethine was boiled in 16% hydrogen bromide in glacial acetic acid for three hours, the solution diluted with water, and ammonia added, pure (mono) acetyltetrahydro-α-morphimethine was precipitated.

Tetrahydro-α-methylmorphimethine from tetrahydro-α-morphimethine. To a suspension of 1 g. of tetrahydro-α-morphimethine in 25 cc. of methanol was added an ethereal diazomethane solution (from 5 cc. of nitrosomethylurethane). The reaction-mixture yielded (after two days) 1.1 g. of non-phenolic base, which was converted into the hydrochloride. The latter crystallized from alcohol-ether in felted needles that melted at 228–230° (evac. tube), and showed no melting point depression when mixed with an authentic sample of tetrahydro-α-methylmorphimethine hydrochloride; $[\alpha]_D^{25}$ −36.2° (water, c = 1.02).

Anal. Calc'd for $C_{19}H_{28}ClNO_3$: C, 64.46; H, 7.98.
Found: C, 64.82; H, 7.90.

Acetyltetrahydro-α-methylmorphimethine. A solution of 2.6 g. of tetrahydro-α-methylmorphimethine in 20 cc. of pyridine and 10 cc. of acetic anhydride was allowed to stand for 24 hours. The solution was evaporated to dryness in a vacuum, and the remaining oil was dissolved in ice water, decomposed with sodium carbonate, and extracted with ether. The hydrochloride of the acetylated base crystallized from an alcohol-ether mixture in elongated rectangular prisms, m.p. 240–245° (evac. tube, sintering at 232°); $[\alpha]_D^{26}$ −47.53° (water, c = 1.03).

Anal. Calc'd for $C_{21}H_{30}ClNO_4$: C, 63.68; H, 7.64.
Found: C, 63.51; H, 7.79.

This acetyl product was also formed when a solution of tetrahydro-α-methylmorphimethine hydrochloride in glacial acetic acid, containing 16% hydrogen bromide, was allowed to stand for a day.

β-Morphimethine. Sixty grams of finely pulverized morphine methiodide, dried in a vacuum at 100°, was suspended in 200 cc. of acetic anhydride, and the suspension was carefully heated to boiling. The solid dissolved gradually within an hour and the heating was interrupted. On cooling, the reaction-mixture solidified to a pasty crystalline mass, from which the liquid was separated by suction. The precipitate was repeatedly washed with an alcohol-ether mixture (1:3), and finally with ether. It consisted of nearly white, glittering leaflets (65 g.), and was used in this form for further experiments. It crystallized from methyl alcohol in glittering, colorless leaflets, and melted at 233–239°; $[\alpha]_D^{25}$ −111° (water, c = 1.04). A sample prepared from diacetylmorphine and methyl iodide (10) was practically identical in melting point and rotation.

A mixture of 70 g. of diacetylmorphine methiodide and 28 g. of silver acetate in 150 cc. of acetic anhydride was boiled for three and one-half hours, and the dark brown filtrate from the silver salts was heated in sealed tubes at 170–180° for about four hours. The content of the tubes was poured into 500 cc. of water, and after three days the precipitate had become solid enough to be readily filtered (22 g.). The filtrate was concentrated to about one-half of its volume, was made alkaline with sodium carbonate and then extracted exhaustively with ether. In this procedure a considerable amount of tarry material was formed, which was insoluble in water and in ether. The ethereal extracts left on evaporation a brown, half-crystalline and half-oily mass (6 g.), from which, however, no individual compound could be isolated. In order to obtain a homogeneous product, the whole mass was dissolved in a mixture of 30 cc. of dry pyridine and 15 cc. of acetic anhydride and allowed to stand at room temperature for two days. The acetylated product (a heavy oil) was isolated from the mixture in the usual manner, and distilled very slowly in an oil-pump vacuum at 130–180°. The yellowish, oily distillate (2 g.) was redistilled at 110–150°. First a clear, colorless, viscous oil came over, then a mixture of oil and crystals, and finally only crystalline material. The last fraction was washed with very little cold ether and sublimed at 125°; broad, feather-like needles, m.p. 183–185° (evac. tube, sintering at 182°). The values for carbon and hydrogen are in fair agreement with those of a monoacetylmorphimethine.

Anal. Calc'd for $C_{20}H_{23}NO_4$: C, 70.34; H, 6.79.
Found: C, 70.78; H, 6.86.
(Calc'd for morphimethine $C_{18}H_{21}NO_3$: C, 72.19, H, 7.07.)[7]

When the acetyl compound was dissolved in 10% hydrochloric acid, a hydrochloride precipitated immediately.

The oily part of the distillate (approximately 80% of the whole amount), which was apparently the diacetyl product of a morphimethine, was dissolved in 10% hydrochloric acid. A hydrochloride gradually precipitated in fine white needles, which, after drying, showed no definite melting point (200–210°, evac. tube, sintering at 145°). Since an alcoholic solution of the salt darkened rapidly, a crystallization from alcohol-ether was unsuccessful. One-tenth gram of the dried hydrochloride in 10

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[7] It should be noted that Vongerichten's (5) analytical values for "β-morphimethine hydrochloride": Found: C, 63.60; H, 6.38, are in better agreement with those calculated for the corresponding acetyl derivative,—C, 63.54; H, 6.40,—than with the values calculated for a morphimethine hydrochloride,—C, 64.34; H, 6.60.

cc. of water with 0.05 g. of platinum oxide took up the calculated amount of hydrogen quite rapidly. The solution was filtered from the catalyst and evaporated in a vacuum to a small volume. By addition of ammonia, a crystalline precipitate was obtained, which melted in a vacuum unsharply at 220–232°. The melting point did not change after the product was sublimed. Crystallization from absolute alcohol gave short needles of m.p. 238–241° (evac. tube, sintering at 235°). Acetyltetrahydro-α-morphimethine, when recrystallized from alcohol, had the same appearance and melted at 241–243° (evac. tube, sintering at 235°). The mixture of the two compounds melted at 241–243° (evac. tube, sintering at 238°). The reduction-product apparently contained some tetrahydro-α-morphimethine, which is decidedly more soluble in alcohol than its acetyl derivative. The catalytic reduction of the acetylmorphimethine was unsuccessful, the base being rather unstable when dissolved in alcohol.

A mixture of monoacetylmorphimethine in methanol and ethereal diazomethane solution was allowed to stand for 24 hours. An alkali-insoluble oil was obtained. It was boiled for a short time in 10% hydrochloric acid. From this acid solution, on precipitation with alkali, a base of m.p. 131–134° was obtained. It melted after sublimation at 134.5–135.5°. An authentic sample of β-methylmorphimethine, after sublimation, had the same appearance and the same melting point. The mixture of the two compounds melted at 134–135.5°.

Since a rearrangement from the α- to the β-form could have occurred during saponification with 10% hydrochloric acid, the possibility that the above acetylmorphimethine belongs to the α-series cannot be excluded entirely. This is, however, improbable. In agreement with similar observations of Knorr (11), Vongerichten's assumption of a rearrangement of the primarily-formed α-methylmorphimethine to β-methylmorphimethine under the influence of acetic anhydride appears to be correct.

SUMMARY

The preparation of the crystalline dihydro-β-methylmorphimethine is described.

Dihydro-β-methylmorphimethine and tetrahydro-α-methylmorphimethine were demethylated with 16% hydrogen bromide in glacial acetic acid. During the demethylation of the former base, a migration of the isolated double bond took place.

By a drastic degradation according to Vongerichten, an acetyl-β-morphimethine was obtained in a yield of about 1%.

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[CONTRIBUTION FROM THE CHEMISTRY LABORATORY OF THE UNIVERSITY OF MICHIGAN]

THE SYNTHESIS OF METHYLCHRYSENES AND RELATED COMPOUNDS[1]

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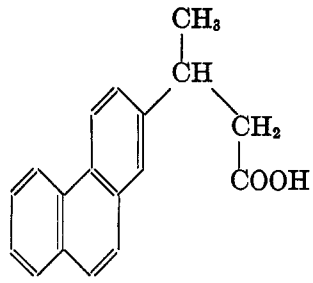
Only three of the six possible monomethylchrysenes have been synthesized. In a previous paper (1) we have reported the preparation of 2-methylchrysene and 4-methylchrysene. The latter isomer has also been synthesized independently by Fieser and Johnson (2), and 6-methylchrysene has been obtained by Newman (3). In this paper we are reporting the synthesis of 1-methylchrysene and 3-methylchrysene, each by two independent methods, as well as new procedures for obtaining 2-methylchrysene and 4-methylchrysene.

The starting material for the preparation of 1-methylchrysene (V) was 2-acetylphenanthrene, which can be obtained readily by acetylation of phenanthrene. This ketone was reduced to methyl-2-phenanthryl carbinol in excellent yield by means of aluminum isopropoxide (4). The bromide, obtained by interaction of the carbinol and phosphorus tribromide, was condensed with sodio-malonic ester, and the product was converted into β-(2-phenanthryl) butyric acid (I). The side chain of this acid was lengthened by means of the Arndt-Eistert reaction (5) and γ-(2-phenanthryl) valeric acid (II) was obtained in good yield. Cyclization of the acid chloride in carbon disulfide by stannic chloride yielded 1-methyl-4-keto-1,2,3,4-tetrahydrochrysene (III). Clemmensen reduction of this cyclic ketone gave 1-methyl-1,2,3,4-tetrahydrochrysene (IV), which was smoothly dehydrogenated to 1-methylchrysene (V) by palladium on charcoal. This hydrocarbon possesses properties which are quite different from those of 5-methyl-1,2-benzanthracene, which would have resulted if cyclization had occurred in the 3 position of the phenanthrene nucleus. Further proof of the structure of the compound was obtained by its synthesis by the method to be described.

By reaction of 1-methyl-4-ketotetrahydrochrysene (III) with methylmagnesium iodide, followed by dehydration and dehydrogenation of the product, 1,4-dimethylchrysene was prepared.

[1] From the Ph.D. dissertation of W. S. Struve.



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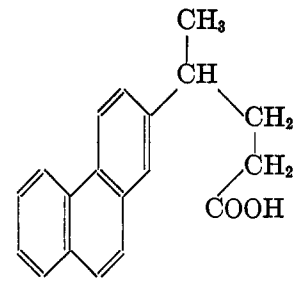

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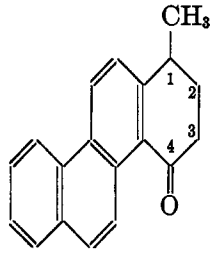

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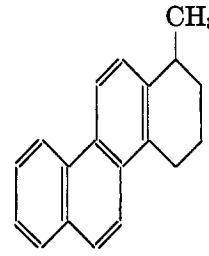

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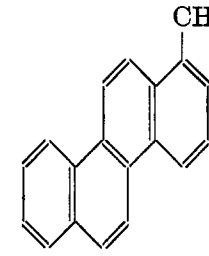

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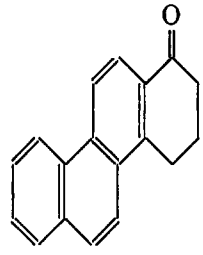

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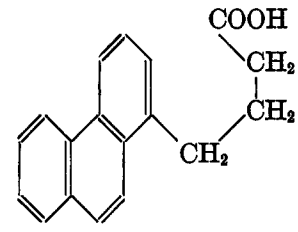

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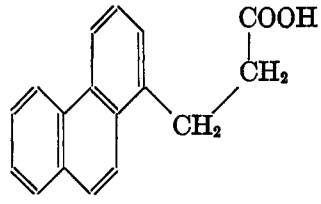

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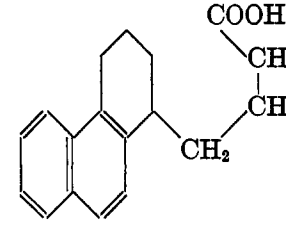
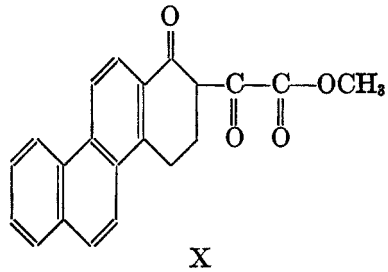


IX

In the second synthesis, 1-methylchrysene was obtained by dehydration and dehydrogenation of the carbinol formed by interaction of methylmagnesium iodide and 1-keto-1,2,3,4-tetrahydrochrysene (VI). The latter compound was first prepared by Hoch (6) by cyclization of γ-(1-phenanthryl)butyric acid (VII) by means of stannic chloride. We em-

ployed the acid chloride rather than the free acid for cyclization. The acid was obtained in two ways: from 1-keto-1,2,3,4-tetrahydrophenanthrene according to Hoch's procedure, and from β-(1-phenanthryl)propionic acid, which can be prepared readily from 1-phenanthraldehyde. In the first method we dehydrogenated the methyl ester of the intermediate γ-[1-(1,2,3,4-tetrahydrophenanthryl)]butyric acid (IX) by palladized charcoal in excellent yields, whereas Hoch used sulfur for this purpose. In the second method the Arndt-Eistert reaction was employed to convert the β-(1-phenanthryl)propionic acid (VIII) to γ-(1-phenanthryl)butyric acid. The products obtained by the two methods were identical. 1-Ethylchrysene was obtained by dehydration and dehydrogenation of the product formed by interaction of the 1-ketotetrahydrochrysene and ethylmagnesium bromide.

In order to prepare 2-methylchrysene, the 1-ketotetrahydrochrysene was condensed with methyl oxalate by means of sodium methoxide in an



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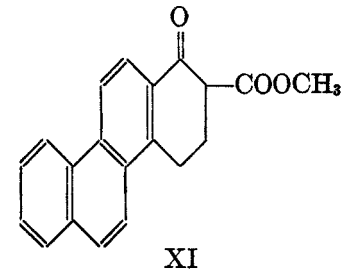

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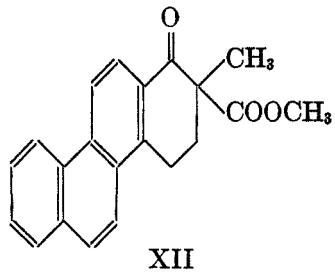

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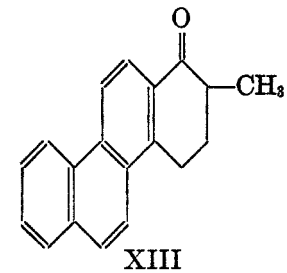

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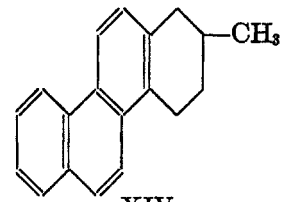
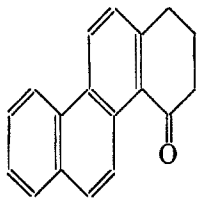


XIV

atmosphere of nitrogen to give methyl 1-keto-1,2,3,4-tetrahydrochrysene-2-glyoxalate (X). The yield of glyoxalate was lower when the reac-

tion was carried out in air, presumably through the susceptibility of the sodio derivative to oxygen. The glyoxalate was smoothly converted to 1-keto-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XI) by loss of carbon monoxide when it was heated to 180–190° with powdered soft glass, the procedure recently developed by Bachmann, Cole, and Wilds (7). By treating the sodio derivative of this compound with methyl iodide, 1-keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XII) was obtained. The latter compound, on hydrolysis and subsequent decarboxylation, gave 1-keto-2-methyl-1,2,3,4-tetrahydrochrysene (XIII) in excellent yield. Clemmensen reduction of the ketone gave 2-methyl-1,2,3,4-tetrahydrochrysene (XIV), identical with that which had previously been made by a different method. The dehydrogenation of the compound to 2-methylchrysene was described in the previous paper (1).

In a similar manner, 4-keto-1,2,3,4-tetrahydrochrysene (XV) was condensed with methyl oxalate and the product converted to 3-methylchrysene (XVII) by the reactions just described. The intermediate 3-methyl-4-keto-1,2,3,4-tetrahydrochrysene (XVI) was also prepared from ω-bromo-2-acetylphenanthrene (XVIII). Condensation of this compound with sodio-methylmalonic ester, followed by hydrolysis and decarboxylation of the product of the reaction, gave β-(2-phenanthroyl)-α-methyl-



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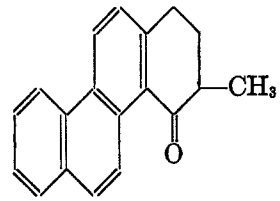

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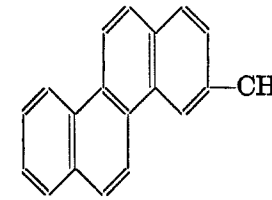

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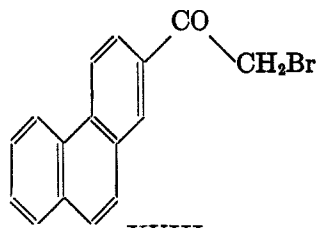

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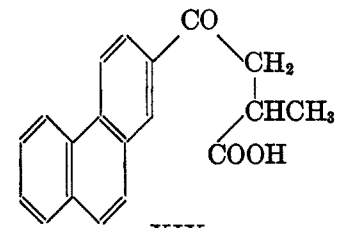
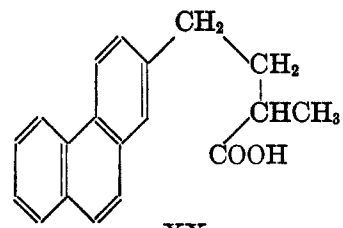


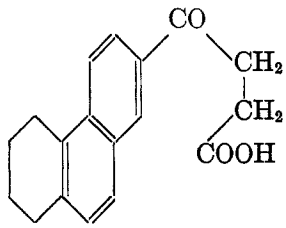
XIX



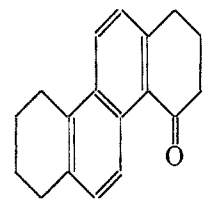
XX

propionic acid (XIX) in poor yield. Clemmensen reduction of the keto acid gave a good yield of γ-(2-phenanthryl)-α-methylbutyric acid (XX), which was cyclized through its acid chloride by stannic chloride to XVI.

In a previous paper (8) we reported that tetrahydrophenanthrene reacts with succinic anhydride chiefly in the 9 position to give β-[9-(1,2,3,4-tetrahydrophenanthroyl)]propionic acid, but there was some evidence of the formation of an isomeric acid. We have now succeeded in isolating the isomeric acid and have shown it to be β-[7-(1,2,3,4-tetrahydrophenanthroyl)]propionic acid (XXI). The structure of the acid followed from the formation of γ-(2-phenanthryl)butyric acid when the reduced acid (γ-[7-(1,2,3,4-tetrahydrophenanthryl)]butyric acid) was dehydrogenated (in the form of its methyl ester) by palladized charcoal. Cyclization of the γ-[7-(1,2,3,4-tetrahydrophenanthryl)]butyric acid through its acid chloride by stannic chloride gave 4-keto-1,2,3,4,7,8,9,10-octahydrochrysene



XXI



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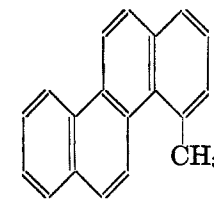

XXIII

(XXII). From this compound 4-methylchrysene (XXIII) was obtained through the action of methylmagnesium iodide, followed by dehydration and dehydrogenation of the product. The formation of this product constitutes further proof of the structure of the keto acid and shows that ring closure took place from the 7 to the 8 position in the 1,2,3,4-tetrahydrophenanthrene molecule.

EXPERIMENTAL

All melting points are uncorrected.

Methyl-2-phenanthryl carbinol. To a solution of aluminum isopropoxide prepared by refluxing 10 g. of aluminum wire, 5 drops of carbon tetrachloride, a pinch of mercuric chloride, and 250 cc. of isopropyl alcohol was added 10 g. of 2-acetylphenanthrene (9) and 250 cc. of isopropyl alcohol. The mixture was refluxed for one hour, and then 250 cc. of isopropyl alcohol was distilled off over a period of two hours. The complex was decomposed with ice-cold 10% sulfuric acid, the carbinol was taken up in benzene, the benzene extract was washed with dilute ammonium hydroxide and then with water, and the benzene was evaporated at room temperature. The residue crystallized from benzene-petroleum ether; weight, 9.60 g. (95%); m.p. 131–131.5°. Mosettig and van de Kamp (10), who prepared the compound by catalytic hydrogenation of the ketone, give 134–135° as the melting point of the carbinol.

α-(2-Phenanthryl)ethyl bromide. To an ice-cold suspension of 10 g. of the above

carbinol in 70 cc. of dry ether was added 2.95 cc. of phosphorus tribromide. The mixture was allowed to stand for an hour in the cold, the ether was evaporated at room temperature, and the residue was triturated with a small amount of methanol, cooled, and filtered; weight, 11.47 g. (89%); m.p. 84–85.5°. For further purification the bromide was dissolved in benzene, the benzene solution was washed with dilute sodium bicarbonate solution, the benzene was evaporated at room temperature, and the residue was crystallized several times from benzene-petroleum ether, from which it was obtained as colorless leaflets; m.p. 86–88°.

Anal. Calc'd for $C_{16}H_{13}Br$: Br, 28.1. Found: Br, 28.5.

β-(2-Phenanthryl)butyric acid (I). To a solution of ethyl sodio-malonate prepared from 0.48 g. of sodium, 4.2 cc. of malonic ester, and 20 cc. of absolute alcohol was added 3.89 g. of purified 2-phenanthrylethyl bromide dissolved in 30 cc. of benzene. The solution was allowed to stand at room temperature overnight and was then refluxed for two hours. If the bromide is added to a hot suspension of sodio-malonic ester in benzene and the whole is refluxed for twelve hours, the yield of product is low. As much alcohol as possible was distilled off, benzene and dilute hydrochloric acid were added, the benzene layer was washed with water, the benzene was evaporated, and the residue was heated for an hour with 45% potassium hydroxide solution. The mixture was diluted to dissolve the potassium salt and acidified. The dicarboxylic acid was heated at 180° for a half hour, and the decarboxylated product was crystallized from chloroform-petroleum ether; weight, 3.14 g. (87%); m.p. 128–130°, resolidifying on further heating and remelting at 137–138°. After two recrystallizations from chloroform-petroleum ether and seeding with the high-melting form, the acid melted at 138–139°. It is not necessary to use purified bromide; in a run, using 5 g. of the crude bromide, 3.83 g. (83%) of acid softening at 129°, resolidifying on further heating and melting completely at 137.5–138.5°, was obtained. Bergmann and Hillemann (11), who prepared this acid by the Reformatsky reaction, give 125–127° as the melting point of this compound.

γ-(2-Phenanthryl)valeric acid (II). To a suspension of 1.32 g. of β-(2-phenanthryl)butyric acid in 2 cc. of dry ether and 1 drop of pyridine was added 1 cc. of thionyl chloride, and the mixture was allowed to stand at room temperature for a half hour. The ether and thionyl chloride were then evaporated under reduced pressure, the acid chloride was dissolved in ether, and was added drop by drop to a solution of diazomethane in 25 cc. of ether, the diazomethane being prepared from 3 cc. of ethyl N-methyl-N-nitrosocarbamate. After standing at room temperature for two hours, the ether was evaporated under reduced pressure and the oily diazo ketone was dissolved in 15 cc. of dry methanol. The methanol solution was refluxed for one hour, with addition of silver oxide from 2.5 cc. of 10% silver nitrate solution. Half of the silver oxide was added at the beginning of the healting and the rest in five portions at five minute intervals. The methanol solution was filtered and the residue from evaporation of the methanol was heated for an hour with 45% potassium hydroxide solution. The mixture was diluted to dissolve the potassium salts, filtered, and acidified; weight, 1.34 g.; m.p. 124–130°. The crude acid was sublimed at 230° and 0.4 mm. and the sublimate was crystallized from benzene-petroleum ether; weight, 1.15 g. (83%); m.p. 132–134°. After several further crystallizations from benzene-petroleum ether the acid was obtained as colorless leaflets; m.p. 136.5–138.5°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5.
Found: C, 81.9; H, 6.5.

1-Methyl-4-keto-1,2,3,4-tetrahydrochrysene (III). To a suspension of 2.85 g. of γ-(2-phenanthryl)valeric acid in 30 cc. of ether and 2 drops of pyridine was added 6

cc. of thionyl chloride. After standing at room temperature for a half hour, the ether and thionyl chloride were removed under reduced pressure. The acid chloride was dissolved in 30 cc. of carbon disulfide (benzene proved less satisfactory) and 4.5 cc. of stannic chloride was added to the chilled solution. After standing at room temperature for one hour, the mixture was hydrolyzed with ice and hydrochloric acid, the carbon disulfide layer was washed with water, and the carbon disulfide was evaporated. The residue was dissolved in benzene, the benzene solution was washed with ammonium hydroxide and then with water, the benzene was evaporated, and the ketone was crystallized from acetone-alcohol; weight, 1.91 g. (72%); m.p. 94–96.5°. After two further crystallizations from alcohol-acetone, colorless prisms of the ketone were obtained; m.p. 98.5–99.5°. Sometimes on crystallization the ketone separates as leaflets which melt at 75–77° and can be changed to the higher-melting form by seeding with it.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 88.0; H, 6.1.

1-Methyl-1,2,3,4-tetrahydrochrysene (IV). A mixture of 1 g. of 1-methyl-4-keto-1,2,3,4-tetrahydrochrysene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of a 1:1 mixture of acetic and concentrated hydrochloric acids being added in portions over that time. The toluene layer was separated, the toluene was evaporated, and the residue was sublimed at 200° and 0.4 mm. The sublimate crystallized from alcohol-acetone as colorless leaflets; yield, 0.81 g. (86%); m.p. 120–121°. After two further crystallizations from alcohol-acetone the compound melted at 120.5–121°.

Anal. Calc'd for $C_{19}H_{18}$: C, 92.7; H, 7.3.
Found: C, 92.3; H, 7.4.

The *picrate* crystallizes from absolute alcohol in yellowish-orange needles; m.p. 124–124.5°.

Anal. Calc'd for $C_{19}H_{18}\cdot C_6H_3N_3O_7$: N, 8.8. Found: N, 8.7.

1,4-Dimethylchrysene. To a Grignard reagent made from 0.5 cc. of methyl iodide and 0.15 g. of magnesium in 5 cc. of dry ether was added 0.5 g. of 1-methyl-4-keto-1,2,3,4-tetrahydrochrysene and 10 cc. of dry benzene. The mixture was allowed to stand at room temperature overnight and was then decomposed with ice and ammonium chloride. To the residue from evaporation of the benzene-ether layer was added 0.05 g. of palladium-charcoal catalyst (12) and the mixture was heated at 300–320° for one hour. The mixture was then taken up in benzene, the filtered benzene solution was evaporated, and the hydrocarbon was crystallized from benzene-petroleum ether; yield, 0.39 g. (79%); m.p. 140–141°. After two recrystallizations from benzene-petroleum ether, the compound was obtained as clusters of small, colorless needles; m.p. 141.5–142.5°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.8; H, 6.3.
Found: C, 93.6; H, 6.2.

The *picrate* crystallizes from absolute alcohol containing an excess of picric acid as deep red needles; m.p. 140.5–141°.

Anal. Calc'd for $C_{20}H_{16}\cdot C_6H_3N_3O_7$: N, 8.7. Found: N, 8.6.

γ-(1-Phenanthryl)butyric acid (VII). (a) To a suspension of 2.92 g. of β-(1-phenanthryl)propionic acid (VIII) (13) in 5 cc. of dry ether and 1 drop of pyridine was added 3.3 cc. of thionyl chloride. The mixture was allowed to stand at room temperature for a half hour and then the ether and thionyl chloride were evaporated under reduced pressure. The acid chloride was dissolved in a mixture of benzene and ether and added drop by drop to a solution of diazomethane in 60 cc. of dry ether, the

diazomethane being made from 7 cc. of ethyl N-methyl-N-nitrosocarbamate. After standing for two hours at room temperature, the ether and benzene were evaporated under reduced pressure and the crystalline diazo ketone was dissolved in 50 cc. of dry methanol. The methanol solution was refluxed for two hours (one hour was insufficient), with addition of silver oxide from 6 cc. of 10% silver nitrate solution over this time, a quarter at the beginning, another quarter in five portions at five minute intervals after this, another quarter at the end of the first hour, and the last quarter in five portions at five minute intervals after this. The methanol solution was filtered to remove the silver oxide, and the residue obtained from evaporation of the methanol was heated for an hour with an excess of 45% potassium hydroxide solution. The mixture was diluted to dissolve the potassium salts and then acidified. The precipitated acid was sublimed at 230° and 0.4 mm. and the sublimate was crystallized twice from dilute acetic acid; yield, 1.88 g. (61%); m.p. 153–154°. After several further crystallizations from dilute acetic acid, the acid separated as colorless leaflets; m.p. 154.5–155.5°.

(b) Five and seven-tenths grams of γ-[1-(1,2,3,4-tetrahydrophenanthryl)]butyric acid (IX) prepared from 1-keto-1,2,3,4-tetrahydrophenanthrene according to the procedure of Hoch (6) was esterified with an ethereal solution of diazomethane, the ether was evaporated, and the ester was heated for three hours at 250–260° with 0.55 g. of palladium-charcoal catalyst. The mixture was taken up in benzene, and the filtered benzene solution was evaporated. The ester was heated for one hour with 45% potassium hydroxide solution and the solution was diluted and acidified; weight, 5.42 g. (95%); m.p. 149–154°. After two crystallizations from dilute acetic acid, the compound melted at 154–155.5°. Hoch reports 152° as the melting point of this compound.

Anal. Calc'd for $C_{18}H_{16}O_2$: C, 81.9; H, 6.1.
Found: C, 81.5; H, 6.0.

1-Keto-1,2,3,4-tetrahydrochrysene (VI). To a suspension of 5.63 g. of the above acid in 60 cc. of dry ether and 2 drops of pyridine was added 12 cc. of thionyl chloride. After standing at room temperature for a half hour, the ether and thionyl chloride were removed under reduced pressure, the acid chloride was dissolved in 80 cc. of dry benzene, and 9 cc. of stannic chloride was added to the chilled solution. After standing for twenty minutes at room temperature, the mixture was hydrolyzed with ice and hydrochloric acid, the benzene layer was washed with ammonium hydroxide and then with water, the benzene was evaporated, and the ketone was crystallized from benzene; weight, 4.85 g. (92%); m.p. 226.5–228°. After two recrystallizations from benzene the compound was obtained as colorless prisms; m.p. 228–229°. Hoch gives 222° as the melting point of this compound:

Anal. Calc'd for $C_{18}H_{14}O$: C, 88.0; H, 5.7.
Found: C, 87.7; H, 5.7.

1-Methylchrysene (V). (a) A mixture of 0.69 g. of 1-methyl-1,2,3,4-tetrahydrochrysene and 0.07 g. of palladium-charcoal catalyst was heated at 300–320° for one hour and the mixture was taken up in benzene and filtered. The hydrocarbon obtained by evaporation of the benzene solution was crystallized from toluene; yield, 0.63 g. (94%); m.p. 248–250°. After two further crystallizations from toluene, colorless, glistening leaflets were obtained; m.p. 249.5–250°. The mixture melting point with chrysene (m.p. 246–247°) was 243–245°.

(b) To a Grignard solution made from 0.5 cc. of methyl iodide, 0.15 g. of magnesium, and 10 cc. of ether were added 0.5 g. of 1-keto-1,2,3,4-tetrahydrochrysene and 15 cc. of dry benzene. The mixture was allowed to stand at room temperature overnight and was then hydrolyzed with ice and ammonium chloride. The benzene-

ether layer was separated, the benzene and ether were evaporated, and the residue was heated for one hour with 0.05 g. of palladium-charcoal catalyst. The reaction-product was taken up in benzene, and the hydrocarbon obtained by evaporation of the filtered benzene solution was crystallized from benzene, giving colorless, glistening leaflets; weight, 0.42 g. (86%); m.p. 249.5–250°. The melting point was unchanged after two further crystallizations from benzene. The mixture melting point with the material prepared in part (a) was 249.5–250°. The mixture melting point with chrysene was 242.5–244°. The hydrocarbon, like chrysene, does not form a very stable picrate and we were unable to prepare a satisfactory picrate.

Anal. Calc'd for $C_{19}H_{14}$: C, 94.2; H, 5.8.
Found: C, 94.3; H, 5.8.

1-Ethylchrysene. To a Grignard solution made from 0.55 cc. of ethyl bromide and 0.15 g. of magnesium in 10 cc. of ether were added 0.5 g. of 1-ketotetrahydrochrysene and 15 cc. of dry benzene. The mixture was allowed to stand at room temperature for twelve hours, and ice and ammonium chloride were added to decompose the complex. The benzene-ether layer was evaporated and the residue was heated for one hour at 300-320° with 0.05 g. of palladium-charcoal catalyst. The mixture was taken up in benzene, the filtered solution was evaporated, and the hydrocarbon was crystallized from benzene-methanol; yield, 0.38 g. (73%); m.p. 183–184°. After two recrystallizations from benzene-methanol, colorless leaflets were obtained; m.p. 183.5–184°.

Anal. Calc'd for $C_{20}H_{16}$: C, 93.8; H, 6.3.
Found: C, 93.5; H, 6.1.

Methyl 1-keto-1,2,3,4-tetrahydrochrysene-2-glyoxalate (X). Sixty-nine hundredths gram of sodium was dissolved in 15 cc. of methanol and the excess methanol was then evaporated under reduced pressure. A mixture of 3 g. of 1-keto-1,2,3,4-tetrahydrochrysene and 3.6 g. of methyl oxalate was then added, the flask was filled with nitrogen, and 75 cc. of dry benzene was added. After the mixture had stood for five hours with occasional agitation, water and a few drops of 45% potassium hydroxide solution were added, the benzene layer was extracted twice with 2% potassium hydroxide solution, and the alkaline washings were acidified; weight, 3.92 g. (97%); m.p. 167–168°. After two crystallizations from benzene-methanol, deep yellow prisms were obtained; m.p. 176–177° with decomposition. Upon crystallization, two forms usually separate: light yellow, flocculent leaflets and thick, deep yellow prisms. On standing, the leaflets, which melt about 169–170°, change over almost completely to the prisms, and the remaining leaflets can be removed by decantation before filtering. The compound gives an immediate, reddish-brown color with alcoholic ferric chloride.

Anal. Calc'd for $C_{21}H_{16}O_4$: C, 75.9; H, 4.8.
Found: C, 76.0; H, 4.8.

1-Keto-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XI). A mixture of 2.90 g. of the above compound and 1.5 g. of powdered glass was heated at 180–190° for a half hour. The mixture was taken up in benzene and the filtered benzene solution was evaporated. The residue crystallized from benzene-methanol as colorless needles; weight, 2.10 g. (79%); m.p. 156–157.5°. After two recrystallizations from benzene-methanol the compound melted at 156.5–157.5°. This carbomethoxy ketone gives a green color on standing with alcoholic ferric chloride.

Anal. Calc'd for $C_{20}H_{16}O_3$: C, 79.0; H, 5.3.
Found: C, 79.2; H, 5.3.

1-Keto-2-methyl-2-carbomethoxy-1,2,3,4-tetrahydrochrysene (XII). To a solution of 0.3 g. of sodium in 10 cc. of methanol was added 1 g. of 1-keto-2-carbomethoxy-

1,2,3,4-tetrahydrochrysene in 30 cc. of benzene. The mixture was refluxed for two hours and then cooled. One and one-half cubic centimeters of methyl iodide was added and the mixture was allowed to stand at room temperature for an hour. Another 1.5 cc. of methyl iodide was then added and the mixture was refluxed for an hour, cooled, and acidified with acetic acid. The benzene and methanol were evaporated, benzene and water were added, the benzene layer was evaporated, and the residue was crystallized from benzene-methanol, giving colorless needles; weight, 0.93 g. (89%); m.p. 154–155°, unchanged after two further crystallizations. The melting point when the compound was mixed with the original 1-keto-2-carbomethoxytetrahydrochrysene was 125–135°. The compound gives no color with alcoholic ferric chloride.

Anal. Calc'd for $C_{21}H_{18}O_3$: C, 79.2; H, 5.7.
Found: C, 79.4; H, 5.7.

1-Keto-2-methyl-1,2,3,4-tetrahydrochrysene (XIII). A mixture of 0.75 g. of 1-keto-2-methyl-2-carbomethoxytetrahydrochrysene, 23 cc. of acetic acid, and 12 cc. of concentrated hydrochloric acid was refluxed for three hours, and then water was added to complete the precipitation of the ketone; weight, 0.59 g. (93%); m.p. 183–184.5°. After two crystallizations from benzene-methanol, colorless leaflets were obtained; m.p. 184–184.5°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 87.5; H, 6.2.

2-Methyl-1,2,3,4-tetrahydrochrysene (XIV). A mixture of 0.2 g. of 1-keto-2-methyl-1,2,3,4-tetrahydrochrysene, 5 g. of amalgamated zinc, 10 cc. of acetic acid, 6 cc. of concentrated hydrochloric acid, and 2 cc. of toluene was refluxed for twenty-four hours. An additional 10 cc. of a 1:1 mixture of acetic and hydrochloric acids was added in portions over this period. The organic layer was evaporated, the residue was sublimed at 200° and 0.4 mm., and the sublimate was crystallized from alcohol-acetone, giving colorless, glistening leaflets; weight, 0.145 g. (77%); m.p. 145–146°, unchanged after two more recrystallizations. The mixture melting point with 2-methyl-1,2,3,4-tetrahydrochrysene (m.p. 141.5–142°) prepared from 2-methyl-4-keto-1,2,3,4-tetrahydrochrysene (1) was 143.5–145°.

β-(2-Phenanthroyl)-α-methylpropionic acid (XIX). A mixture of 0.5 g. of powdered sodium, 5.1 cc. of malonic ester, and 30 cc. of benzene was refluxed until the sodium had reacted. The suspension was cooled, 5 g. of ω-bromo-2-acetylphenanthrene (14) (XVIII) was added, and the mixture was allowed to stand at room temperature for twelve hours and then heated for three hours. Dilute hydrochloric acid was added to the cooled solution, the organic layer was evaporated, and the residue was heated for an hour with 45% potassium hydroxide solution. The mixture was diluted to dissolve the potassium salts and then acidified. The dicarboxylic acid was heated for an hour at 180–200° and the product was crystallized from acetic acid-toluene; yield, 1.8 g. (37%); m.p. 222–224°. After two further crystallizations from acetic acid-toluene, colorless needles with the melting point 228–229° were obtained.

Anal. Calc'd for $C_{19}H_{16}O_3$: C, 78.1; H, 5.5.
Found: C, 77.9; H, 5.5.

γ-(2-Phenanthryl)-α-methylbutyric acid (XX). A mixture of 1 g. of β-(2-phenanthroyl)-α-methylpropionic acid, 5 g. of amalgamated zinc, 7.5 cc. of acetic acid, 7.5 cc. of concentrated hydrochloric acid, and 4 cc. of toluene was refluxed for twenty-four hours. An additional 7.5 cc. of concentrated hydrochloric acid was added in portions over this period. The organic layer was evaporated and the reduced acid was crystallized from benzene-petroleum ether; weight, 0.89 g. (94%); m.p. 122–124°.

After two recrystallizations from benzene-petroleum ether, colorless leaflets were obtained; m.p. 124–124.5°.

Anal. Calc'd for $C_{19}H_{18}O_2$: C, 82.0; H, 6.5.
Found: C, 82.1; H, 6.4.

Methyl 4-keto-1,2,3,4-tetrahydrochrysene-3-glyoxalate. Twenty-three hundredths gram of sodium was dissolved in 5 cc. of methanol and the excess methanol was removed under reduced pressure. A mixture of 1 g. of 4-keto-1,2,3,4-tetrahydrochrysene (XV) (1) and 1.2 g. of methyl oxalate was added, the apparatus was filled with nitrogen, and 25 cc. of dry benzene was added. After the mixture had stood at room temperature for three hours with occasional shaking, water and a few drops of 45% potassium hydroxide solution were added, the benzene layer was washed with 2% potassium hydroxide solution, and the alkaline washings were acidified; weight, 1.27 g. (95%); m.p. 112–115°. After three recrystallizations from acetone-methanol, lemon-yellow needles of melting point 116–117.5° were obtained. The compound gives an immediate, deep brown color with alcoholic ferric chloride.

Anal. Calc'd for $C_{21}H_{16}O_4$: C, 75.9; H, 4.8.
Found: C, 75.5; H, 4.7.

3-Carbomethoxy-4-keto-1,2,3,4-tetrahydrochrysene. A mixture of 0.59 g. of the above glyoxalate and 0.3 g. of powdered soft glass was heated for one hour at 180° and the decarbonylated product was taken up in benzene, the benzene solution was filtered, the benzene was evaporated, and the residue was crystallized from benzene-alcohol; weight, 0.44 g. (82%); m.p. 153–155°. After two further crystallizations from benzene-alcohol, colorless needles were obtained; m.p. 154–155°. This compound gives an emerald-green color on standing with alcoholic ferric chloride.

Anal. Calc'd for $C_{20}H_{16}O_3$: C, 79.0; H, 5.3.
Found: C, 78.8; H, 5.3.

3-Methyl-3-carbomethoxy-4-keto-1,2,3,4-tetrahydrochrysene. To a solution of 0.45 g. of sodium in 15 cc. of methanol was added 1.5 g. of 3-carbomethoxy-4-keto-1,2,3,4-tetrahydrochrysene in 30 cc. of benzene and the mixture was refluxed for two hours. To the cooled mixture was added 2.3 cc. of methyl iodide, and the reaction-mixture was allowed to stand at room temperature for an hour. Another 2.3 cc. of methyl iodide was then added and the whole was refluxed for an hour. The mixture was acidified with acetic acid and the benzene and methanol were evaporated. Water and benzene were added, the benzene layer was evaporated, and the residue was crystallized from acetone-methanol, giving colorless needles; weight, 1.32 g. (84%); m.p. 114–116°. After several recrystallizations from acetone-methanol, the melting point was 115.5–117°. The methylcarbomethoxy ketone gives no color with alcoholic ferric chloride.

Anal. Calc'd for $C_{21}H_{18}O_3$: C, 79.2; H, 5.7.
Found: C, 79.2; H, 5.7.

3-Methyl-4-keto-1,2,3,4-tetrahydrochrysene (XVI). (a) To a suspension of 0.75 g. of γ-(2-phenanthryl)-α-methylbutyric acid in 7.5 cc. of dry ether and 1 drop of pyridine was added 1.5 cc. of thionyl chloride and the mixture was allowed to stand at room temperature for a half hour. The ether and thionyl chloride were evaporated under reduced pressure, the acid chloride was dissolved in 7.5 cc. of carbon disulfide, and 1.2 cc. of stannic chloride was added to the solution cooled in ice-water. After standing at room temperature for ten minutes, the mixture was hydrolyzed with ice and hydrochloric acid and the carbon disulfide layer was evaporated. The residue was dissolved in benzene, the benzene solution was washed with ammonium hydroxide, the benzene was evaporated, and the ketone was crystallized from alcohol-acetone; m.p. 108–111°; weight, 0.45 g. (64%). After several recrystalliza-

tions from alcohol-acetone, the ketone was obtained as colorless prisms; m.p. 114–115°.

(b) A mixture of 2.1 g. of 3-methyl-3-carbomethoxy-4-keto-1,2,3,4-tetrahydrochrysene, 60 cc. of acetic acid, and 30 cc. of concentrated hydrochloric acid was refluxed for four hours. Water was added to the cooled mixture, which was then extracted with benzene. The benzene was evaporated, the residue was sublimed at 200° and 0.4 mm., and the sublimate was crystallized from alcohol-acetone; weight, 1.58 g. (92%); m.p. 114–115.5°. The mixture melting point with the material prepared in part (a) was 114–115.5°.

Anal. Calc'd for $C_{19}H_{16}O$: C, 87.7; H, 6.2.
Found: C, 87.2; H, 6.1.

3-Methyl-1,2,3,4-tetrahydrochrysene. A mixture of 1 g. of 3-methyl-4-keto-1,2,3,4-tetrahydrochrysene, 10 g. of amalgamated zinc, 20 cc. of acetic acid, 12 cc. of concentrated hydrochloric acid, and 5 cc. of toluene was refluxed for twenty-four hours, an additional 20 cc. of a 1:1 mixture of acetic and hydrochloric acids being added in portions over this period. The organic layer was evaporated, the residue was sublimed at 200° and 0.4 mm., and the sublimate was crystallized from benzene-petroleum ether, giving colorless needles; weight, 0.82 g. (86%); m.p. 129–130.5°. After several recrystallizations from benzene-petroleum ether, the hydrocarbon melted at 130–131°.

Anal. Calc'd for $C_{19}H_{18}$: C, 92.7; H, 7.3.
Found: C, 92.4; H, 7.3.

3-Methylchrysene (XVII). A mixture of 0.74 g. of 3-methyl-1,2,3,4-tetrahydrochrysene and 0.07 g. of palladium-charcoal catalyst was heated for one hour at 300–320°. The mixture was taken up in benzene, the filtered benzene solution was evaporated, and the residue was crystallized from benzene-petroleum ether, giving colorless, glistening leaflets; weight, 0.67 g. (92%); m.p. 170–170.5°, unchanged after several further crystallizations.

Anal. Calc'd for $C_{19}H_{14}$: C, 94.2; H, 5.8.
Found: C, 93.8; H, 5.8.

The *picrate* crystallizes from absolute alcohol as orange needles; m.p. 164–164.5°.

Anal. Calc'd for $C_{19}H_{14} \cdot C_6H_3N_3O_7$: N, 8.9. Found: N, 8.9.

β-[7-(1,2,3,4-Tetrahydrophenanthroyl)]propionic acid (XXI). The combined mother liquors from the crystallizations of about 35 g. of crude β-[9-(1,2,3,4-tetrahydrophenanthroyl)]propionic acid (8) deposited about 2 g. of crystals after standing for about two months at room temperature; m.p. 150–154°. After several recrystallizations from toluene-acetic acid, colorless, rhombic prisms of melting point 158–159° were obtained. Concentration of the filtered mother liquors did not give any more acid of this melting point and, although crops were obtained which melted over wide ranges, from 125–165°, no other pure products were isolated.

Anal. Calc'd for $C_{18}H_{18}O_3$: C, 76.6; H, 6.4.
Found: C, 76.8: H, 6.3.

γ-[7-(1,2,3,4-Tetrahydrophenanthryl)]butyric acid. A mixture of 1 g. of the above keto acid, 2.5 g. of amalgamated zinc, 4 cc. of acetic acid, 4 cc. of concentrated hydrochloric acid, and 2 cc. of toluene was refluxed for twenty-four hours. An additional 4 cc. of concentrated hydrochloric acid was added in portions over this time. The organic layer was evaporated, and the residue was crystallized from benzene; weight, 0.80 g. (84%); m.p. 92–95.5°. After several crystallizations, colorless prisms of melting point 95.5–97° were obtained.

Anal. Calc'd for $C_{18}H_{20}O_2$: C, 80.6; H, 7.5.
Found: C, 81.1; H, 7.3.

The structure of the acid was proved by catalytic dehydrogenation to γ-(2-phenanthryl)butyric acid. Two-tenths gram of γ-[7-(1,2,3,4-tetrahydrophenanthryl)]-butyric acid was esterfied with an ethereal solution of diazomethane, the ether was evaporated, and the ester was heated at 250–270° for two hours with 0.03 g. of palladium-charcoal catalyst. The mixture was taken up in benzene and filtered, the benzene was evaporated, and the residue was heated for an hour with 3 cc. of 45% potassium hydroxide solution. The mixture was diluted to dissolve the potassium salt and then acidified; weight, 0.162 g. (82%); m.p. 130–131°. After two crystallizations from benzene the acid melted at 133.5–134.5°. The mixture melting point with authentic γ-(2-phenanthryl)butyric acid (1) (m.p. 134–135°) was 134–135°.

4-Keto-1,2,3,4,7,8,9,10-octahydrochrysene (XXII). To a suspension of 0.24 g. of γ-[7-(1,2,3,4-tetrahydrophenanthryl)]butyric acid in 5 cc. of ether and 1 drop of pyridine was added 1 cc. of thionyl chloride. After standing for a half hour at room temperature, the ether and thionyl chloride were removed under reduced pressure, the acid chloride was dissolved in 3 cc. of dry benzene, and to the chilled solution was added 0.4 cc. of stannic chloride. After standing for ten minutes in the cold, the mixture was hydrolyzed with ice and hydrochloric acid, the benzene layer was washed with ammonium hydroxide, the benzene was evaporated, and the residue was crystallized from methanol, giving colorless leaflets; m.p. 91–94°; weight, 0.15 g. (68%). After several recrystallizations from methanol, the ketone was obtained as leaflets which melted at 93.5–95°. Sometimes on crystallization needles are obtained which melt at 89.5–91° and which remelt at 93.5–95°.

Anal. Calc'd for $C_{18}H_{18}O$: C, 86.4; H, 7.2.
Found: C, 86.1; H, 7.55.

4-Methylchrysene (XXIII). To a Grignard reagent prepared from 0.12 g. of magnesium and 0.40 cc. of methyl iodide in 10 cc. of dry ether was added 0.475 g. of 4-ketoöctahydrochrysene in 5 cc. of benzene. After standing at room temperature for twelve hours, the mixture was hydrolyzed with ice and hydrochloric acid, the benzene-ether layer was evaporated, and the residue was heated at 300–320° for one hour with 0.1 g. of palladium-charcoal catalyst. The mixture was taken up in benzene and filtered, the benzene was evaporated, and the residue was crystallized from benzene-petroleum ether; weight, 0.28 g. (61%); m.p. 147–149°. After sublimation and several recrystallizations from benzene-petroleum ether, the hydrocarbon melted at 149–149.5°. The mixture melting point with authentic 4-methylchrysene (1) showed no depression.

SUMMARY

The 1- and 3- methylchrysenes have been prepared, both by two independent syntheses.

New methods of preparation of 2- and 4- methylchrysenes are given.

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ALLENES. III. A COMPARISON OF SOME SUBSTITUTED ALLENES WITH PYRETHRONE WITH RESPECT TO THEIR BEHAVIOR TOWARD HALOGENS

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In their investigations on the nature of the unsaturated side chain present in pyrethrolone and its desoxy derivative, pyrethrone, LaForge and Haller (1) observed that, whereas these compounds reacted with one equivalent of bromine in indifferent solvents, yielding dibromo addition-products, amorphous monobromo compounds and about an equivalent quantity of hydrobromic acid resulted when the reaction was carried out in alcoholic solution. The latter reaction was interpreted as one of substitution, which seemed incompatible with the assumption of the presence of a cumulated system of double bonds as originally proposed by Staudinger and Ruzicka (2) or of the conjugated system as later suggested by Ruzicka and Pfeiffer (3). The reaction-products, on treatment with zinc, yielded the original pyrethrolone or pyrethrone.

As the conjugated system seemed unlikely for other reasons, an investigation of the behavior of compounds with the cumulated system toward halogens became of interest with reference to the results obtained with pyrethrolone and pyrethrone.

In previous communications (4, 5) the preparation of the heretofore unknown 1-phenyl-1,2-butadiene and 1-cyclohexyl-2,3-pentadiene was reported. These compounds and also the known 2,3-pentadiene have been subjected to reactions with halogens carried out in a manner parallel to those performed on pyrethrone by LaForge and Haller.

Reactions of allenes with halogens in indifferent solvents. All the allenes mentioned above absorb one molecular equivalent of bromine or chlorine when treated with dilute solutions of the reagent in carbon disulfide or other indifferent solvents in the cold. The end-point is easily observed by the persistence of the color in the solution. An insignificant quantity of the corresponding halogen acid is always formed during the reaction, but the respective dibromo or dichloro addition-products are readily isolated in good yields.

When 2,3-pentadiene is treated with bromine in chloroform solution in the cold, rapid absorption of one equivalent of the halogen takes place

with the formation of the 2,3-dibromo-3-pentene in nearly quantitative yield.

The addition of bromine to 1-phenyl-1,2-butadiene furnishes 1-phenyl-2,3-dibromo-1-butene as the main reaction-product. That the halogen has added mainly in the 2,3 position follows from the behavior of the reaction-product on treatment with aqueous alkali. When the reagent is gradually added to a hot aqueous suspension of the dibromo compound in the presence of phenolphthalein indicator, an equivalent of the alkali is neutralized in a few minutes. The reaction-mixture consists of three main products, which may be separated by fractional distillation. The bromine content of the lowest-boiling fraction indicates that it is formed by the loss of hydrobromic acid. It is probably 1-phenyl-2-bromo-1,3-butadiene ($C_6H_5CH{=}CBrCH{=}CH_2$). The middle fraction has a lower bromine content, corresponding to the formula $C_{10}H_{11}BrO$. It is formed by substitution of a hydroxyl group for one bromine and is without doubt 1-phenyl-2-bromo-3-hydroxy-1-butene ($C_6H_5CH{=}CBrCHOHCH_3$), for on hydrogenation with elimination of the double bond and the bromine, it is converted into 1-phenyl-3-butanol, which was identified as the phenylurethane. The third fraction, boiling much higher than the others, is probably a dimolecular compound, $C_{20}H_{20}Br_2O$, formed by the condensation of two molecules of 1-phenyl-2-bromo-3-hydroxy-1-butene with loss of one molecule of water or by some other mechanism. Essentially the same reactions occur when the dichloro substitution-product of 1-phenyl-1,2-butadiene, *i.e.*, 1-phenyl-2,3-dichloro-1-butene, is treated in ethanol solution with aqueous potassium hydroxide solution. The main reaction-product, on hydrogenation, yields a liquid of the same boiling point and refractive index as 1-phenyl-3-butanol. It is oxidized by chromic acid to the corresponding ketone, which was isolated and purified as the semicarbazone, having the melting point recorded for the semicarbazone of 1-phenyl-3-butanone. The addition of halogen to 1-phenyl-1,2-butadiene therefore takes place at least mainly in the 2,3 position.

Although it has no direct bearing on the subject of this article, it may be mentioned that in the chlorination of 1-phenyl-1-hydroxy-2-chloro-2-butene there is a tendency for the halogen to shift away from the phenyl group. This is true when hydrochloric acid is the chlorinating agent, but to a much less extent when thionyl chloride is employed. The 1-phenyl-dichlorobutene (4) prepared by the action of hydrochloric acid on 1-phenyl-1-hydroxy-2-chloro-2-butene is a mixture of 1-phenyl-1,2-dichloro-2-butene ($C_6H_5CHClCCl{=}CHCH_3$) and 1-phenyl-2,3-dichloro-1-butene ($C_6H_5CH{=}CClCHClCH_3$). When the mixture is treated with aqueous alkali, one chlorine is replaced by hydroxyl and the resulting chloro carbinol yields on hydrogenation a mixture of 1-phenyl-1-butanol

and 1-phenyl-3-butanol. Oxidation of the mixture with chromic acid yields the corresponding ketones, 1-phenyl-1-butanone and 1-phenyl-3-butanone, which are easily separated as their semicarbazones. The phenylurethane of 1-phenyl-3-butanol can be isolated also from the hydrogenation-product before oxidation. When thionyl chloride is the chlorinating agent for the preparation of 1-phenyldichlorobutene, the product is essentially 1-phenyl-2,3-dichloro-1-butene. The dichloro derivative, on aqueous alkaline hydrolysis, is converted into a monochloromonohydroxy derivative. This compound on hydrogenation furnishes 1-phenyl-3-butanol, which can be isolated in good yield as its phenylurethane.

In contrast to the 1-phenyldichlorobutenes, the 1-cyclohexyldichloropentene, which is probably 1-cyclohexyl-2,3-dichloro-3-pentene, prepared from 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene by the action of phosphorus pentachloride, is practically inert toward boiling dilute aqueous alkali. This is also true of the dibromo product obtained by the addition of bromine to 1-cyclohexyl-2,3-pentadiene.

Reactions of allenes with halogen in alcoholic solution. Since the observations of LaForge and Haller (1) were published, a search of the literature revealed articles that relate very closely to the behavior of pyrethrone toward bromine in alcoholic solution. Conant and Jackson (6) and later Jackson and co-workers (7,8) have reported that certain compounds with an ethylene linkage, on treatment with bromine in methanol, react to form methoxybromo addition-products as well as the normal dibromo addition-products. The first reaction takes place with liberation of free hydrobromic acid according to the scheme $\diagdown C{=}C \diagup + ROH + Br_2 \rightarrow \diagdown COR\text{-}CBr \diagup + HBr$. Both reactions proceeded at a rather slow rate. With knowledge of this reaction, it seemed very likely that the unsaturated side chain of pyrethrone had reacted in the same sense as compounds with the simple unsaturation, with formation of alkoxybromo derivatives and free hydrobromic acid and also a certain amount of the dibromo addition-product. The quantity of free hydrobromic acid formed when pyrethrone was treated with bromine in alcoholic solution indicated that the first reaction predominated. Since reduction of the reaction-product with zinc furnished unchanged pyrethrone in yields that far exceeded the quantity that would be expected from the dehalogenation of the dibromo derivative that might be present, it would be necessary, in order to explain this fact, to assume that the alkoxybromo addition-products reacted with zinc like a dibromo addition-product, with regeneration of the double

bond. Analogy for such a reaction is found in an article by Dykstra, Lewis, and Boord (9), who reported that α,β-alkoxybromo compounds are readily dehalogenated by zinc with formation of a double bond between the carbon atoms that carried the substituents.

It now became of interest to consider the reactions of compounds with the cumulated system from the standpoint of their behavior toward halogens in methanol solutions. In all cases methoxybromo addition-products were obtained together with dibromo addition-compounds. Free hydrobromic acid was liberated corresponding to 60–70% of one-half of the bromine added. In contrast to the simple unsaturated compounds, the allenes reacted with bromine in methanol instantaneously in the cold. 1-Phenyl-1,2-butadiene reacted with bromine in methanol to form a methoxybromo addition-compound as the main product. 1-Cyclohexyl-2,3-pentadiene was treated with bromine under the same conditions, and from the reaction-product two fractions could be separated by distillation. Bromine and methoxyl determinations indicated that in the lower-boiling fraction the methoxybromo addition-product predominated while the higher-boiling fraction contained more of the dibromo addition-product. Redistillation of the higher-boiling fraction yielded almost pure dibromo compound. The reaction of 2,3-pentadiene with bromine in methanol proceeded analogously. The products of the reaction were methoxybromopentene and 2,3-dibromopentene, which could be separated by fractional distillation. In no case was the exact relative position of bromine to methoxyl determined, but it seems safe to predict that the structure was $\rangle C(OCH_3)CBr{=}C\langle$ and not $\rangle CBrC(OCH_3){=}C\langle$.

Addition of bromine to pyrethrone in methanol solution. In the experiments of LaForge and Haller (1) the reaction of pyrethrone with bromine was always carried out in ethanol solution and the reaction-product was not analyzed. The experiment was repeated with methanol as the solvent. After neutralization of the free hydrobromic acid, the reaction-mixture was freed from solvent, and the product, as indicated by the bromine and methoxyl content, was found to consist of a mixture of the bromomethoxy derivative and the dibromide, the former predominating.

Conclusions. Three compounds containing the cumulated system of double bonds react in indifferent solvents with one molecule of bromine to form dibromo addition-compounds. In alcoholic solution bromine reacts with these compounds to furnish monobromoalkoxy addition-products with liberation of free hydrobromic acid.

The reactions of pyrethrone with bromine in both classes of solvent are strictly analogous to those exhibited by the allenes. Its behavior, therefore, is not incompatible with the presence of the cumulated system of

double bonds in its side chain, which from the facts now available seems to be the most likely arrangement.

EXPERIMENTAL

Addition of bromine to 1-phenyl-1,2-butadiene in carbon disulfide solution. Six and one-tenth grams of 1-phenyl-1,2-butadiene was dissolved in 50 cc. of carbon disulfide to which 15 cc. of water (saturated with sodium sulfate to prevent freezing) was added to absorb the hydrobromic acid, the solution was cooled in an ice-salt mixture, and 6.8 g. of bromine (1 equivalent of Br_2) in 50 cc. of the same solvent was slowly added. After all the bromine had been introduced, the solution was colored yellow by the slight excess of the reagent. The aqueous solution was separated and titrated with 0.1 *N* alkali, of which 4.1 cc. was required, corresponding to only 0.33 g. of hydrobromic acid. The carbon disulfide solution was washed with 5% sodium carbonate solution and then with water, dried, and the solvent removed under reduced pressure. The residue on distillation yielded 8.25 g. of practically pure product that boiled at 118° (0.5 mm.); $n^{28}D$ 1.6177.

Anal. Calc'd for $C_{10}H_{10}Br_2$: Br, 55.2. Found: Br, 54.0.

The following experiment indicates that the addition of bromine has occurred mainly at the 2,3 position. Eight and two-tenths grams of the dibromo addition-product was suspended in 20 cc. of water, heated to 100°, and while the suspension was being agitated mechanically a 4.7% aqueous solution of potassium hydroxide was added in small portions at 5-minute intervals. After 28 cc. (calc'd for 1 equivalent of bromine, 34 cc.) had been added, the solution was permanently alkaline. The reaction-products were extracted with ether and, after they had been washed with water and dried, the solvent was removed. On distillation three fractions were obtained.

The first fraction, 1.65 g., boiled at 84–89° (0.5 mm.); $n^{27}D$ 1.6208. It is probably 1-phenyl-3-bromo-1,3-butadiene.

Anal. Calc'd for $C_{10}H_9Br$: Br, 38.27. Found: Br, 38.1.

The second fraction, 1.74 g., boiled at 108–109° (0.5 mm.); $n^{27}D$ 1.5910.

Anal. Calc'd for $C_{10}H_{11}BrO$: Br, 35.24. Found: Br, 36.5.

This fraction is mainly 1-phenyl-2-bromo-3-hydroxy-1-butene, since on hydrogenation it is converted into 1-phenyl-3-butanol.

One and seven-tenths grams of the second fraction was hydrogenated in 23 cc. of 2.5% ethanol solution of potassium hydroxide with a palladium-calcium carbonate catalyst. In a few minutes 345 cc. of hydrogen was absorbed (calc'd for 2 H_2, 335 cc.). The ethanol solution was filtered and diluted with water, and the reaction-product was extracted with petroleum ether, which was washed with water, dried, and evaporated. The residue yielded on distillation 0.7 g. of product; b.p. 108–110° (8 mm.); $n^{28}D$ 1.5130. Three-tenths gram of the distillate was allowed to react with 0.24 g. of phenyl isocyanate, and gave 0.37 g. of recrystallized phenylurethane melting at 112–114°. The melting point of the phenylurethane of 1-phenyl-3-butanol is reported as 113° (10). The corresponding derivative of 1-phenyl-1-butanol has not been obtained in crystalline form.

The third fraction, 1.85 g., boiled at 200–210° (0.5 mm.).

Anal. Calc'd for $C_{20}H_{20}Br_2O$: Br, 36.7. Found: Br, 36.7.

This product is probably a dimolecular compound formed by the condensation of two molecules of the bromohydroxy compound with loss of water.

Addition of chlorine in carbon tetrachloride to 1-phenyl-1,2-butadiene. Five grams (slight excess) of chlorine was passed slowly into a solution of 8.5 g. of 1-phenyl-1,2-butadiene in 50 cc. of purified carbon tetrachloride. There was a slight evolution of

hydrochloric acid. After removal of the excess chlorine by evaporation, the solution was washed with dilute sodium carbonate solution and dried, and the solvent was removed under reduced pressure. After three fractionations, 5.5 g. of product was obtained, boiling at 130° (13 mm.); $n^{28}D$ 1.5745.

Anal. Calc'd for $C_{10}H_{10}Cl_2$: Cl, 35.27. Found: Cl, 35.38.

Action of aqueous potassium hydroxide on the dichloro addition-product of 1-phenyl-1,2-butadiene. Five grams of the dichloro compound was suspended in 25 cc. of boiling water and, while the suspension was being agitated with a turbine, 18 cc. of 4.7% aqueous potassium hydroxide was added dropwise over a period of about 1 hour. The reaction-mixture then remained permanently alkaline. The reaction-product was extracted with ether and, after drying and removal of the solvent, the residue was distilled and separated into two fractions.

The first fraction, 1.09 g., boiled at 70–90° (0.7 mm.); $n^{26}D$ 1.594.

Anal. Calc'd for $C_{10}H_9Cl$: Cl, 21.6; for $C_{10}H_{11}ClO$: Cl, 19.4; for $C_{10}H_{10}Cl_2$: Cl, 35.3. Found: Cl, 24.9.

The second fraction, 2.5 g., boiled at 95–100° (0.7 mm.); $n^{26}D$ 1.5730.

Anal. Found: Cl, 26.8.

Both fractions are probably mixtures of all three compounds.

Two and two-tenths grams of the second fraction absorbed 590 cc. of hydrogen in ethanolic potassium hydroxide solution with palladium-calcium carbonate catalyst, and from the reaction-product, in addition to 0.3 g. of distillate boiling at 60° (8 mm.), 0.8 g. of a fraction boiling at 108–111° (8 mm.), was obtained. Four-tenths gram of this fraction, when treated with 0.32 g. of phenyl isocyanate, yielded 0.62 g. of recrystallized phenylurethane derivative melting at 114°, identical with the corresponding derivative obtained after hydrolysis and hydrogenation of the dibromo addition-product of 1-phenyl-1,2-butadiene.

Another experiment was made in which aqueous ethanol was used instead of water. Eight-tenths gram of the same dichloride fraction as that employed for the preceding experiment was dissolved in 8 cc. of boiling ethanol, and 2.5 cc. of 10% aqueous potassium hydroxide solution was added, producing a permanent alkaline reaction. The solution was diluted with water and the product extracted with ether. The solution was washed and dried and the solvent removed. The residue, on distillation, yielded 0.5 g. of distillate; b.p. 85–90° (0.7 mm.); $n^{29}D$ 1.551. On hydrogenation under the conditions described above 3.25 g. of the product prepared as just described absorbed two moles of hydrogen. The hydrogenated material was isolated by dilution of the reaction-mixture with water and extraction with petroleum ether. On distillation 1.4 g. was obtained; b.p. 118–122° (15 mm.); $n^{27}D$ 1.510. One gram was oxidized in acetic acid solution with a slight excess of chromic acid. The product, isolated from the reaction-mixture by dilution with water and extraction with petroleum ether, was treated with semicarbazide hydrochloride in pyridine-ethanol solution and yielded 0.4 g. of semicarbazone. After being twice recrystallized from ethanol, it melted at 138–140°, which agrees well with the melting point recorded for the semicarbazone of 1-phenyl-3-butanone (142°) (10).

The 1-phenyldichloropentene prepared by the action of hydrochloric acid on 1-phenyl-1-hydroxy-2-chloro-2-butene ($C_6H_5CHOHCCl{=}CHCH_3$) (4) is a mixture of 1-phenyl-1,2-dichloro-2-butene and 1-phenyl-2,3-dichloro-1-butene. When 2 g. of the reaction-product was treated with boiling aqueous potassium hydroxide as described above, but with addition of 20 cc. of acetone to facilitate solution, 1.3 g. of distilled material was obtained; b.p. 100–105° (0.7 mm.); $n^{29}D$ 1.5659.

Anal. Calc'd for $C_{10}H_{11}ClO$: C, 65.75; H, 6.04.
Found: C, 65.20; H, 6.11.

On hydrogenation in ethanolic potassium hydroxide solution with palladium-

calcium carbonate catalyst, 3 g. absorbed 765 cc. of hydrogen (calc'd for 2 H_2, 748 cc.). The hydrogenation-product boiled at 105–110° (10 mm.); $n^{28}D$ 1.5115.

Anal. Calc'd for $C_{10}H_{14}O$: C, 80.00; H, 9.33.
Found: C, 78.4; H, 9.24.

The phenylurethane was prepared from 0.12 g.; yield, 0.15 g.; m.p. 114–115°.

Chromic acid oxidation of 1.5 g. yielded 1.15 g. of product, boiling at 105–108° (10 mm.); $n^{28}D$ 1.5117.

Anal. Calc'd for $C_{10}H_{12}O$: C, 81.08; H, 8.10.
Found: C, 77.98; H, 8.48.

Six-tenths gram of the oxidation-product and 0.6 g. of semicarbazide hydrochloride in 6 cc. of ethanol and 0.5 cc. of pyridine were allowed to react. From the solution 0.25 g. of semicarbazone separated, which after recrystallization from ethanol melted at 190°. The melting point of the semicarbazone of 1-phenyl-1-butanone is recorded as 188° (11). From the mother liquor 0.35 g. of recrystallized semicarbazone melting at 145° was obtained. As already stated, the melting point of 1-phenyl-3-butanone semicarbazone is recorded as 142°.

When prepared from 1-phenyl-1-hydroxy-2-chloro-2-butene (4) by the action of thionyl chloride, the dichloro derivative is practically all 1-phenyl-2,3-dichloro-1-butene. On hydrolysis with aqueous alkali, 3.6 g. yielded 1.8 g. of product; b.p. 100–105° (0.7 mm.); $n^{28}D$ 1.5708.

Anal. Calc'd for $C_{10}H_{11}ClO$: Cl, 19.4. Found: Cl, 19.7.

On hydrogenation of 1.9 g., 490 cc. of hydrogen was absorbed (calc'd for 2 moles, 465 cc.). The hydrogenated product was isolated in the usual manner; yield, 1.1 g.; b.p. 110–112° (10 mm.); $n^{27}D$ 1.5130.

Anal. Calc'd for $C_{10}H_{14}O$: C, 80.00; H, 9.33.
Found: C, 79.81; H, 9.38.

The phenylurethane melted at 114°.

Addition of bromine to 1-cyclohexyl-2,3-pentadiene in carbon disulfide. Fifteen cubic centimeters of a cold carbon disulfide solution of 1.6 g. of bromine (1 equivalent of Br_2) was slowly added to a cold solution of 1.5 g. of 1-cyclohexyl-2,3-pentadiene in 15 cc. of the same solvent. There was a slight evolution of hydrobromic acid, which was not measured. The solution was washed with sodium bicarbonate and then with water, and dried. After removal of the solvent under reduced pressure, the residue was distilled; it boiled at 110–115° (1 mm.); $n^{27}D$ 1.5357; yield, 2.6 g.

Anal. Calc'd for $C_{11}H_{18}Br_2$: Br, 51.6. Found: Br, 51.6.

One and nine-tenths grams of the dibromo compound was suspended in 15 cc. of water and boiled for 5 minutes. The addition of 0.6 cc. of 5% alkali gave an alkaline reaction which did not change after boiling an additional 15 minutes. The recovered product (1.4 g.) distilled at 100–110° (1 mm.); $n^{26}D$ 1.5340. Therefore, practically no reaction had occurred.

The 1-cyclohexyldichloropentene prepared by the action of phosphorus pentachloride on 1-cyclohexyl-2-hydroxy-3-chloro-3-pentene (5) was likewise inert when subjected to the same treatment. Two and two-tenths grams of the dichloro compound yielded 1.8 g. of recovered product, boiling at 128–130° (10 mm.); $n^{27}D$ 1.4938. The constants agree with those found for the starting material. No further attempts were made to determine the positions of the halogens in these compounds.

Addition of bromine to 2,3-pentadiene in chloroform solution. Ten cubic centimeters of a chloroform solution containing 1.66 g. of bromine (1 equivalent of Br_2) was added to a solution of 0.75 g. of 2,3-pentadiene (12) in the same solvent. The reaction was carried out with cooling in an ice-salt-bath. The solution was extracted with dilute sodium bicarbonate solution, then with water, and dried. After

removal of the solvent, the residue was distilled; b.p. 87–90° (25 mm.); yield, 1.5 g.

Anal. Calc'd for $C_5H_8Br_2$: C, 26.31; H, 3.50.
Found: C, 26.40, 26.50; H, 3.61, 3.57.

Addition of bromine to 1-phenyl-1,2-butadiene in methanol solution. A cold solution of 5.4 g. of bromine (calc'd for 1 equivalent of Br_2, 5.5 g.) dissolved in 30 cc. of methanol was added slowly to a solution of 4.5 g. of 1-phenyl-1,2-butadiene dissolved in 30 cc. of methanol and cooled in an ice-salt-bath. The bromine was rapidly absorbed until the addition of the last few drops produced a permanent orange color. The reaction-mixture was diluted with an equal volume of water and neutralized to the end-point of phenolphthalein with 24.0 cc. of *N* aqueous sodium hydroxide solution, corresponding to 71% of the theoretical 33.7 cc. calculated for one-half of the bromine added. The reaction-mixture was diluted with several volumes of water and extracted with ether. The ether solution was washed with water and dried. The residue obtained after removal of the solvent was separated into two fractions by distillation. The first fraction weighed 6.15 g. and boiled at 87–90° (0.5 mm.).

Anal. Calc'd for $C_{11}H_{13}BrO$: OCH_3, 12.86; Br, 33.2.
Found: OCH_3, 10.2; Br, 38.1.

The second fraction weighed 1.35 g. and boiled at 90–100° (0.5 mm.).

Anal. Calc'd for $C_{10}H_{10}Br_2$: Br, 55.2, OCH_3, 0.0. Found: Br, 52.5; OCH_3, 1.7.

Addition of bromine to 1-cyclohexyl-2,3-pentadiene in methanol solution. Four grams of 1-cyclohexyl-2,3-pentadiene was mixed with 30 cc. of methanol, cooled in a freezing mixture, and treated with a solution of 4.3 g. of bromine in 40 cc. of cold methanol (theory for 1 equivalent of Br_2, 4.25 g.). The bromine solution was decolorized instantly until the addition of the last few cubic centimeters, which were absorbed more slowly. The reaction-mixture was diluted with an equal volume of water and neutralized with 16.9 cc. of *N* aqueous sodium hydroxide to the end-point of phenolphthalein (theory for one-half of the bromine added, 26.87 cc.). The reaction-products were extracted with ether. The ether solution was washed thoroughly with water and then dried. The solvent was removed, and the residue was separated into two fractions by distillation at 0.5 mm. pressure. The first fraction weighed 2.95 g. and boiled at 81–86°; n_D^{27} 1.4950.

Anal. Calc'd for $C_{12}H_{21}BrO$: OCH_3, 11.9; Br, 30.7.
Found: OCH_3, 10.5; Br, 31.6.

The second fraction weighed 2.45 g. and boiled at 93–99°.

Anal. Calc'd for $C_{11}H_{18}Br_2$: Br, 51.6; OCH_3, 0.0.
Found: Br, 47.8; OCH_3, 2.4.

From another experiment the material corresponding to this second fraction contained 49.7% of bromine.

Addition of bromine to 2,3-pentadiene in methanol solution. Nine-tenths gram of 2,3-pentadiene was dissolved in 5 cc. of absolute methanol, and 2.2 g. of bromine in 10.3 g. of the same solvent was slowly added to the cold solution of the pentadiene. The bromine was instantly absorbed until 8.4 g. of the solution (corresponding to 1.8 g. of bromine or 85% of an equivalent of Br_2) had been added. After the solution was diluted with water, titration showed that hydrobromic acid had been liberated in quantity corresponding to 6.7 cc. of *N* alkali or 0.54 g. of hydrobromic acid. The reaction-product was extracted with ether, and the ether solution was washed with water and dried. The residue obtained after removal of the solvent yielded two fractions on distillation. This first fraction boiled at 65–70° (27 mm.).

Anal. Calc'd for $C_6H_{11}BrO$: Br, 44.7; OCH_3, 17.5.
Found: Br, 47.3; OCH_3, 14.8.

The second fraction boiled at 78–85° (27 mm.).

Anal. Calc'd for $C_5H_8Br_2$: Br, 70.0; OCH_3, 0.0.
Found: Br, 59.4; OCH_3, 6.5.

Both fractions are mixtures, the bromomethoxy derivative predominating in the first and the dibromo addition-product in the second.

Reaction of pyrethrone with bromine in methanol solution. One and two-tenths grams of pyrethrone was dissolved in 10 cc. of methanol, the solution was cooled in an ice-salt-bath, and 1.2 g. of bromine (1 equivalent of Br_2) in 10 cc. of the same solvent was slowly added. The bromine was rapidly absorbed. Five cubic centimeters of 1.7 *N* methanolic solution of potassium hydroxide was added, producing a precipitate of potassium bromide. The solution was acidified with acetic acid and the solvent removed under reduced pressure. The residue was dissolved in benzene, and the solution was washed, first with dilute sodium bicarbonate solution and then repeatedly with water, and dried. The benzene was removed under reduced pressure and the residue analyzed for methoxyl.

Anal. Calc'd for $C_{12}H_{17}BrO_2$: OCH_3, 11.35. Found: OCH_3, 6.6.

The crude product therefore contained about 60% of the bromomethoxy derivative. On distillation, which was accompanied by some decomposition, 1 g. of distillate was obtained, boiling at 140-145° (0.5 mm.). Redistillation yielded 0.8 g. of a slightly yellow oil that boiled at 134–142° (0.5 mm.). A dark residue was left after each distillation. The final product was also a mixture of the dibromo and methoxybromo derivatives.

Anal. Calc'd for $C_{11}H_{14}Br_2O$: Br, 49.7; for $C_{12}H_{17}BrO_2$: Br, 29.3; OCH_3, 11.4. Found: Br, 36.1; OCH_3, 4.9.

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[CONTRIBUTION FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

THE CHEMISTRY OF UNSATURATED STEROIDS. VII. THE ACTION OF PERBENZOIC ACID ON 2,4-CHOLESTADIENE[1]

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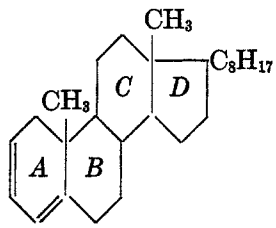
In a previous communication (1) it was pointed out that 2,5-peroxidocholestene-3 can readily be rearranged into ketones which were interpreted as derivatives of a trans-annular steroid oxide (III). Since then other derivatives of this oxide have been prepared by Ellis and Petrow (2). The work described in this paper was undertaken with the purpose of preparing a trans-annular steroid oxide and ketones similar to, or identical with, the rearrangement-products of 2,5-peroxidocholestene-3. An attractive route for the preparation of the desired compounds appeared to be the oxidation of 2,4-cholestadiene (I) with perbenzoic acid. Because of the ease with which molecular oxygen is added to the diene to give the trans-annular peroxide, it seemed conceivable that the diene would react with one mole of perbenzoic acid to give 2,5-oxidocholestene-3 (II). Further addition of oxygen to the remaining double bond might then lead to a dioxide, which would probably rearrange to a ketone (III). It is true that ergosterol, which contains a system of conjugated double bonds in ring *B*, forms a 5,6-oxide rather than a trans-annular oxide, when treated with one mole of perbenzoic acid. The conjugated system of 2,4-cholestadiene, however, is different from that of ergosterol, because it is not enclosed between two quaternary carbon atoms, an arrangement which might be more favorable for the formation of a trans-annular oxide.



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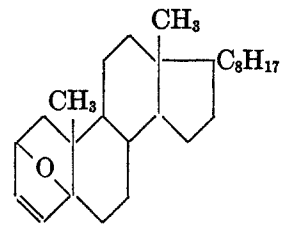

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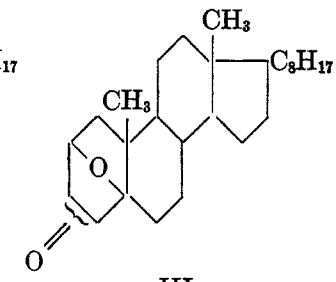
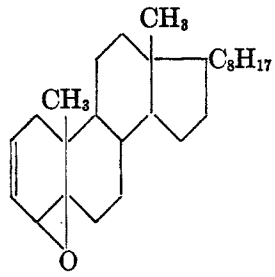


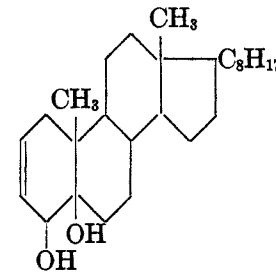
III

[1] Aided by grants from the International Cancer Research Foundation and The Jane Coffin Childs Memorial Fund for Medical Research.

The only crystalline product which was obtained as the result of the interaction between 2,4-cholestadiene and one mole of perbenzoic acid was a compound $C_{27}H_{46}O_2$ (m.p. 136–136.5°, $[\alpha]_D$ +132°). It remained unchanged when treated with a solution of potassium hydroxide in alcohol and reacted with acetic anhydride to give a monoacetate. It appears, therefore, that perbenzoic acid oxidizes the diene to a monoxide which is rapidly hydrolyzed to the corresponding diol. One of the hydroxyl groups of the diol is of tertiary nature and probably located at C-5. On catalytic hydrogenation the diol absorbed one mole of hydrogen to give a saturated diol $C_{27}H_{48}O_2$ (m.p. 171–172, $[\alpha]_D$ +35.5°) which gave a monoacetate on acetylation. The saturated diol reacted with one mole of lead tetra-acetate indicating the presence of two hydroxyl groups in adjacent positions. Since one of the two hydroxyls is at C-5, the second must be attached to C-4. The saturated diol is therefore a 4,5-dihydroxycholestene (VI), and it is probably identical with the diol which Heilbron (3) obtained by the hydrolysis of cholestene-4-oxide. These results demonstrate that the action of one mole of perbenzoic acid on 2,4-cholestadiene does not lead to a trans-annular oxide, but to cholestene-2-diol-4,5 (V).



IV



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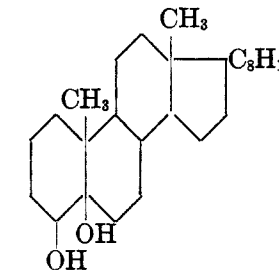

VI

The action of an excess of perbenzoic acid on a solution of 2,4-cholestadiene in chloroform leads to results which are as yet difficult to interpret. So far, only one crystalline compound has been isolated. It contained chlorine and gave analytical values for $C_{27}H_{45}ClO_2$ (m.p. 112–113°; $[\alpha]_D$ +72°). It is probably an oxidohydroxychlorocholestane. The entrance of the chlorine atom into the molecule is as yet difficult to explain. When the chloride was treated with a solution of potassium hydroxide in methanol, it lost one mole of hydrochloric acid and gave a compound $C_{27}H_{44}O_2$ (m.p. 120–121°; $[\alpha]_D$ +76°) which is probably a dioxide of cholestane. The same compound was also obtained in small yield when the oily residues of the reaction-mixture of 2,4-cholestadiene and an excess of perbenzoic acid were distilled *in vacuo*.

EXPERIMENTAL

4,5-Dihydroxycholestene-2. A 1.05 g. sample of 2,4-cholestadiene was dissolved in 35 cc. of chloroform in a glass-stoppered flask and cooled in an ice-bath. Fourteen and two-tenths cubic centimeters of cold 0.44 *N* perbenzoic acid solution was added slowly over a period of 30 minutes with occasional shaking. After standing for 24 hours in a refrigerator, the solution was evaporated to dryness. The crystalline residue was dissolved in 10 cc. of ether and the solution was washed with an aqueous solution of sodium bicarbonate and dried over anhydrous potassium carbonate. It was then evaporated to dryness at 40° and the residue was recrystallized from dilute alcohol. After filtration, washing with 50% ethanol, and drying, 0.85 g. of a crude product of m.p. 97–103° was obtained. After three recrystallizations from hot acetone the diol melted at 136–136.5°, $[\alpha]_D^{25}$ +132° (39.8 mg. in 3.06 cc. of pyridine). The total yield was about 35%.

Anal. Calc'd for $C_{27}H_{46}O_2$: C, 80.53; H, 11.52.
Found: C, 80.51; H, 11.19.

A 170 mg. sample of the diol was refluxed with 20 cc. of a 5% solution of potassium hydroxide in methanol for five hours. Water was added to the boiling solution and the material which separated on cooling was recrystallized from acetone. It was unchanged starting material, m.p. 136–136.5°.

4-Acetoxy-5-hydroxycholestene-2. The monoacetate was prepared by refluxing the diol with acetic anhydride for 150 minutes. It was recrystallized several times from acetone. The material which separated on cooling was recrystallized from acetone. The acetate melted at 159–160°, $[\alpha]_D^{25}$ +16° (30 mg. in 3.06 cc. of acetone).

Anal. Calc'd for $C_{29}H_{48}O_3$: C, 78.31; H, 10.89.
Found: C, 78.02; H, 11.17.

4,5-Dihydroxycholestane. A 290 mg. sample of 4,5-dihydroxycholestene-2 was dissolved in 75 cc. of ethyl acetate and shaken with platinum catalyst, prepared from 100 mg. of platinum oxide in an atmosphere of hydrogen. After ten minutes, one mole of hydrogen had been absorbed. The solution was filtered and evaporated to dryness *in vacuo*. The residue was recrystallized several times from acetone. The saturated diol melted at 171–172°, $[\alpha]_D^{25}$ +35.5° (43.2 mg. in 3.06 cc. of acetone).

Anal. Calc'd for $C_{27}H_{48}O_2$: C, 80.12; H, 11.97.
Found: C, 79.90; H. 11.95.

Titration with lead tetra-acetate. Ten cubic centimeters of a saturated solution of lead tetra-acetate in glacial acetic acid was added to 31.1 mg. of the saturated diol. After 29 hours standing, the excess lead tetra-acetate was determined by the method described by Criegee (4). The solution containing the sample used 13.25 cc. of 0.099 *N* sodium thiosulfate solution, and the two blanks 14.78 cc. and 14.79 cc., corresponding to a consumption of 0.98 moles of lead tetra-acetate per mole of sample.

4-Acetoxy-5-hydroxycholestane. The monoacetate was prepared by refluxing the diol with acetic anhydride for 90 minutes. It was recrystallized several times from dilute acetone. The acetate melted at 174–175°.

Anal. Calc'd $C_{29}H_{50}O_3$: C, 77.97; H, 11.28.
Found: C, 77.86; H, 11.15.

2,4-Cholestadiene and two moles of perbenzoic acid. A 3.03 g. sample of 2,4-cholestadiene was dissolved in 10 cc. of chloroform in a glass-stoppered flask and cooled to 0°. Seventy cubic centimeters of 0.765 *N* perbenzoic acid solution in chloroform was then added and the mixture was allowed to stand in the refrigerator for one month, at which time slightly more than 2 moles of perbenzoic acid per mole of diene had been consumed. The solution was then washed with a 2.5% aqueous solu-

tion of sodium bicarbonate, dried over anhydrous sodium sulfate and evaporated to dryness *in vacuo*. The oily residue was dissolved in a small amount of ether and alcohol, and the ether was partially distilled. Some viscous material precipitated which was filtered. The filtrate was then evaporated until a viscous oil remained, which crystallized slowly. After a few days the solid material was washed with a little absolute alcohol, filtered (1.5 g.) and recrystallized first from alcohol and ether and then several times from acetone. In this manner 550 mg. of a compound of m.p. 112–113° was obtained $[\alpha]_D^{25}$ +72° (32.8 mg. in 3.06 cc. of acetone).

Anal. Calc'd for $C_{27}H_{45}ClO_2$: C, 74.20; H, 10.38; Cl, 8.11.
Found: C, 74.18; H, 10.29; Cl, 8.38.

Hydrolysis of the chloride. A 103.6 mg. sample of the chloride was refluxed for 90 minutes with exactly 20 cc. of 0.05 *N* solution of potassium hydroxide in methanol. The excess alkali was then titrated with standard acid using phenolphthalein as an indicator. The sample required 4.59 cc. of 0.132 *N* sulfuric acid, and the blanks 6.40 cc. and 6.43 cc., respectively. Hence one equivalent of alkali was used by the sample, indicating a molecular weight of 432. (Calc'd for $C_{27}H_{45}ClO_2$: 437). After the titration, the flocculent precipitate was filtered, washed with water, and dried; yield 80 mg. After several recrystallizations from small amounts of petroleum ether, the reaction-product was obtained in the form of well-crystallized narrow plates. The substance melted at 120–121°, and after resolidification it always remelted sharply at 134.5–135°, $[\alpha]_D^{25}$ +76° (28.5 mg. in 3.06 cc. of ether).

Anal. Calc'd for $C_{27}H_{44}O_2$: C, 80.93; H, 11.08.
Found: C, 81.05; H, 11.08.

The compound remained unchanged when distilled *in vacuo*, or treated with benzoyl chloride in pyridine, or hydroxylamine in methanol. When refluxed with acetic anhydride, or when treated at room temperature with glacial acetic acid containing a trace of sulfuric acid decomposition took place.

SUMMARY

1. 2,4-Cholestadiene reacts with one mole of perbenzoic acid to form 4,5-dihydroxycholestene-2.

2. From the reaction-mixture obtained by treating 2,4-cholestadiene with an excess of perbenzoic acid in chloroform, a chloride of the formula $C_{27}H_{45}ClO_2$ has been isolated. On treatment with potassium hydroxide in alcohol the chloride lost hydrochloric acid to give a dioxide, $C_{27}H_{44}O_2$.

NEW HAVEN, CONN.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. (II). THE REACTIONS OF SILICOORTHOESTERS WITH CERTAIN ACID ANHYDRIDES[1]

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The purpose of this investigation was to study the acylation of silicoorthoesters, including the alkyl orthosilicates.

As far back as 1866, Friedel and Crafts reported that ethyl orthosilicate reacted with acetic anhydride (1), to give triethoxysilicomethyl acetate and the simple ester, thus:

I. $Si(OC_2H_5)_4 + (CH_3CO)_2O \leftrightharpoons CH_3COOSi(OC_2H_5)_3 + CH_3COOC_2H_5$

The same authors attempted the acetylation of ethyl orthosilicate with acetyl chloride. The products obtained from this reaction were ethyl acetate and triethoxysilicomethyl chloride.

Later, Friedel and Ladenburg attempted a similar reaction with acetyl chloride and ethyl ethane orthosiliconate (2). The product was not obtained as such, but was hydrolyzed to an impure ethane siliconic acid. Dearing and Reid also attempted the acylation of ethyl orthosilicate by the action of phthalic anhydride (3). The products of the reaction were written as diethyl phthalate and diethyl silicate. The latter product was not reported as identified.

Evidence for the dissociation of the carbon orthoesters into ions in the presence of a polar medium such as an acid anhydride has been presented by Post and Erickson (4). Many other reactions of acid anhydrides can be readily explained on the assumption of a similar reversible, spontaneous decomposition. By combining these two equilibria it is possible to predict for the silicoorthoesters, as well as for the carbon compounds, a possible interaction between the silicoorthoester and an acid anhydride according to the following equations:

II. $$C_2H_5Si(OR)_3 \leftrightharpoons (C_2H_5Si(OR)_2)^+ + (OR)^-$$

III. $$(CH_3CO)_2O \leftrightharpoons (CH_3COO)^- + (CH_3CO)^+$$

IV. $$(C_2H_5Si(OR)_2)^+ + (CH_3COO)^- \leftrightharpoons CH_3COOSi(C_2H_5)(OC_2H_5)_2$$

V. $$(CH_3CO)^+ + (OR)^- \leftrightharpoons CH_3COOR$$

[1] Abstracted from the thesis presented by the second author to the faculty of the University of Buffalo in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

This reaction would be expected to take place at room temperature, but was carried out at the refluxing temperature of the particular acetate formed according to the R group in the silicoorthoester. Ethyl, propyl, and butyl ethane orthosiliconates were found to react with acetic anhydride. In all cases the reaction was found to go to completion. Three moles of the respective acetates were obtained when three moles of acetic anhydride were used with one mole of the orthoester. The lowest yield of the alkyl acetate from this reaction was 96.7%. The triacetylated products were unstable and decomposed when fractionation at reduced pressures was attempted. A 23% yield of ethyl diethoxysilicomethyl acetate was obtained when equimolal quantities of acetic anhydride and ethyl ethane orthosiliconate were used.

When the reactants were mixed at room temperature, there was no conclusive evidence that the reaction began to take place immediately. However, as soon as the temperature was raised to the boiling point of the alkyl acetate, the simple ester began to distill off immediately. Attempts were made to follow these reactions quantitatively by following the amount of the simple ester which had been removed at specified times after the reaction had been initiated. Large quantities of reactants gave the qualitative general trend, but the data were too erratic to depend upon. Smaller quantities of reactants made it possible to calculate the equilibrium constant and specific reaction velocity constant for the reaction between propyl ethane orthosiliconate and acetic anhydride. The data were obtained by allowing the reaction-mixture to reflux for thirty-eight hours until, as was assumed on the basis of other experimental data appearing later, the mixture had reached equilibrium. In the course of the following ten minutes, all of the propyl acetate that had been formed was removed by distillation. The volume was accurately measured. To ensure that none of the propyl acetate remained, the time was recorded; this time was taken as t_0 and the reaction rate followed at regular intervals thereafter. The data are given for one-half hour later and at one and one-half hour intervals thereafter. The results obtained appear in tabular form.

	A	*B*	*C*	*D*
VI.	$C_2H_5Si(OC_3H_7)_3$ +	$3(CH_3CO)_2O$ ⇋	$3CH_3COOC_3H_7$ +	$C_2H_5Si(OOCCH_3)_3$
at start	0.254 moles	1.060 moles	0	0
at equilibrium	0.122 moles	0.663 moles	0.397 moles	0.132 moles

$$K = \frac{(C)^3 \times (D)}{(A) \times (B)^3} = \frac{(0.132) \times (0.397)^3}{(0.122) \times (0.663)^3} = 0.232$$

These data correspond to the temperature at which the mixture refluxes, which can be specified as 110° ± 5°. The final temperature was very

close to the temperature of boiling propyl acetate. The data for the specific reaction velocity constant were taken at a somewhat higher temperature, necessarily in the vicinity of 140°. It was obvious, that in order to remove all the propyl acetate and maintain a proper reflux ratio, the temperature had to be maintained slightly above the boiling point of acetic anhydride (139.6°), the next lower boiling constituent. The specific reaction velocity constant was calculated according to the following equation for a second order reaction:

$$k = \frac{2.303}{t(a-b)} \log_{10} \frac{b(a-x)}{a(b-x/3)}$$

where a equals the initial concentration in moles of acetic anhydride, b equals the initial concentration in moles of propyl ethane orthosiliconate, and x equals the accumulated number of moles of propyl acetate removed at any time t.

t	x	$a-x$	$b-x/3$	$k \times 10^{-5}$
0	0	0.663	0.122	
1800	0.037	0.626	0.110	4.92
7200	0.109	0.554	0.086	4.37
12600	0.172	0.491	0.065	4.85
18000	0.223	0.440	0.048	5.37

$k = 4.9 \pm 0.3 \times 10^{-5}$.

When calculated for a first order reaction, the data give constants which deviate from each other by 40%. Therefore, in view of the above data, it can be said that the reaction is more nearly of the second order than the first.

Experimental evidence shows that the same type of reaction takes place between the acid anhydrides and ethyl orthosilicate. When equimolar proportions of the reactants were taken, not only were the monoacylation products formed but also the diacylation products. It is assumed that the mechanism postulated in reactions II–V for the ethane orthosiliconates holds also for the acylation reactions of ethyl orthosilicate. The characteristics of the two reactions are quite similar. In order to obtain a diacetylation product, a second ionization must take place, thus:

VII. $CH_3COOSi(OC_2H_5)_3 \rightleftharpoons (CH_3COOSi(OC_2H_5)_2)^+ + (OC_2H_5)^-$

VIII. $(CH_3COOSi(OC_2H_5)_2)^+ + (CH_3COO)^- = (CH_3COO)_2Si(OC_2H_5)_2$

Furthermore, when heated to their boiling points, these compounds decompose to give ethyl acetate and high-boiling products. However,

intramolecular decomposition does not take place. Diethyl silicate would be the product in this case. In the number of similar experiments attempted, this compound was never found to be present among the products. Intermolecular decomposition predicts the formation of high molecular weight compounds in accordance with experimental facts. In order that this type of decomposition should take place, a second type of ionization is necessary, thus:

IX. $CH_3COOSi(OC_2H_5)_3 \leftrightharpoons (CH_3CO)^+ + (OSi(OC_2H_5)_3)^-$

X. $(CH_3COOSi(OC_2H_5)_2)^+ + (OSi(OC_2H_5)_3)^- \rightleftharpoons$ Products of high molecular weight

EXPERIMENTAL PART

Ethyl orthosilicate, $Si(OC_2H_5)_4$, was purchased from the Carbide and Carbon Chemicals Corp. Constants found: b.p. 165.5° (760 mm.); $n^{20}D$ 1.3821.

Ethyl ethane orthosiliconate, $C_2H_5Si(OC_2H_5)_3$, was prepared according to the known method of the action of ethylmagnesium bromide on ethyl orthosilicate (5, 6). The column used for fractionation has been described (6). Constants found: b.p. 158–160° (760 mm.); $n^{22}D$ 1.3853.

Propyl ethane orthosiliconate, $C_2H_5Si(OC_3H_7)_3$, was prepared by the method outlined by Post and Hofrichter (6). Constants found: b.p. 202–204° (760 mm.); $n^{23}D$ 1.4017.

Butyl ethane orthosiliconate, $C_2H_5Si(OC_4H_9)_3$, was prepared in the same manner as the propyl. Constants found: b.p. 235–238° (760 mm.); $n^{24}D$ 1.4128.

Acetic anhydride, $(CH_3CO)_2O$, was purchased from the Eastman Kodak Co., redistilled; b.p. 138.5–139.5° (760 mm.).

Propionic anhydride, $(C_2H_5CO)_2O$, was purchased from the Eastman Kodak Co., redistilled; b.p. 168° (760 mm.).

Benzoic anhydride, $(C_6H_5CO)_2O$, was a commercial product; m.p. 42°.

Ethyl diethoxysilicomethyl acetate, $CH_3COOSi(C_2H_5)(OC_2H_5)_2$. Ninety-eight milliliters (1 mole) of acetic anhydride was allowed to reflux for two hours with 208 ml. (1 mole) of ethyl ethane orthosiliconate. The ethyl acetate was then fractionated from the mixture. The temperature of the column was held at the boiling point of ethyl acetate until the reaction was complete. This procedure removed all ethyl acetate as it was formed, and the reaction was complete in a few minutes over five hours. Fractionation of the remaining mixture at 15 mm. gave a 23% yield of the above product, as well as other high-boiling products. The physical properties of the compound were then determined, b.p. 94° (15 mm.); a micro determination at atmospheric pressure gave 191.5°. Decomposition took place, and each succeeding reading was lower, d_4^{20} 1.020; $n^{20}D$ 1.4048; M. w. (cryoscopic in benzene) 209; theoretical 206.

Anal. Calc'd for $C_8H_{18}O_4Si$: C, 46.56; H, 8.80; Si, 13.63.
Found: C, 46.25, 46.04; H, 8.64, 8.59; Si, 14.01, 14.03.

The complete acetylation of ethyl, propyl, and butyl ethane orthosiliconates was attempted. The yields of acetate in the respective reactions were 99.3%, 96.7%, and 97.3%. The acetylated ethane orthosiliconate decomposed during fractionation in each case.

Triethoxysilicomethyl acetate, $CH_3COOSi(OC_2H_5)_3$. One mole of ethyl ortho-

silicate was mixed with one mole of acetic anhydride. A 99.3% yield of ethyl acetate was fractionated away from the mixture in the course of the following four hours. Fractionation of the mixture produced a 45% yield of the above product. Constants found: b.p. 81° (19 mm.); d_4^{20} 1.020; $n^{20}D$ 1.3910; literature (1), b.p. 135-140° (52 mm.).

Anal. Calc'd: Si, 12.63. Found: Si, 12.76, 12.58.

Diethoxysilicomethyl diacetate, $(CH_3COO)_2Si(OC_2H_5)_2$. In addition to the above product, a 40% yield of this compound was obtained from the above reaction-mixture. Constants found: b.p. 100° (19 mm.); d_4^{20} 1.076; $n^{20}D$ 1.3960.

Anal. Calc'd: Si, 11.88. Found: Si, 11.98, 11.95.

Triethoxysilicomethyl propionate, $C_2H_5COOSi(OC_2H_5)_3$, was prepared like triethoxysilicomethyl acetate. A yield of 98.5% of ethyl propionate was obtained. The remaining mixture was fractionated at 15 mm., and a 37% yield of the desired product was obtained. Constants found: b.p. 101° (15 mm.); d_4^{20} 0.999; $n^{20}D$ 1.3946.

Anal. Calc'd: Si, 11.90. Found: Si, 11.94, 11.82.

Diethoxysilicomethyl dipropionate, $(C_2H_5COO)_2Si(OC_2H_5)_2$. In addition to the above product, a 36% yield of this compound was obtained from the above reaction-mixture. Constants found: b.p. 125° (15 mm.); d_4^{20} 1.025; $n^{20}D$ 1.3998.

Anal. Calc'd: Si, 10.62. Found: Si, 10.71, 10.68.

A reaction similar to those above was attempted with benzoic anhydride. Ethyl benzoate was obtained and identified by its boiling point, 211° (160 mm.). A mixture of silicate products was also obtained but not identified.

In compounds where carbon was attached to silicon, the silicon analysis was carried out by using a sodium peroxide fusion. With products such as the last four, which were easily hydrolyzable, concentrated (40%) perchloric acid served to oxidize the compounds to silica. The analysis from either point was then carried out according to approved methods. Ethyl diethoxysilicomethyl acetate, however, was spontaneously inflammable with sodium peroxide and was not oxidized by perchloric acid. A dilute mixture of chromic and perchloric acids, concentrated by heating until the temperature of the mixture reaches 200°, will oxidize the silicon-carbon linkage.

CONCLUSIONS

The experimental work herein presented indicates that the reaction between silicoorthoesters and acid anhydrides follows a mechanism which can be explained on the assumption of an ionic splitting. It is indicated, furthermore, that the monoacylated compound, once formed, may dissociate in two different ways. This fact is shown: (a) by the decomposition of the monoacetate and propionate without the production of diethyl silicate, but with the formation of high molecular weight products; (b) by the interaction with the second molecule of the acid anhydride to form the diacetate or dipropionate. These two types of dissociation are shown in equations VII and IX.

The determination of the specific reaction velocity constant at the refluxing temperature of the mixture of propyl ethane orthosiliconate and acetic anhydride has served to show that the acetylation reaction is most probably of the second order. This fact is in agreement with an ionic mechanism such as is postulated. It is reasonable to assume that propionylation also follows the same mechanism.

In the fractionation of the product obtained from the reaction between ethyl orthosilicate and benzoic anhydride, the reaction was forced to the left, since the ethyl orthosilicate is the lowest-boiling fraction. This is undoubtedly one reason why a pure compound could not be isolated.

SUMMARY

1. The acylation of alkyl orthosilicates and silicoorthoesters has been extended, and the methods for the preparation of triethoxysilicomethyl acetate and propionate, diethoxysilicomethyl diacetate and dipropionate, and ethyl diethoxysilicomethyl acetate have been described. The data covering their simple physical properties are given.

2. The equilibrium constant and the specific reaction velocity constant under certain conditions for the reaction between propyl ethane orthosiliconate and acetic anhydride have been measured and presented.

BUFFALO, N. Y.

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[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY]

THE HIGH-TEMPERATURE CHLORINATION OF PARAFFIN HYDROCARBONS[1]

WILLIAM E. VAUGHAN AND FREDERICK F. RUST

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Since the discovery of the photochemical chlorination of methane in 1840 by Dumas (6), a vast amount of study has been given the subject of the halogenation of hydrocarbons. Extensive reviews[2] make unnecessary any broad recapitulation at the present time. The following study[3] is an extension of the very considerable amount of research done previously in these laboratories on halogenation processes and was initiated with the object of better correlating and explaining existing data. A number of articles bearing importantly on this and its companion paper have recently appeared and reference to these will be made at the appropriate points.

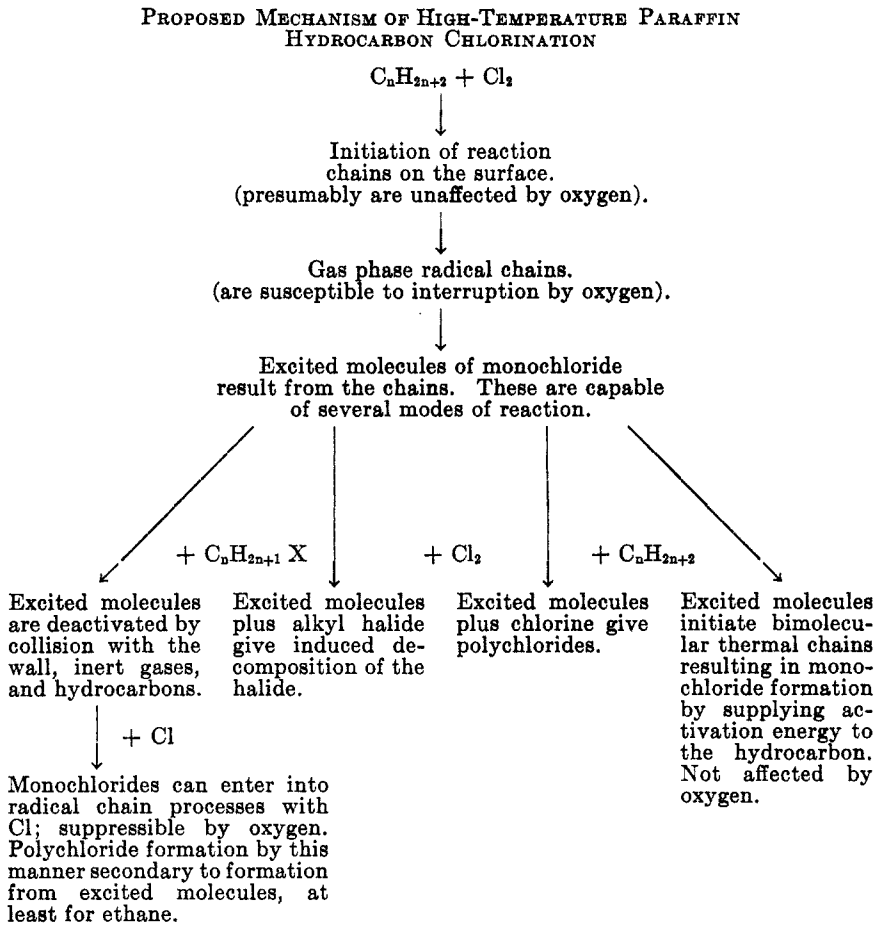
Unusually interesting has been the finding of Groll and Hearne that, contrary to the implications of "classical" organic chemistry, under certain conditions propylene can be readily chlorinated substitutively rather than additively (10, 11, 12). Thus, at temperatures ranging from 400° to 600°, by an apparently homogeneous reaction, the halogen in a 1:7 mixture with the olefin is utilized almost entirely by substitution, and allyl chloride is the principal product. This can be employed as a useful intermediate in syntheses, for example, that of glycerol (27), and consequently the process has far-reaching implications. This seemingly paradoxical reaction, wherein chlorine reacts with a saturated group in direct preference to an ethylenic linkage, was deemed to merit further study. While an absolute delimitation cannot be made because of the interrelationships and interdependencies of the reactions involved, in this paper an attempt will be made to deal primarily with the gas-phase chlorination of paraffins (and of the chlorides derived therefrom), while the succeeding one will treat the high-temperature reactions of chlorine with olefins.

[1] This paper was presented at the 99th Meeting of the American Chemical Society, Cincinnati, Ohio, April 8–12, 1940.

[2] See, for example, (7), (8), and (9).

[3] A number of points revealed during the work are now subjects of several patent applications.

The subject of the chlorination reactions of both saturates and unsaturates in liquid phase and in the presence of a liquid film, especially in regard to substitution, has been discussed at length by previous workers (see, for example, 3, 13, 22, 23). In passing brief consideration of these researches, it may be noted that the extremely fast liquid-phase com-



bination of isobutene with chlorine to give methallyl chloride and hydrogen chloride is not inhibited by oxygen (3), while the relatively slow substitution into paraffins or other saturates is markedly suppressed. Addition, which in solution could readily occur as an association process, and presumably does to a considerable extent, is likewise seemingly little affected. However, so-called "induced substitution" into paraffins or

saturated chlorides concurrently present with an olefin participating in addition reaction, is effectively diminished by oxygen, indicating that the process involves free radicals or atoms initiated in some manner by the interaction of chlorine with the ethylenic linkage. These observations indicate that chlorination reactions take place in a diversity of ways, such as by chain mechanisms involving atoms and radicals, bimolecular metatheses, and association processes involving a third body. The same complexity is found in the vapor-phase experiments to be described.

Attention has thus far been focused on only the simplest compounds, to reduce analytical difficulties to a reasonable degree. Even with this simplification, it has been possible to gain an increased insight into the mechanisms of the several reactions.

MATERIALS AND TECHNIQUE

A flow system has been utilized, as it permits greater flexibility in variation of conditions and in obtaining samples of product for analysis. Against these advantages, however, is the objection that the rate dependencies are somewhat less certain, especially when the amount of reaction is high. Despite this difficulty some kinetic functions may be given with certainty.

The ethane, ethylene, and propane were the same samples used previously (13). The ethyl chloride was a commercial product, which analysis showed to be better than 99.8% pure. Eastman *n*-propyl and isopropyl chlorides and ethyl bromide were carefully refractionated to give pure materials. Only chlorine purified by the distillation process described in the earlier paper was employed; it is felt that this material contained at most only a very low percentage of oxygen (<0.005 mole %). The hydrocarbons, the ethyl chloride, and the gaseous diluents (tank nitrogen or carbon dioxide) were freed of oxygen by scrubbing with chromous sulfate or chloride solution (24) and after drying were metered at constant rates to the reactors. Steady flows of inert diluent (nitrogen or carbon dioxide) through efficient saturating devices filled with the *n*-propyl or isopropyl chlorides or the ethyl bromide, held at predetermined constant temperature, served to introduce desired concentrations of the halides into the reactor. Dissolved oxygen was removed by first sweeping the saturator and its contents with a stream of gas flowing to waste. Before the reactants were commingled by means of a multiply-perforated jet, they were preheated to the desired reaction temperature. The reactor, measuring 1.3 × 45 cm., and the two heating coils, fitted snugly into a massive aluminum core. The vertical furnace surrounding the core was wound with three separately controllable heating units; by manual operation it was easily possible to maintain at constancy the temperature of the reactor to within one degree over its entire length. Light was rigidly excluded from the furnace.

The mixtures effluent from the reactor were analyzed either by titration or by distillation. Care was taken in the cases where the gases contained olefins to eliminate the possibility of the occurrence of catalyzed interaction with chlorine in the absorbing solution. It has been shown (13) that this error can be very serious if improper analytical reagents and conditions are employed. The methods of analysis for chlorine and hydrogen chloride were those used previously. The amount of

addition in any given case was taken as the difference of the total flow of chlorine per minute and the sum of the amounts per minute of unreacted halogen and that reacting by substitution. Consequently, being determined from three experimental values, the amounts of addition may be said to be somewhat less certain than the others. Further, under extreme conditions, where the hydrogen chloride evolved approaches, and even exceeds, the maximum stoichiometric amount of substitution (so-called "excess HCl"), addition becomes even less clearly defined.

In this connection it may be mentioned that under conditions of violent reaction relatively little tar or carbonaceous matter was produced from paraffins, whereas on occasion, thick deposits resulted from olefin chlorination. Outbursts of uncontrolled reaction were readily detected by the appearance of smoke from the delivery capillary tube; at such moments the experiments were stopped and the reactor carefully cleaned with hot mixed sulfuric and nitric acids. It is also worth noting that the surfaces of the reactors were reasonably reproducible in almost all cases. This finding was repeatedly checked during the long period of study with reactors of varying age. However, Pyrex glass wool packing showed a considerable amount of variability, not a surprising result. Yuster and Reyerson (28) reported difficulty in obtaining duplicable results on the thermal chlorination of propane; they attributed the trouble to slight traces of oxygen in the reactants and to variable surface conditions. The consistency of our data is evidence of the absence of these complications.

The titration analyses were supplemented by distillations of the products of chlorination. The gaseous materials effluent from the furnace were scrubbed with 10% potassium hydroxide in order to remove chlorine and hydrogen chloride. Practically no carbon-containing substances were ever found in the wash; the products passed over as vapors into cold traps where they were condensed. After drying, they were fractionated in either a small 17-theoretical-plate column, or a micro still.

Approximately constant reaction times were obtained by using invariant total flows of gas. By holding the total input and the concentrations of all but one of the reactants at fixed values, it was possible to determine the effect of variation of the concentration of the participant in question simply by compensating the rise in its input rate by a corresponding decrease in that of the diluent. Obviously this is not a strictly valid procedure, but under the present conditions, departures from accuracy, because of decomposition reactions or of anomalous temperature gradients, are usually second-order effects which do not vitiate the results found.

RESULTS

Chlorination of paraffins. Figure 1 illustrates the temperature profiles for the chlorinations of ethane, ethylene, and ethyl chloride under identical conditions. Only the total amount of reacted chlorine is given; the distribution between addition and substitution for the unsaturate will be discussed more fully in the following paper. Suffice it for the moment to indicate, that while the onset of reaction under the particular set of conditions occurs at approximately the same temperature for all three compounds, the temperature coefficient is much the greatest for ethane and is the least for the ethyl chloride. With rise in temperature, the reaction with ethane is accelerated enormously. Figures 2 and 3 show that its rate of reaction under these conditions (essentially gas phase) at moderate

temperatures is directly proportional to the concentrations of both the paraffin and the halogen.

$$\frac{d\,[HCl]}{dt} = k\,[Cl_2]\;[C_2H_6]$$

A simple mechanism of the following type would apply:

$$Cl_2 \longrightarrow Cl + Cl$$
$$Cl + C_2H_6 \longrightarrow C_2H_5 + HCl$$
$$C_2H_5 + Cl_2 \longrightarrow C_2H_5Cl + Cl$$
$$Cl + W \longrightarrow \text{chain ending}$$

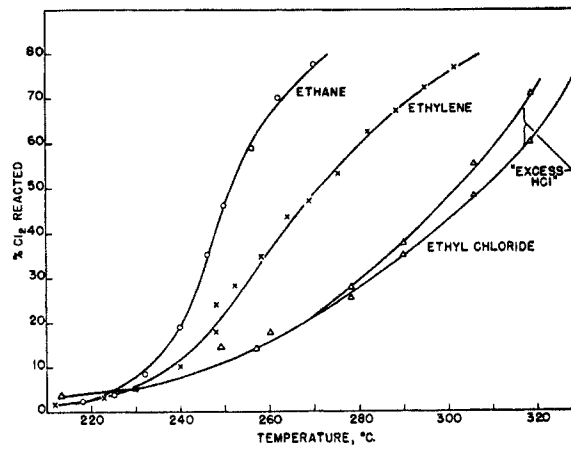


FIG. 1. CHLORINATIONS OF ETHANE, ETHYLENE AND ETHYL CHLORIDE. TEMPERATURE PROFILES

Flow (cc./min.): 50 Cl_2; 100 C_2H_4, C_2H_6 or C_2H_5Cl; 150 N_2 or CO_2

All the steps of this chain are energetically possible, and the ethyl chloride produced should possess a high energy content, as a result of the high exothermicity (*ca.* 22 Cals.) of the step leading to its formation. There are, obviously, several other possibilities for chain termination, such as clean-up of ethyl radicals, and the less probable recombination of chlorine atoms in the gas phase as a result of triple collisions. The inert diluent has little or no effect on the amount of reaction; nitrogen, carbon dioxide, and helium all gave results which were identical within the limits of experimental error.

This equation is the same as that found by Pease and Walz (19) for the thermal chlorination of methane in the absence of oxygen. Pease (18)

gives a similar expression for the thermal, oxygen-free, hydrogen-chlorine reaction.

The chain character of the reaction is further demonstrated by the powerful inhibiting action of oxygen. Under conditions identical with

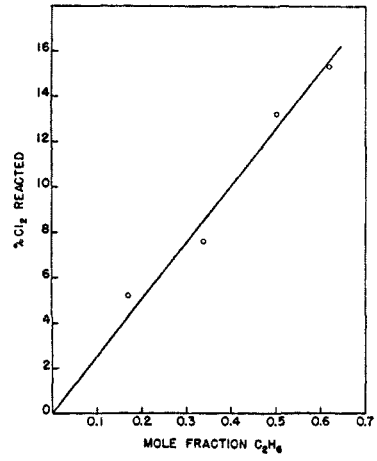


FIG. 2. CHLORINATION OF ETHANE AT 240°C. VARIATION OF ETHANE INPUT
Flow (cc./min.): 50 Cl_2; (50–185) C_2H_6; (200–65)N_2

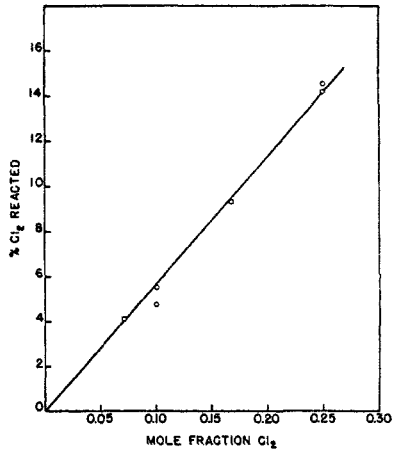


FIG. 3. CHLORINATION OF ETHANE AT 232°C. VARIATION OF CHLORINE INPUT
Flow (cc./min.): (20–75)Cl_2; 150 C_2H_6; (130–75)N_2

those above, 20 cc. of oxygen per minute in the flow suppresses all reaction until a temperature of approximately 350° is reached. At or near this temperature, where in the absence of oxygen an uncontrollable reaction would occur, hydrogen chloride is produced according to the regularities

shown in Figures 4, 5, and 6; that is, in proportion to the 3/2 power of the ethane concentration and the 1/2 power of the chlorine and inversely with that of oxygen. We are unable to deduce a mechanism which leads to this equation.

$$\frac{d\,[HCl]}{dt} = \frac{k\,[Cl_2]^{1/2}\,[C_2H_6]^{3/2}}{[O_2]}$$

The analogous thermal reaction between methane and chlorine in the presence of oxygen has a rate proportional to the square of the halogen concentration, independent of the hydrocarbon and inversely proportional

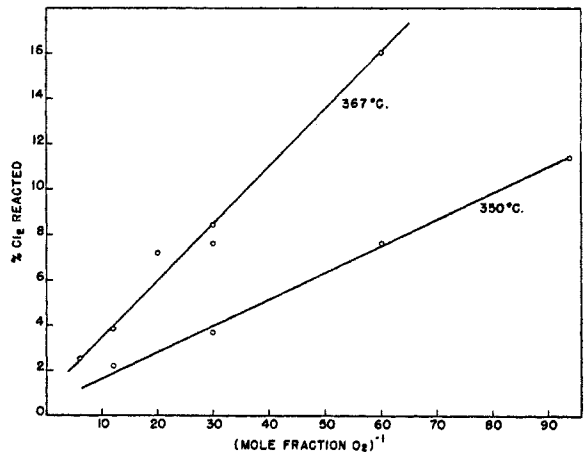


FIG. 4. CHLORINATION OF ETHANE IN THE PRESENCE OF OXYGEN. VARIATION OF OXYGEN INPUT

Flow (cc./min.): 50 Cl_2; 100 C_2H_6; 150 (N_2 + O_2)

to the oxygen concentration (19). The high-temperature non-photochemical combination of hydrogen and chlorine is also strongly retarded by oxygen, but the exact kinetic dependencies are very complex and are not definitely settled (17, 18).

The chlorination of ethane is highly dependent on the surface; the surface presumably acts both to produce chlorine atoms and to terminate chains. Figure 7 reveals that slight increases in the surface/volume ratio result in positive catalysis near the onset temperature. At higher temperatures, apparently some suppression by surface occurs; this would be the result if some chains are initiated in the gas phase. On the other hand, Pyrex glass wool packing almost always showed only accelerating action. In one series of runs with such packing, it was possible to demonstrate that with rising temperature there occurred at first promotion

and then suppression similar to the results with rod and helices packing. At the high temperatures employed by Hass and his co-workers (15), their glass wool soon became coated with a carbonaceous deposit. They also

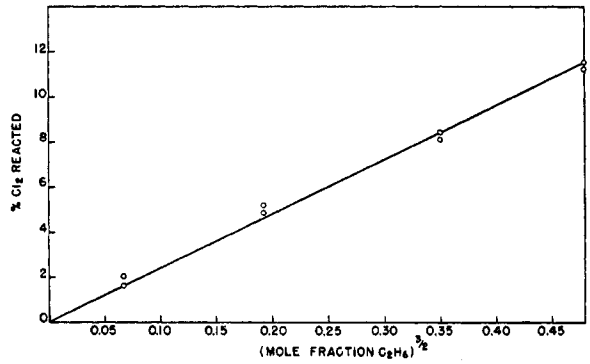


FIG. 5. CHLORINATION OF ETHANE IN PRESENCE OF OXYGEN AT 362°C. VARIATION OF ETHANE INPUT

Flow (cc./min.): 50 Cl_2; (50–185)C_2H_6; (195–60)N_2; 5 O_2

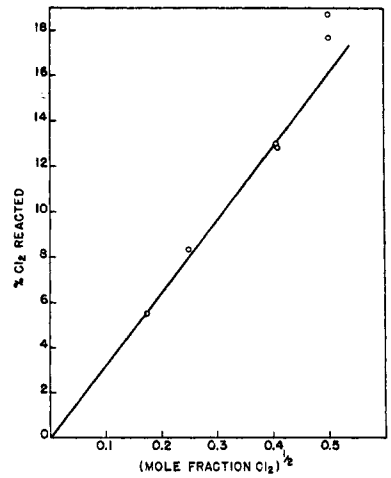


FIG. 6. CHLORINATION OF ETHANE IN THE PRESENCE OF OXYGEN AT 360°C. VARIATION OF CHLORINE INPUT

Flow (cc./min.): (13–70)Cl_2; 150 C_2H_6; (132–75)N_2; 5 O_2

observed marked induction periods. In the present work, high and low temperature points were duplicable at random on so-called "clean" glass surfaces.

Thus far it has been indicated that chlorination of paraffin hydro-

carbons occurs by a free radical chain mechanism. However, other experimental evidence shows that thermal bimolecular processes are

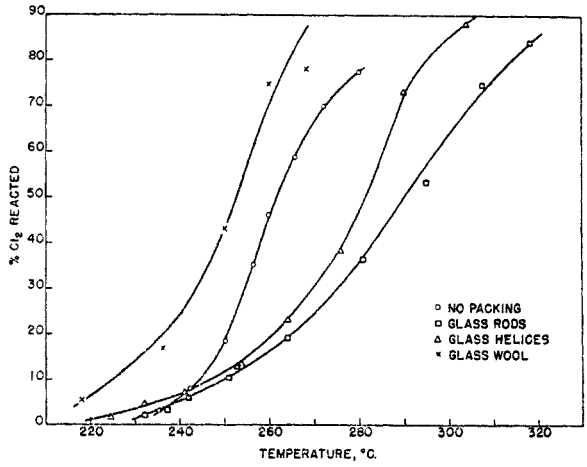


FIG. 7. CHLORINATION OF ETHANE. EFFECT OF SURFACE
Flow (cc./min.): 50 Cl_2; 100 C_2H_6; 150 N_2

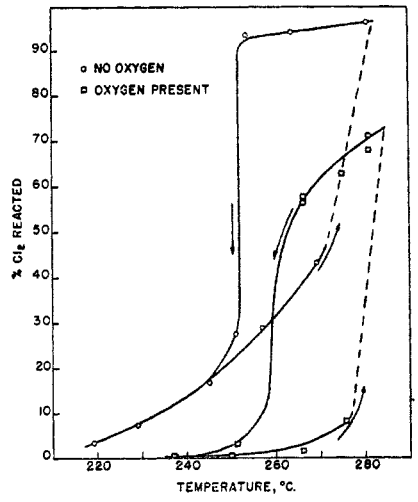


FIG. 8. CHLORINATION OF ETHANE OVER GLASS WOOL. EFFECT OF OXYGEN
Flow (cc./min.): 50 Cl_2; 100 C_2H_6; 150 N_2; or 50 Cl_2; 100 C_2H_6; 130 N_2; 20 O_2

important at higher temperatures. The data of Figure 8 are illustrative. In this case, above 270° a very sudden increase in the rate of halogenation occurred, and free chlorine was substantially eliminated. With *decrease*

in temperature, the high rate persisted to as low as 250°, where it resumed its original value. Admixture of oxygen with the input gases resulted in a very pronounced suppression of reaction but, again, with *rising* temperature, at 276° a violent increase was observed. Decrease in temperature again resulted in the restoration of the original low-temperature rate. It is to be remembered that in the absence of glass wool, oxygen eliminated all detectable reaction. Because a considerable fraction of the chlorination is not suppressible by oxygen, and persists on lowering the temperature, it is felt that the point of suddenly accelerated reaction marks the strong development of thermal chains, which by their dominance impart to the system the character of a mild explosion. The reaction, while violent, is not accompanied by formation of carbon or tar, but yields ethyl chloride and considerable amounts of higher chlorides. The notable fact is the persistence into lower temperature regions of thermal chains. Such a phenomenon of necessity implies the existence of regions of thermal inhomogeneity in the reactor. In the reaction $Cl_2 + C_2H_6 \rightarrow C_2H_5Cl + HCl$ the exothermicity amounts to approximately 26.8 kilocalories.[4] The uniform dissipation at a constant temperature of such an amount of energy constitutes a very considerable problem, and under conditions of high reaction, excited newly-formed molecules, before losing their excess energy to the walls, could by collision provide the necessary activation to promote thermal chains. The generation of chlorine atoms on the surface, probably as a consequence of activated adsorption, the propagation of gas-phase chains from the walls, and the clean-up of radicals, atoms, or energy-rich molecules are all specific functions of surface conditions. Precise treatment of these problems is difficult under the present set of conditions, and only the qualitative aspects can be indicated. Yuster and Reyerson (28) also noted the onset of "explosions", but chose to attribute the effect chiefly to chain branching.

The rate of chlorination of propane is strikingly similar to that of ethane. Typical sets of experiments are shown by Figure 9, in which are included data on normal propyl and isopropyl chlorides, to which reference will be made later. The "excess HCl" produced by decomposition is not indicated in the figure. These comparisons were made by passing the gases alternately through the reactor rather than from four independent sets of runs. The rather pronounced similarity in the lower temperature region is puzzling, as it is not a result of reaction of chlorine and primary hydrogen atoms of methyl groups (common to all four compounds). While at, say, 250°, ethyl chloride is the product from ethane, both *n*-propyl and isopropyl chlorides in approximately equi-

[4] Calculated from heats of formation (1) at 25°.

molar amounts were formed from propane. [This is in substantial agreement with Hass (14).] *n*-Propyl chloride yielded all three dichlorides. The secondary hydrogen atoms, despite their lesser number, are extremely reactive. However, isopropyl chloride is less reactive than the normal compound, and this may be ascribed to its having but one secondary hydrogen atom.

Chlorination of alkyl halides; induced decomposition and other side reactions. In an attempt to clarify the problem of the mechanisms of the secondary processes occurring during the chlorination of paraffins, the reactivities of ethyl, *n*-propyl, and isopropyl chlorides have been studied.

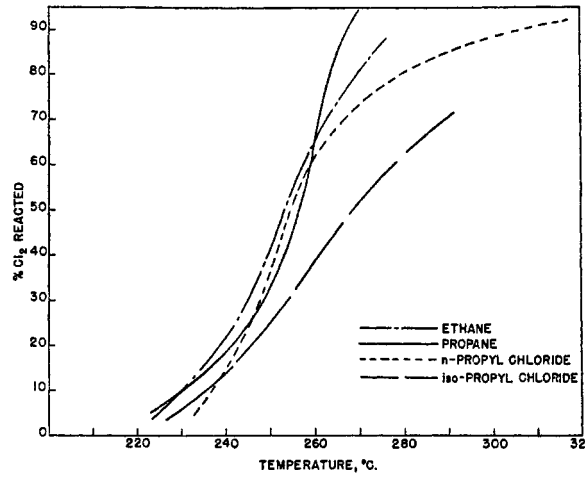


FIG. 9. CHLORINATIONS OF ETHANE, PROPANE, n-PROPYL CHLORIDE AND ISO-PROPYL CHLORIDE. TEMPERATURE PROFILES

Flow (cc./min.): 50 Cl_2; 100 Reactant; 150 N_2

Ethyl chloride is much less reactive than ethane (Figure 1). In fact, as Figure 10 shows, the amount of chlorine reacting with an ethane-ethyl chloride mixture is very close to that found with pure ethane. A significant difference, however, is that, in the presence of admixed chloride the amount of hydrogen chloride evolved is greater than for ethane alone. This condition holds above 280°, where ethyl chloride itself reacts much more slowly than does ethane.

Chlorination of ethyl chloride above 280° yields large quantities of ethylene (measured in the gases effluent from the potassium iodide absorbing solution) together with "excess HCl". Yet, at 415° in the absence of free halogen, but under otherwise comparable experimental conditions, there is practically no decomposition of ethyl chloride into

olefin and hydrogen chloride. Thus, chlorination results in production of the unsaturate under seemingly adverse thermal circumstances. The products resulting from such chlorination at two temperatures are given

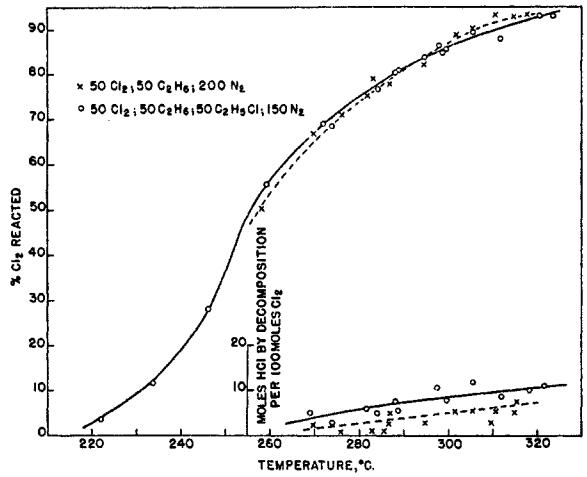


FIG. 10. CHLORINATIONS OF ETHANE AND OF ETHANE-ETHYL CHLORIDE MIXTURE. TEMPERATURE PROFILES

Flows (cc./min.): x 50 Cl_2; 50 C_2H_6; 200 N_2; o 50 Cl_2; 50 C_2H_6; 50 C_2H_5Cl; 150 N_2

TABLE I

CHLORINATION OF ETHYL CHLORIDE

Flows (cc./min.): 50 Cl_2; 100 C_2H_5Cl; 150 CO_2

	320°		415°	
	Moles	Mole %	Moles	Mole %
Ethylene	0.12 (est.)	16.7	0.45	41.7
Vinyl chloride	—	—	0.073	6.8
Unsaturated dichloride	—	—	0.023	2.1
1,1-Dichloroethane	0.47	65.3	0.356	33.0
1,1,1-Trichloroethane	—	—	0.109	10.1
1,2-Dichloroethane	0.12	16.7	0.046	4.3
Bottoms	0.01 (est.)	1.3	0.021[a]	2.0

[a] As tetrachloride.

in Table I. The foregoing results are strong evidence that splitting off of hydrogen chloride occurs as an "induced" decomposition.

The principal product is probably a consequence of a radical chain of the type:

$$Cl + C_2H_5Cl \longrightarrow HCl + C_2H_4Cl$$
$$C_2H_4Cl + Cl_2 \longrightarrow C_2H_4Cl_2 + Cl$$

We have found that small amounts of oxygen suppress the reaction almost completely. At higher temperatures, in the presence of glass wool, some reaction (20% at 320° with O_2; 85% without O_2) does occur. This residual

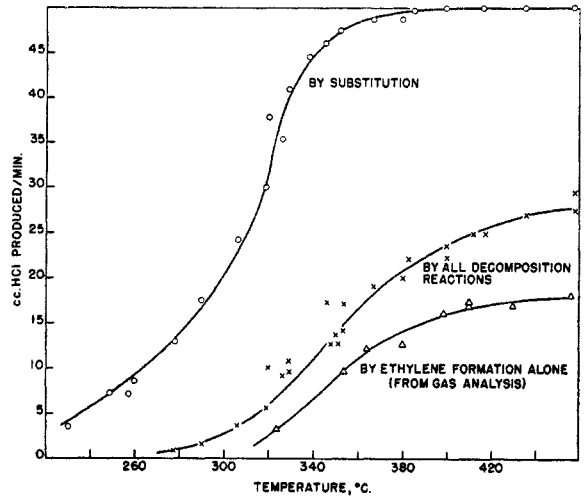


FIG. 11. CHLORINATION OF ETHYL CHLORIDE. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_2H_5Cl; 150 N_2

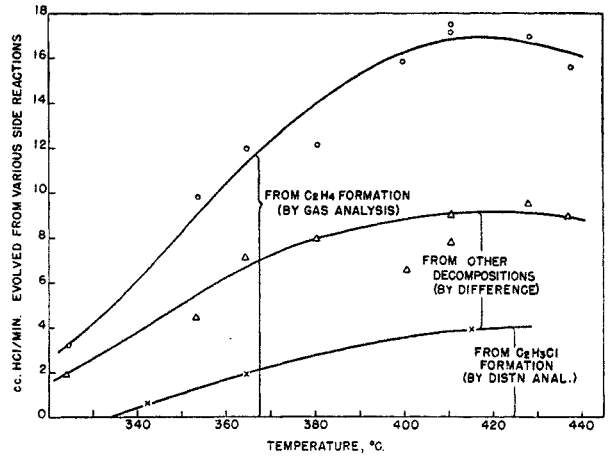


FIG. 12. CHLORINATION OF ETHYL CHLORIDE. VARIOUS SIDE REACTIONS
Flow (cc./min.): 50 Cl_2; 100 C_2H_5Cl; 150 N_2

reaction in the presence of oxygen may be due to thermal chains, as with the paraffins, or to unsuppressed radical chains. It may also be mentioned that increase in the surface/volume ratio slightly inhibits reaction throughout the temperature range studied. The newly-formed mole-

cules of dichloride are probably energy-rich by reason of the high heat of reaction of the second step. Presumably they transfer their energy to ethyl chloride present, to cause its disruption. Similarly, it is quite possible that dichlorides can gain energy with resultant loss of hydrogen chloride to give vinyl chloride. However, the unsaturated chloride might also be produced by direct substitution into the ethylene. Hass, McBee, and Weber (15) likewise observed the formation of olefin during chlorination of paraffins, but attributed it to the decomposition of alkyl radicals, yielding hydrogen atoms and the unsaturate.

In addition to the formation of olefin and chloroölefin, other decomposition reactions occur during the chlorination of ethyl chloride. Table I is illustrative of this, as are Figures 11 and 12. At 364°, with flows (cc./min.) of 50 Cl_2; 100 C_2H_5Cl; 150 N_2 the following results were obtained, which show the magnitude of such changes:

Total HCl evolved (cc./min.)		66.6
Cl_2 input	50.0	
Cl_2 unreacted	6.2	
HCl by substitution		47.4
∴ HCl by decomposition reactions		19.2
HCl released during formation of unsaturates (ethylene and vinyl chloride)		12.0
∴ HCl released by some other decompositions		7.2

The contention that energy-rich, newly-formed molecules "induce" a decomposition of ethyl chloride in a reacting ethane-chlorine mixture has been further substantiated by experiments involving ethyl bromide. The following inputs of vapors were reacted at 278°:

(cc./min.) 50 Cl_2; 50 C_2H_6; 50 C_2H_5Br; 150 N_2

and the following products obtained:

C_2H_5Cl	0.35(4) moles
C_2H_5Br	0.95
C_2H_4	0.14(3)
C_2H_4BrCl	<0.04
Bottoms[5]	5 cc.

At 278° the amount of ethylene evolved by chlorination of ethane alone is so very small that in the present case it must come almost entirely from ethyl bromide. When ethyl bromide alone is chlorinated at this

[5] 2,3-Dichlorobutane was added to the still bottoms to push over the C_2H_4BrCl; thus, a more quantitative indication of the amount of the bottoms is not possible. The 5 cc. is the difference between the amount of bottoms recovered and the quantity of dichlorobutane added.

same temperature, the ethylene evolved is of the order of 40% of the chlorinated alkyl bromide. The following balance is pertinent:

Ethyl bromide input	1.12(5) moles
Ethyl bromide recovered	0.95
C_2H_4BrCl	0.04
Ethylene obtained	0.14
Ethyl bromide accounted for	1.13 moles

Furthermore:

Ethane reacted	0.36(8) moles
Ethyl chloride obtained	0.35(4) moles

Thus, in view of the small amount of the chlorobromide and the large amount of ethylene derived from the ethyl bromide, a mechanism of decomposition by "induction" may be considered well established.

Another important side-reaction in the chlorination of ethane, that of the formation of polychlorides, has also been studied. Considerable amounts of dichloride and higher chlorides are always found, and these are produced under conditions where the monohalide is ordinarily relatively unreactive compared to the paraffin (see Figure 1). Also, admixed monohalide does not enhance the amount of chlorine reacted to produce polyhalides (see Figure 10, wherein ethyl chloride was used; also recall the above experiment with ethyl bromide). In the light of these facts, it would seem that polychloride formation is a direct consequence of the interaction of energy-rich, newly-formed monohalides with chlorine. This type of bimolecular process would lead to the initiation of a thermal chain producing polyhalides, and the length of the chain would be dependent upon the frequency of deactivating collisions with other molecules or the walls.

The nature of the polyhalides produced presents a problem of considerable complexity. Hass and his co-workers (14, 15) have done extensive work on the factors affecting yields of isomeric monochlorides and dichlorides, which has enabled them to formulate a set of rules covering the cases. One of the principal findings was that, whereas ordinarily the reactivity of the hydrogen atoms toward substitution is in the order primary < secondary < tertiary, with increasing temperature there is increasingly close approach to relative rates of 1:1:1 in both liquid and vapor phase. This means that at sufficiently high temperature, providing the reactions can be controlled and no pyrolysis occurs, the yields of the several monochlorides are simply calculable from the *a priori* statistics of the numbers of the various kinds of hydrogen atoms. In the attempt to clarify the nature of the secondary reactions accompanying

the chlorination of paraffins, a considerable number of data bearing on this subject have now been assembled. These results will be presented in a later publication. It is interesting, however, to note that, while ethyl chloride contains a methyl group as does ethane, the former is by far the less reactive. Also, isopropyl chloride is less reactive than either propane or *n*-propyl chloride and only slightly more so than ethyl chloride. And, further, reaction, when it does occur, involves principally those hydrogen atoms bonded to the carbon atom already holding chlorine. Apparently a chlorine atom on a carbon atom in the 2-position inhibits substitution on adjacent methyl groups. Table I bears out this statement, at least insofar as the reactions of ethyl chloride are concerned. At 320°, the 1,1-dichloroethane predominates over the 1,2 compound in the ratio of 4:1. At 415°, the ratio is 7.7:1 and even the amount of 1,1,1-trichloride is greater than that of 1,2 in the proportion of 2.4:1. This finding, which is also borne out by experiments on the chlorination of ethane-ethylene mixtures (see Table II), suggests amendment of Hass' chlorination rule No. 9, which states that "in vapor-phase chlorination the presence of a chlorine atom on a carbon atom tends to hinder further reaction upon that carbon atom during the second substitution." Kharasch and Brown (16) concur in this rule insofar as the liquid-phase chlorination of hydrocarbons and chlorides by means of sulfuryl chloride in the presence of peroxides is concerned. This environment is, of course, quite different from the gas phase.

Chlorination of ethane-ethylene mixtures. In Figure 13 are shown the temperature profiles for the chlorinations of ethane (curve 1) and of ethylene (curve 2) under identical circumstances. It is seen that ethane is the more reactive. With the olefin, the addition process sets in first, rises to the maximum, and then falls off, while substitution rises steadily. The comparative curves for ethane and ethyl chloride (Figure 1) suggested that in a mixture of the two compounds, only the paraffin would be chlorinated. This, as has been shown, was borne out by test. Similarly, with an ethylene-paraffin mixture, the saturate would be expected to play the dominant rôle. This is the case. Figure 14 gives some data for such a system. It is seen that the amount of chlorine reacted by addition is greatly reduced, rising to the maximum of only 13% as compared with 54% for pure ethylene. At 293° it is zero, while in the absence of ethane it is 53% for a two-fold increase in the ethylene concentration. It is also to be noted that the total amount of chlorine reacted is somewhat less for the mixture than for ethane, but with a reduction in concentration of one-half for both hydrocarbons, the amount of substitution is surprisingly high. Indeed, above 293°, substitution is the only process of change.

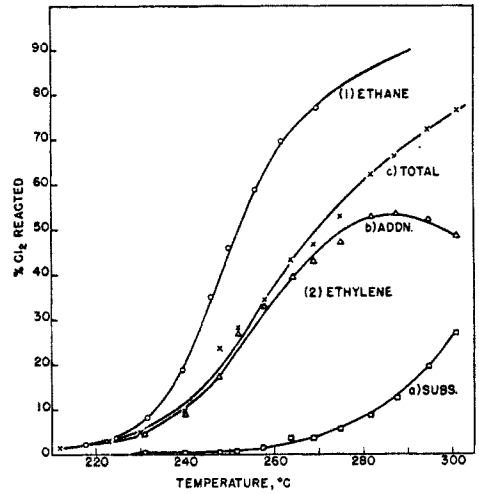


FIG. 13. CHLORINATIONS OF ETHANE, (1) AND OF ETHYLENE, (2). TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_2H_4 or C_2H_6; 150 CO_2

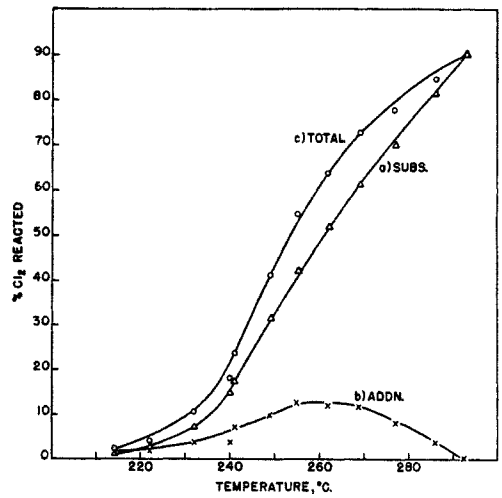


FIG. 14. CHLORINATION OF ETHANE-ETHYLENE MIXTURE. TEMPERATURE PROFILE
Flow (cc./min.): 50 Cl_2; 50 C_2H_6; 50 C_2H_4; 150 CO_2

Inasmuch as addition (curve 14b) is reduced to zero, it is reasonable to assume that substitution into ethylene plays little part.

In order to test this assumption, a collection and analysis of the product

formed at 314° was made. For this particular test, in order to conserve time, a reactor measuring 2.2 × 42 cm. was used with proportionately larger flows (cc./min.: 200 Cl_2; 200 C_2H_4; 200 C_2H_6; 600 N_2). The vapors effluent from the reactor were washed free from halogen and acid; the liquid product was condensed, dried and distilled. The analysis was as follows:

That reaction is largely confined to the ethane is also conclusively shown by an analysis of the product formed under conditions of *uncontrolled reaction*, which simulates the conditions which would hold above 300° according to curves in Figure 14. The flows used were (cc./min.): 75 Cl_2; 112 C_2H_4; 112 C_2H_6. With these high concentrations the mixture ignited at *ca.* 235°, but the reaction was entirely free from charring, a noteworthy qualitative observation, inasmuch as under such violent conditions ethylene-chlorine mixtures often yield tars while ethane-chlorine mixtures usually do not. The analysis of the product is given in Table

TABLE II

ANALYSIS OF PRODUCT FROM CHLORINATION OF ETHANE-ETHYLENE MIXTURE

	Mole %
Vinyl chloride	3.6
Ethyl chloride	67.8
1,1-Dichloroethane	22.6
1,1,1-Trichloroethane	2.2 (est.)
1,2-Dichloroethane	2.5 "
Heavier	1.3 "

III, together with explanatory remarks regarding the origin of the compounds. The notes point out that ethane is being chlorinated almost to the exclusion of the olefin. The gaseous product non-condensible by solid carbon dioxide gave analysis for 67.2% C_2H_4. On the assumption that all of the products listed in Table III were derived from the paraffin, it can be calculated that the effluent gas would be 65.5% olefin, an excellent agreement. The larger the amount of ethylene assumed to be reacting to give chloro derivatives, the greater would be the discrepancy between the actual gas analysis and that computed.

If, to a 50 Cl_2:50 C_2H_4:50 C_2H_6:150 CO_2 mixture, as little as 5% of oxygen is added, all reaction, both addition and substitution, is suppressed, to at least 284°.

Tables II and III prove the contention that ethane is dominantly, in fact almost exclusively, the reactive component of the mixture. This discovery serves to clarify the mechanism of the high-temperature chlorination of propylene. It has been suspected for some time that allyl chloride is formed by direct substitution on the saturated carbon atom

of propylene. Nevertheless, the possibility of interaction of chlorine with the double bond could not be disregarded, inasmuch as allyl chloride is formed in considerable amounts by pyrolysis of propylene dichloride. However, these new data with ethane-ethylene eliminate the possibility of a mechanism of addition of one Cl atom in the 1-position, followed by ejection of an H atom from the 3-position and shift of the double bond (26). In effect, the problem has been treated by segregating the saturated and unsaturated fragments of the $H_3CCH{=}CH_2$ molecule by using two distinct molecules. It now seems certain that direct substitution occurs by reason of the enormous reactivity of the allylic hydrogen atoms for chlorine

TABLE III

ANALYSIS OF PRODUCT FROM CHLORINATION OF ETHANE-ETHYLENE MIXTURE

PRODUCT	MOLE %	REMARKS
Vinyl chloride	6.3_5	Is probably derived from ethylene, but may have originated by pyrolysis of dichloroethanes.
Ethyl chloride	71.4	It is most unlikely that the ethyl chloride would come from addition of HCl to C_2H_4, particularly in view of the analysis of the effluent gas (see text).
Dichloroethanes	21.7	The larger proportion (*ca.* 80%) of this fraction is 1,1-dichloroethane and is derived from ethane. It is unlikely that ethyl chloride would be chlorinated exclusively to the 1,1-dichloride; thus it seems probable that the *ca.* 20% of the 1,2 compound also came from ethane. This conclusion is confirmed by the gas analysis (see text).
Trichloroethane	0.5_5	

at temperatures above 280°. That the process proceeds by a chain mechanism, at least over a certain temperature range, is likewise quite definite. The subject is discussed more fully in the companion paper.

Homogeneous catalysis of chlorination reactions. On the basis of the evidence which indicated that high-temperature, gas-phase chlorination of paraffins proceeded by a radical chain mechanism, the prediction was made that compounds which decompose or react readily to give radicals would catalyze certain halogenation processes in the dark, at temperatures below those usually required to initiate reaction. The profound catalytic activity of such materials has now been demonstrated in both gas and liquid phase and with a variety of hydrocarbons.

1. Catalysis by tetraethyl lead. Tetraethyl lead has often been used as a source of ethyl radicals, since these are produced by thermal decomposition of the compound at temperatures above 200°. It reacts readily with chlorine to give lead chloride and ethyl chloride (4). In the course of such a transformation, it is reasonable to assume the transient existence of highly reactive species, such as ethyl radicals, and on this premise the catalytic activity was tested.

A carrier gas such as hydrocarbon, carbon dioxide, or nitrogen was bubbled through a saturating device containing the metal alkyl at a predetermined temperature. It was also possible to by-pass the evaporator. The mixture passed to the reactor, where it met the flow of chlorine in the total absence of visible light. The amount of catalyst admitted was adjustable by variation of the temperature of the evaporator and the volume of carrier gas.

(a) *Chlorination of ethane.* With flows of 100 cc. of ethane per minute through the lead alkyl at 0°, 150 cc. per minute of diluent nitrogen, and 50 cc. per minute of chlorine into the reactor at 132°, more than 95% of the chlorine reacted. Without the lead *no* chlorine was consumed. Oxygen (25 cc./min.) completely suppressed all reaction. To accomplish this same degree of removal of halogen by thermal reaction alone requires a temperature of 280–290° (see Figure 1). *All* reaction could be stopped simply by by-passing the ethane around the metal alkyl; on resaturating the hydrocarbon the chlorination was again initiated. The walls of the reactor became coated with a light film of solid lead chloride, and some appeared as smoke in the effluent gases, but catalytic activity of this material is unimportant; alkyl in the input gases is essential for reaction. The product obtained was 80 mole-per cent ethyl chloride and 20 mole-per cent higher chlorides, the same distribution as was found for the thermal reaction. It should be mentioned that this strikingly effective catalysis is brought about by a vapor-phase concentration of lead tetraethyl of the order of 0.002 mole-per cent. (The vapor pressure over the liquid alkyl at 0° is 0.047 mm. and at 25°, 0.377 mm.) (2).

(b) *Chlorination of propane.* This paraffin was also easily chlorinated when the reaction was catalyzed by lead alkyl. At 136–140° no reaction occurred when the following flows (in cc./min.) were passed through the reactor: 50 chlorine; 100 propane; 100 carbon dioxide; 50 nitrogen (see Figure 9). Saturation of the carbon dioxide with lead tetraethyl at 0° caused more than 95% of the halogen to react. As with ethane above, the presence of the lead alkyl was essential to the occurrence of reaction; chlorination ceased when the lead was by-passed and began again with its admission. The product consisted of 33 mole-per cent isopropyl chloride, 43% *n*-propyl chloride, and 24% dichlorides.

(c) *Chlorination of cyclopentane.* The following flows (in cc./min.) were used: 50 chlorine; 135 nitrogen, which served to vaporize cyclopentane in a saturator to the extent of 100 cc. of vapor per minute; 15 carbon dioxide, which could be passed through tetraethyl lead at 25°. At 155°, saturation of the carbon dioxide with the metal alkyl caused more than 95% of the chlorine to react; in the absence of lead alkyl *no* reaction occurred. Oxygen completely suppressed activity. At lower temperatures condensation of a liquid film on the tube also inhibited reaction.

(d) *Chlorination of* n-*pentane in liquid phase.* Two flasks containing 175 cc. of de-aerated *n*-pentane at 10° were fitted to permit the entry of 50 cc. of chlorine per minute and 50 cc. of carbon dioxide per minute. In one case, the carbon dioxide was saturated with tetraethyl lead at 25°. After equal periods (22 minutes) the effluent gas from the flask receiving the catalyst showed 26 times the amount of substitution in the other (76.6 cc. of 0.1 *N* thiosulfate equivalent to the HCl, as compared with 2.9 cc.). Inspection of the contents of the flasks revealed that complete reaction had occurred in the presence of the trace of lead alkyl, while the pentane in the other was colored with unreacted chlorine.

2. Catalysis by hexaphenylethane in liquid phase. In addition to the metal alkyls as possible catalysts of chlorination reactions, hexaphenylethane was tested. It was prepared by reduction of triphenylchloromethane with vanadous chloride (5). The solid hydrocarbon was dissolved in *n*-pentane; the saturated solution contained a maximum of 0.00003 moles of triphenylmethyl per cubic centimeter. Into 100 cc. of de-aerated *n*-pentane at 25° in the dark was run gaseous chlorine at the rate of 50 cc. per minute. Simultaneously 1.5 cc./min. of the triphenylmethyl solution was added. The chlorine was completely consumed. When only pure pentane was used, the liquid was yellow with dissolved, unreacted chlorine.

For further comparison, the effluent stream of gas was passed through potassium iodide solution during the last three minutes of each of two twenty-two-minute experiments. When the pentane contained triphenylmethyl, 0.6 cc. of 0.1 *N* thiosulfate solution was required to titrate the iodine liberated by the unreacted chlorine; upon addition of potassium iodate, 54.0 cc. of 0.1 *N* thiosulfate was equivalent to the iodine liberated by the acid. The corresponding figures obtained in the absence of added radical were 48.4 cc. of thiosulfate for unreacted chlorine and 33.0 cc. for hydrogen chloride. The catalytic activity is clearly shown.

3. Catalysis by azomethane. This compound also showed ability to catalyze gas-phase chlorination reactions, although under the one set of conditions used, not to so marked a degree as the metal alkyls or the hexaphenylethane. Azomethane was prepared from hydrazine hydrochloride by the method of Thiele (25), as modified by Ramsperger (20).

A reaction-mixture of approximately 2% azomethane in *n*-butane was made by combining a flow of 20 cc. per minute of butane containing 10% azomethane with 80 cc. of pure *n*-butane per minute. This mixture was further diluted with 150 cc. of nitrogen per minute and then mingled with 50 cc. of chlorine per minute. At 144°, 5.5–6.0% of the chlorine substituted. No chlorine whatsoever reacted when azomethane was not present in the mixture.

MECHANISM OF HIGH-TEMPERATURE PARAFFIN HYDROCARBON CHLORINATION

The accompanying self-explanatory chart summarizes the deductions from the experimental data as they bear upon the mechanisms of the reactions involved. Thermal chains very likely originate by some such process as suggested, but at temperatures above 300–400°, they need not necessarily develop according to this scheme, because more than sufficient activation energy may be available for a bimolecular process. The theoretical calculations by Sherman, Quimby, and Sutherland (21) indicate that there is actually very little difference in the probability of bimolecular or radical chain mechanisms, at least for chlorine substitution into ethylene.

ACKNOWLEDGMENT

The authors wish to express to Dr. E. C. Williams, Vice-President in Charge of Research, their appreciation of his stimulating interest in this work. To their colleagues they acknowledge their indebtedness for many discussions and suggestions.

SUMMARY

A. A study of the high-temperature gas-phase chlorinations of the lower paraffin hydrocarbons suggests the following mechanism:

1. Initiation of reaction at the surface.

2. Propagation of gas-phase radical or atomic chains, suppressible by oxygen. Excited molecules are formed which can react in several ways, to wit: (a) deactivation by collision with walls or other molecules to give stable monohalides; (b) reaction with chlorine to give polychlorides; (c) collision with alkyl halides which may result in an "induced" decomposition to give olefin and hydrogen chloride; and (d) initiation of bimolecular thermal chains, not suppressible by oxygen.

B. It has been found that it is possible to chlorinate the paraffin of either an ethane-ethylene or ethane-ethyl chloride mixture to the practical exclusion of the admixed olefin or monohalide.

C. Gas- and liquid-phase chlorinations are enormously accelerated by the presence of very small amounts (*ca.* 0.002 mole-per cent) of metal

alkyls. Also, hexaphenylethane acts as a catalyst in the liquid phase and azomethane in the vapor phase.

EMERYVILLE, CALIF.

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[CONTRIBUTION FROM SHELL DEVELOPMENT COMPANY]

THE HIGH-TEMPERATURE CHLORINATION OF OLEFIN HYDROCARBONS[1]

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Received April 29, 1940

Although the reactions of olefins with chlorine in the liquid phase [see, for example, (2, 7, 8)] and in the gas phase at comparatively low temperatures (3, 11) have been extensively studied, the investigations have not until recently been extended to higher temperatures. The recent work of Groll and Hearne (10) has shown that straight chain olefins will readily react with chlorine at elevated temperatures to form allylic chlorides. The present study, undertaken in an attempt to provide a better understanding of the mechanisms of reactions above 200°, falls into three distinct divisions, namely,

I. Olefin-chlorine reactions—a study of the mechanisms and conditions determining substitution and addition.

II. Catalysis of chlorine substitution reactions by oxygen.

III. Olefin inhibition of chlorination.

The companion paper (20), to which frequent reference will be made, dealt with the high-temperature chlorination of the lower paraffin hydrocarbons.

MATERIALS AND TECHNIQUE

The ethylene and vinyl chloride were commercial samples, which analysis showed to be 99.5% and 99–100% pure, respectively. The propylene, 2-butene and isobutylene were refinery products; their compositions were as follows:

Propylene	98.(4)% C_3H_6; 1.(6) C_4H_8; (100% olefin).
2-Butene	97.(5)% 2-C_4H_8; (98+% olefin).
Isobutylene	99.(4)% iso-C_4H_8.

The chlorine was the specially prepared material of very low oxygen content (20).

The same technique and apparatus were employed in this research as in the preceding (20). All materials which are normally gaseous, except of course the chlorine, were freed of oxygen by means of chromous chloride or sulfate solutions. The compounds normally liquid were vaporized at a fixed temperature from saturating

[1] This paper was presented at the 99th Meeting of the American Chemical Society, Cincinnati, Ohio, April 8–12, 1940.

devices by means of a flow of oxygen-free nitrogen or carbon dioxide; after a period of sweeping to remove dissolved oxygen, the flows were diverted to the reactor. The reactor, 45 cm. long × 1.35 cm. diameter, was equipped with two preheating coils above the mixing jet and both tube and coils were housed in a massive aluminum core in a vertical furnace. Three separate heating units permitted manual regulation of the furnace temperature to a constancy of 1° over the entire length. The uniformity of temperature within the reactor itself is illustrated by the following test. The position of a thermocouple in a thin-walled glass well in the center of the reactor was varied from the extreme top, next to the mixing jet, to the bottom, near the delivery capillary. Although 65% of the chlorine in a flow containing 50 cc. per minute of halogen was reacting, a maximum temperature variation of only 1° was noted. Of course, under certain conditions, inflammation does occur with consequent severe temperature gradients. This is always accompanied by carbon and tar formation and the appearance of smoke. When such uncontrolled reaction was observed, an experience somewhat more common with olefins than with paraffins, the experiment was discontinued and the reactor cleaned with hot sulfuric-nitric acid mixture.

The analysis of the products of olefin chlorination is a serious problem, especially when a considerable amount of unreacted halogen remains in the effluent gases. There is the possibility of a catalyzed reaction between chlorine and hydrocarbon occurring in the potassium iodide or potassium hydroxide solution used to absorb the unreacted halogen and the acid produced by substitution. If unsatisfactory absorbing solutions are employed, the error thus introduced may amount to as much as 30% of the chlorine. This problem has been discussed at length in a previous paper (11). In the following experiments, titration analyses for the amounts of addition and substitution were made in conformity with earlier experience, and were often supplemented by collection and distillation of the products.

I. MECHANISMS OF THE OLEFIN-CHLORINE REACTIONS

Ethylene. a) Reactions Inhibited by Oxygen—Chain Reactions. It is considered well established that many chlorination reactions occur *via* a chain mechanism. As is often characteristic of such processes, exact control is sometimes very difficult, especially when high concentrations of reactants are present. This has been noted by many workers. Similar observations have been made in the present case, and it has been found that only by diluting the reactants with an inert gas can a systematic study by dynamic methods be made. For example, with rising temperature, undiluted 1:1 ethylene-chlorine mixtures inflamed almost with the inception of reaction at approximately 215°. With small amounts of nitrogen, the temperature of the onset of uncontrolled reaction was raised somewhat. With larger quantities of diluent, control can be maintained to relatively high temperatures.

This is shown by Figures 1, 2, and 3 which are temperature profiles for the following mixtures, for which the concentration of the diluent, nitro-

gen, was varied while holding constant the ratio of the reactants and the total throughput:

Flows in cc./min.			
Cl_2	C_2H_4	Diluent	Total
35	35	230	300
50	50	200	300
75	75	150	300

Below *ca.* 235° no change occurs. The addition-reaction then sets in prior to the substitution and rises gradually with the temperature. However, due to the onset of substitutive processes and their higher temperature coefficient, the amount of addition reaches the maximum and then falls

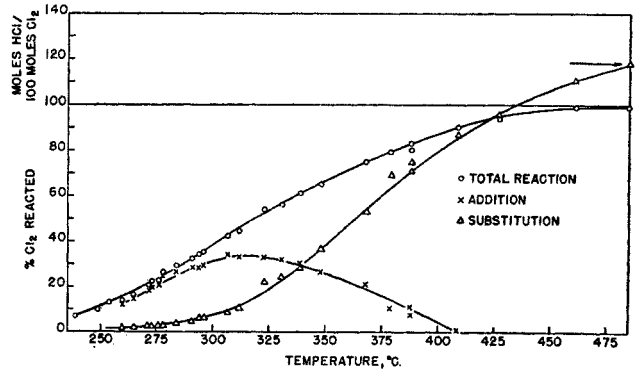

FIG. 1. CHLORINATION OF ETHYLENE. TEMPERATURE PROFILES
Flow (cc./min.): 35 Cl_2; 35 C_2H_4; 230 N_2

towards zero. At higher temperatures the amount of hydrogen chloride produced is in excess of the stoichiometric quantity expected from substitution. At 390° in Figure 2, at the point denoted by the arrow, smoking and charring occurred.

In Table I are given some pertinent data correlating the several mixtures. At a given temperature (275° in Table I), the fraction of the reacted halogen which goes to addition progressively decreases as the concentration of the reactants increases. This means that while both reactions are highly dependent upon the partial pressures of olefin and chlorine, the substitution is of a higher order than the addition and rapidly becomes an important process of change. Curves practically identical with those of Figure 3 were obtained when nitrogen or helium rather than carbon dioxide was used as the diluent; the differences are probably not significant.

In order that the significance of the curves might be more clearly understood, the actual composition of the product at two different temperatures

has been determined. The data in Table II, which clearly shows the effect of temperature on the distribution of products, correspond to points on the curves of Figure 2. The agreement of the distillation analyses with those by titration is very satisfactory. However, it is generally better to have both bits of complementary information. At the lower temperature,

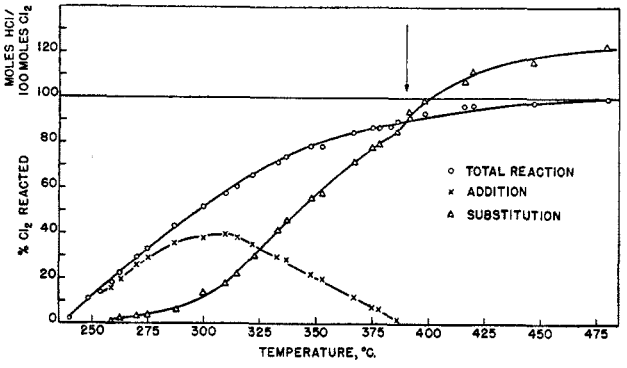

FIG. 2. CHLORINATION OF ETHYLENE. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 50 C_2H_4; 200 N_2

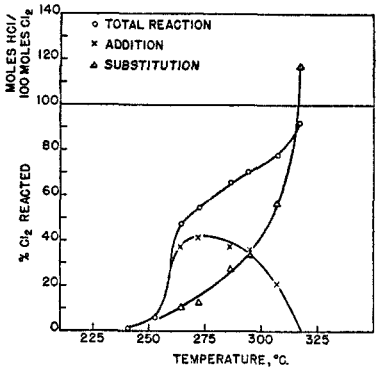

FIG. 3. CHLORINATION OF ETHYLENE. TEMPERATURE PROFILES
Flow (cc./min.): 75 Cl_2; 75 C_2H_4; 150 CO_2

308°, the total amount of addition is much greater than that of substitution; conversely, at the higher, 346°, the substitutive steps are the dominant ones. The mole percentages of trichlorides and tetrachlorides are relatively constant, and the principal variations are in the amounts of unsaturates and the simple addition-product. The formation of higher chlorides from vinyl chloride has an important bearing on the understanding of the reaction; this point will be discussed later.

In conjunction with these product distributions, it is interesting to note that at higher temperatures (say at 485°, as denoted by the arrow in Figure 1), where extensive decomposition ("excess HCl") occurs, acetylene is

TABLE I

CHLORINATION OF ETHYLENE

FLOWS (CC./MIN.)				AT 275°			TEMP. OF MAXIMUM AMOUNT OF ADDITION
Cl_2	C_2H_4	N_2 or CO_2	Total	Total % Cl_2 reacted	% of total Cl_2 added	% of reacted Cl_2 added	
							°C.
35	35	230	300	22	20	91	315
50	50	200	300	33	29	88	310
50	100	150	300[a]	57	49	86	288
75	75	150	300	58	43	74	275

[a] Data for this mixture taken from Figure 13 of (20).

TABLE II

CHLORINATION OF ETHYLENE. ANALYSES OF PRODUCT

Flow (cc./min.): 50 Cl_2; 50 C_2H_4; 200 N_2

	MOLE % OF CHLORINATED PRODUCT	
	308°	346°
Vinyl chloride	20.7	52.7
1,1- and 1,2-Dichloroethylene	4.6	14.8
1,2-Dichloroethane	64.0	20.2
1,1,2-Trichloroethane	10.3	9.9
Tetrachloroethanes (est.)	0.4	2.4
% of total Cl_2 reacted (see Figure 2)	57	77
By distillation analysis:		
% total Cl_2 added	37	25
% total Cl_2 substituted	20	57
By titration analysis:		
% total Cl_2 added	37	23
% total Cl_2 substituted	20	54

found in the gases; this undoubtedly results from a splitting of hydrogen chloride from vinyl chloride.

In the attempt to clarify the mechanism of this gas-phase addition-reaction, the dependency of the rate on the concentrations of the reactants was studied. The same procedure described previously (20) was used.

Although the experiments were conducted at lower temperatures where substitution is relatively unimportant, the data obtained lacked satisfactory precision. This is not surprising, since the addition as determined is a difference involving three experimental values (chlorine input, amount unreacted, and amount substituted). Variation of the halogen input at 268° indicated a rate proportional to the first power of the chlorine concentration. At the same temperature the velocity appeared to vary as the square root of the mole-fraction of olefin. While this function gave an approximate representation of the findings and more or less definitely ruled out a linear dependency, the precision of the data leaves something to be desired.

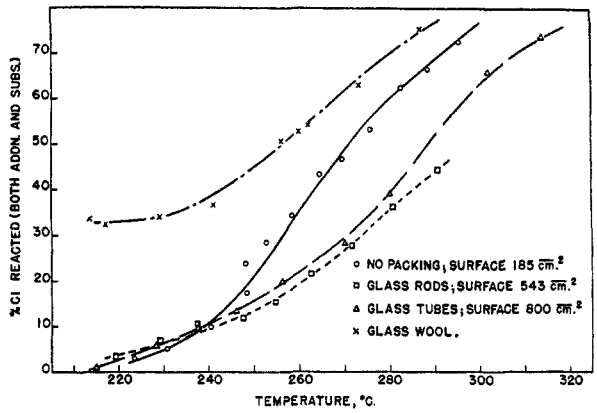

FIG. 4. CHLORINATION OF ETHYLENE. EFFECT OF SURFACE
Flow (cc./min.): 50 Cl_2; 100 C_2H_4; 150 CO_2

Norrish (15, 16) and Williams (22) found that the addition of bromine to ethylene at room temperature in the absence of a liquid film of product was highly dependent on the amount and character of the surface and that the rate was of difficultly reproducible order. They indicate that a dependence on the first powers of both reactant concentrations is probably as good a decision as can be made. Williams ascribes the trouble to surface variation, which would probably be an even more serious factor at the lower temperature at which he worked than in the present study.

In this connection, Figure 4 shows clearly the pronounced influence of surface, in the light of which a study of exact rate dependences seems rather futile. At low temperature, where only addition occurs, increased surface causes an increase in the amount of reaction, probably as a result of catalyzed bimolecular association as well as initiation of chains. Glass wool is particularly effective. At higher temperatures, surface suppresses

reaction, presumably as a consequence of termination of chains initiated in the gas phase. The chains involve both addition and substitution at these temperatures. It is seen that there is a rough parallelism for all three curves for packed systems. Glass wool packing, even at the higher temperatures, accelerates the amount of reaction at the surface [compare Figure 4 with Figure 7 of (20)]. The superiority of quartz over glass as a material for the reactor is noteworthy, as with the former the formation of tar and carbon occurs to a smaller extent, although slightly higher temperatures are necessary to obtain an equivalent amount of reaction. Hearne and La France (12) have made similar observations for the chlorination of propylene.

The powerful inhibiting effect of oxygen on numerous halogenations has been considered strong evidence that the reactions proceed by chain mechanisms involving radicals. In this work when even a very concen-

TABLE III

CHLORINATION OF ETHYLENE. CATALYSIS BY TETRAETHYL LEAD

Flow (cc./min.): 50 Chlorine; 150 Nitrogen; 100 Ethylene through Tetraethyl Lead at 0°

	PER CENT OF CHLORINE REACTING			
	100°		132°	
	Substitution	Addition	Substitution	Addition
Without $PbEt_4$	0	2.6	0	9.1
With $PbEt_4$	0	16.4	0	23.3

trated mixture (137.5 cc. Cl_2/min.; 137.5 C_2H_4; 25 O_2) was flowed through the reactor, no reaction occurred to as high a temperature as 288° (contrast with 227° for 8% N_2). At this temperature the mixture ignited, as much as 1.67 moles of hydrogen chloride being formed for every mole of chlorine used. If at any temperature below 288° the oxygen flow was stopped, ignition immediately occurred. When 3% oxygen was used (145 Cl_2; 145 C_2H_4; 10 O_2), the ignition temperature was 240°; the observations were otherwise the same. The fact that controlled inhibition by oxygen does not persist to as high temperature with olefins as with paraffins (20), will be explained under oxygen catalysis in Section II.

The chain character of the gas-phase reactions of addition and substitution into olefins under certain conditions is further confirmed by experiments wherein catalysis of the processes was obtained by use of tetraethyl lead. The great efficiency of this material in promoting the chlorination of saturates has been discussed at some length (20). The effect is attributed to the formation of radicals by the interaction of chlorine and the

lead alkyl, the radicals initiating a chain reaction involving the halogen and hydrocarbon. It has now been found that in like manner chlorine and olefins can be made to react at temperatures considerably below those normally needed. Table III, which is self-explanatory, shows how the lead alkyl promotes the addition-reaction for ethylene. (The small amounts of reaction in the absence of tetraethyl lead vapor may be a consequence of reaction catalyzed by the lead chloride deposited on the walls.)

More striking are the results for the chlorination of propylene given in Table IV. Although these data are also subject to the criticism of the possibility of surface-catalyzed reaction due to lead chloride (as with ethylene), nevertheless the enhancement of reaction due to tetraethyl lead is very definite. The increased substitution becomes even more significant on the basis of a distillation analysis of product made at 186°,

TABLE IV

CHLORINATION OF PROPYLENE. CATALYSIS BY TETRAETHYL LEAD

Flow (cc./min.): 50 Chlorine; 100 Propylene; 50 Nitrogen; 100 Carbon Dioxide through Tetraethyl Lead at 0°

TEMPERATURE	% CHLORINE REACTING			
	In presence of lead alkyl		In absence of lead alkyl	
	Substitution	Addition	Substitution	Addition
°C.				
132–134	25.3	51.0	2.7	34.0
156–159	28.2	51.8	3.2	34.8
196	36.1	47.9	6.0	37.8

which shows 25 mole-per cent allyl chloride and 75 mole-per cent dichloride. Even though the titration analysis indicated a somewhat larger yield of allyl chloride, it is noteworthy that we have produced the compound at much lower temperatures than has been heretofore considered possible (10).

b) Reactions Unaffected by Oxygen. The ability of oxygen to suppress chains involving radicals has been used to detect other reaction processes. These are as follows:

Association at the surface. Figure 5 illustrates the effect of oxygen on the reacting system in the presence of glass wool. For such flows (50 cc. Cl_2/min.; 100 C_2H_4; 150 CO_2) in an unpacked reactor, 5 cc. of oxygen per minute completely inhibited all reaction to at least 284°. Glass wool, however, strongly promotes the addition even in the presence of oxygen. The suppression, which is apparently independent of the amount of inhibitor, at least in the six-fold range investigated, presumably corresponds to nearly the total amount of true gas-phase radical chain reactions, both

addition and substitution. The magnitude of the persisting reaction is indicative of the surface catalyzed addition.

Gas-phase bimolecular association. At higher temperatures (above 300°), another addition-reaction which is unaffected by oxygen occurs.

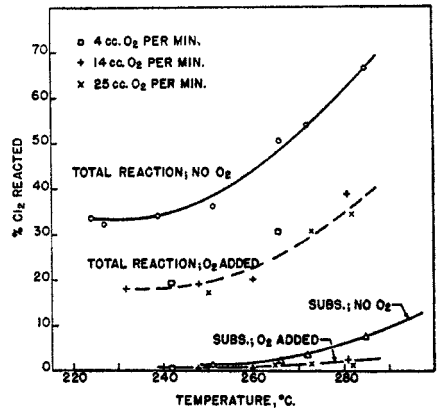

FIG. 5. CHLORINATION OF ETHYLENE OVER GLASS WOOL. EFFECT OF OXYGEN
Flow (cc./min.): 50 Cl_2; 100 C_2H_4; 150 (CO_2 + O_2)

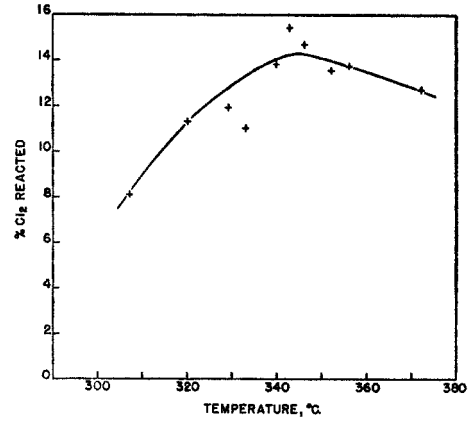

FIG. 6. CHLORINATION OF ETHYLENE OVER GLASS ROD PACKING. UNSUPPRESSIBLE ADDITION
Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 200 N_2; 25 O_2

Its temperature profile is shown by Figure 6. The negative temperature coefficient is not due to onset of a dominant substitutive reaction; under the conditions of the experiments, even at the highest temperature, substitution never amounted to more than 10% of the total chlorine. In

this range of temperature, packing has relatively little effect (Figure 20). The major amount of the addition occurring can logically be interpreted as a straightforward, gas-phase, bimolecular association, a type of reaction which can occur when the intermediate complex is sufficiently large to have a long enough life to permit stabilization by collision with a third body.

Gas-phase bimolecular metathesis. The existence of a gas-phase bimolecular substitution of chlorine into olefins, unaffected by oxygen, can only be postulated by analogy with the findings on the chlorination of paraffins (20).

Sherman, Quimby, and Sutherland (18) have made a rather exhaustive theoretical treatment of the possible reactions between ethylene and the halogens. They have calculated by the Eyring method the activation energies of the several bimolecular reactions. They have also assumed chain mechanisms which would lead to the same products, and estimated the energies involved. In almost all cases they find that free radical chain mechanisms are slightly more favorable than the corresponding bimolecular process. They also show that addition is likely to be dominant over substitution. In the addition of chlorine to ethylene, they find the exception that the molecular process is the more probable. The chain assumed involves the steps:

$$1.\ Cl_2 \rightleftarrows 2Cl;\quad 2.\ C_2H_4 + Cl \rightarrow C_2H_4Cl;$$
$$3.\ C_2H_4Cl + Cl_2 \rightarrow C_2H_4Cl_2 + Cl,$$

which do not lead to the present finding of rate dependence. The marked effect of surface found experimentally indicates that the course of the production of the 1,2-dichloroethane is not the result of a single, simple process, but the facts given herein do show that chain addition is dominant. The substitution chain given by Sherman, Quimby, and Sutherland contains the straightforward chain-carrying steps:

$$1.\ C_2H_4 + Cl \rightarrow C_2H_3 + HCl;\quad 2.\ C_2H_3 + Cl_2 \rightarrow C_2H_3Cl + Cl.$$

From this they deduce that the chain process is very slightly the more favorable, which is in accord with experiment. At higher temperatures, however, molecular mechanisms undoubtedly are operative for both addition and substitution.

Other Olefins. The temperature profiles for propylene, 2-butene, and isobutylene also have been determined; these are given in Figures 7, 8, and 9. The trend of the curves is the same as for ethylene and from this it may reasonably be inferred that the reactions are occurring in the manner outlined above. Control of the reactions so as to eliminate igni-

tion was much more difficult, and for this reason the curves were not extended to higher temperatures.

With propylene, the products are principally the addition-compound and allyl chloride (10). Isobutylene at higher temperatures also reacts by

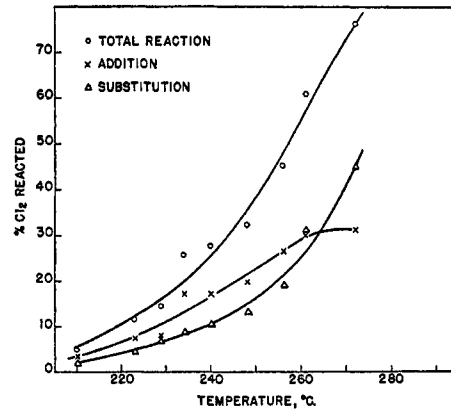

FIG. 7. CHLORINATION OF PROPYLENE. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_3H_6; 150 N_2

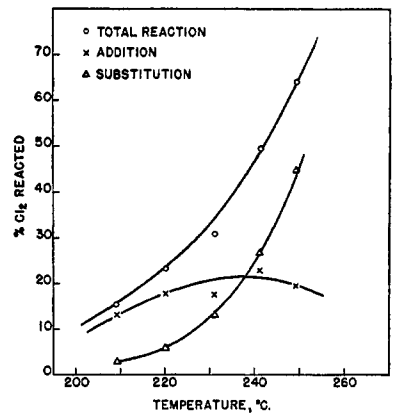

FIG. 8. CHLORINATION OF BUTENE-2. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_4H_8; 150 N_2

both addition and substitution (Figure 9). Below 240°, above which the reaction became violent, 5% of oxygen completely suppressed *all* activity, indicating that both reactions occur by radical chain mechanisms. This is quite contrary to the behavior of isobutylene in liquid phase, where only substitution unaffected by oxygen occurs. It has been found (2) that light accelerates the vapor-phase addition. Admixture of oxygen to such

an illuminated system suppresses the photo process which is further evidence of the presence of radicals.

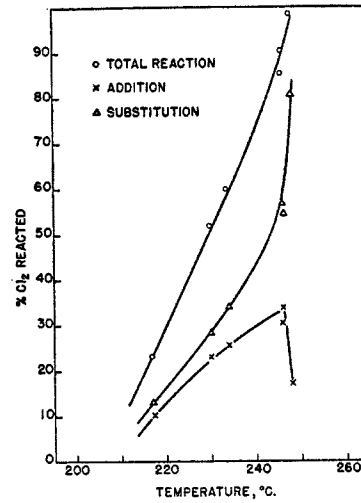

FIG. 9. CHLORINATION OF ISOBUTYLENE. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_4H_8; 150 N_2

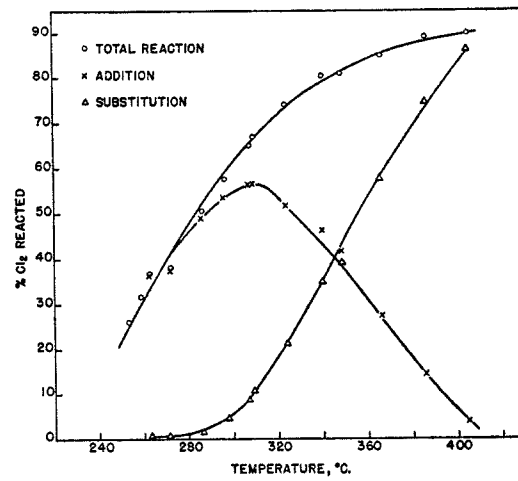

FIG. 10. CHLORINATION OF VINYL CHLORIDE. TEMPERATURE PROFILES
Flow (cc./min.): 50 Cl_2; 100 C_2H_3Cl; 150 N_2

As mentioned earlier (Table II), appreciable quantities of isomeric dichloroethylenes are found in the product from the high-temperature chlorination of ethylene. These secondary products have also been ob-

tained by chlorination of vinyl chloride. Figure 10 illustrates the temperature profiles for the addition- and substitution- reactions of this latter compound. Addition to give 1,1,2-trichloroethane and substitution to give the dichloroethylenes occur simultaneously. Thus, it seems unlikely that the latter compounds are formed by pyrolytic decomposition of the former.

II. OXYGEN-CATALYZED CHLORINE SUBSTITUTION-REACTIONS

Chlorination of Olefin-Oxygen Mixtures. The inhibiting effect of oxygen on gas-phase chlorination-reactions has long been known (1), and workers in the field have usually taken particular care to avoid possible complica-

TABLE V

CHLORINATION OF ETHYLENE. CATALYSIS BY OXYGEN

Flow (cc./min.): 50 Cl_2; 100 C_2H_4; 150 N_2

TEMP.		% Cl_2 REACTED	% Cl_2 SUBS.	% Cl_2 ADDED
°C.				
245		35.2	2.0	33.2
245	+ 3% O_2	0.0	0.0	0.0
264		66.6	11.5	55.1
264	+ 3% O_2	93.4	93.4	?[a]
272		67.6	12.0	55.6
272	+ 3% O_2	95.2	95.2	?[a]
272		69.2	17.1	52.1
272	+ 3% O_2	95.5	95.5	?[a]

[a] Approximately 20% more HCl evolved than corresponds to the amount of substitution on the basis of the chlorine reacted.

tions from this source. Consequently, the discovery that, under certain conditions, oxygen strongly catalyzes substitution of chlorine into olefins was quite unexpected. So powerful is the effect that, for example, in one case with ethylene, as little as 0.5% of oxygen in the gas flow increased the amount of substitution from 16% to 93% of the chlorine.

The catalysis for ethylene and propylene is clearly shown in Tables V and VI, and even more strikingly by Figures 11–14, where the results with more dilute reaction-mixtures and varying oxygen inputs are presented graphically. Only small amounts of oxygen induce catalysis and in fact larger amounts cause the expected inhibition.[2] Experimental conditions,

[2] In this connection, it may be mentioned that Willard and Daniels (21) observed acceleration of addition followed by inhibition by larger amounts of oxygen in the liquid-phase photobromination of tetrachloroethylene.

especially temperature, are very important in the definition of the magnitude of the effect. In general, it may be said that the catalysis seems to be much more pronounced, although more critically dependent on the concentration of the catalyst, with ethylene. For example, in Figure 11,

TABLE VI

CHLORINATION OF PROPYLENE. CATALYSIS BY OXYGEN

Flow (cc./min.): 50 Cl_2; 100 C_3H_6; 150 N_2

TEMP.		% Cl_2 REACTED	% Cl_2 SUBS.	% Cl_2 ADDED
°C.				
261		62.1	31.0	33.1
263	+ 3% O_2	0.0	0.0	0.0
274	+ 3% O_2	90.8	90.8	0.0
272		76.4	45.2	31.2
286	+ 3% O_2	89.6	88.6	1.0
286		83.1	55.0	28.1

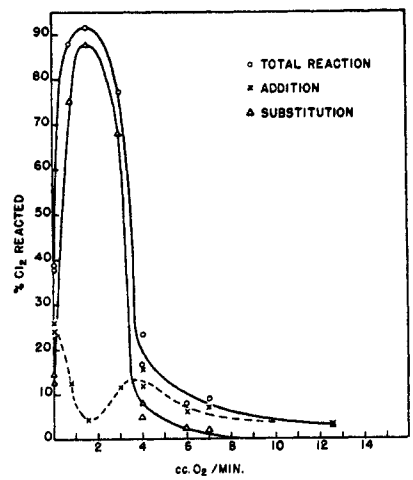

FIG. 11. CHLORINATION OF ETHYLENE AT 324°C. EFFECT OF OXYGEN

Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 225(N_2 + O_2)

2 cc. of oxygen per minute in the flow causes an increase in the amount of substitution from 13% of the total chlorine to 87%, while addition drops from 25% to 4%, presumably because of the faster rate of the competing substitution. Increase in the oxygen input to 4 cc. per minute causes a drop in the latter reaction to only 7% of the total chlorine and

addition undergoes a slight rise to *ca.* 15%. Further oxygen results in an asymptotic leveling-off of addition at 4% and substitution falls toward zero. With propylene chlorination, the positive catalysis is less, amount-

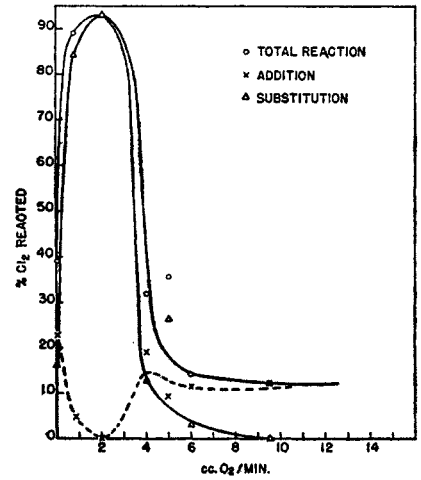

FIG. 12. CHLORINATION OF ETHYLENE AT 334°C. EFFECT OF OXYGEN
Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 225 (N_2 + O_2)

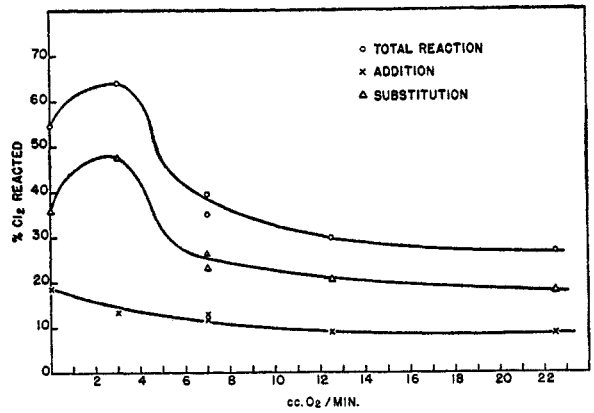

FIG. 13. CHLORINATION OF PROPYLENE AT 310°C. EFFECT OF OXYGEN
Flow (cc./min.): 25 Cl_2; 50 C_3H_6; 225 (N_2 + O_2)

ing at the maximum to only 11% more than the 36% found for substitution in the absence of oxygen (Figure 13). Further oxygen causes substitution to decrease regularly to 18%, and addition to 8%.

The chlorination of 2-butene is also subject to positive catalysis by oxygen. Below 260°, reaction was strongly inhibited by 3% oxygen (in

50 cc. Cl_2/min.; 100 2-C_4H_8; 150 N_2), but at this temperature and above, chlorination was catalyzed. Without oxygen, 76.4% of the chlorine reacted, 56.4% by substitution and 20.0% by addition. With 3% oxygen,

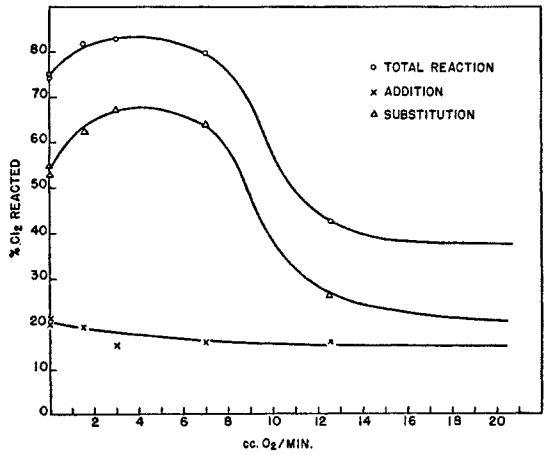

FIG. 14. CHLORINATION OF PROPYLENE AT 315°C. EFFECT OF OXYGEN
Flow (cc./min.): 25 Cl_2; 50 C_3H_6; 225 (N_2 + O_2)

TABLE VII

OXYGEN-CATALYZED CHLORINATION OF ETHYLENE AT 324°
Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 225 N_2; 1.5 O_2

	mole per cent
Vinyl chloride	61
Ethylene dichloride	26
Unsaturated dichlorides	13

OXYGEN-CATALYZED CHLORINATION OF PROPYLENE AT 300°
Flow (cc./min.): 50 Cl_2; 100 C_3H_6; 150 N_2; 1.5 O_2

	mole per cent
Mixed allyl and vinyl type chlorides	7
Allyl chloride	63
Propylene dichloride	17
Unsaturated dichlorides, and polychlorides	13

97.2% of the chlorine was consumed, so violently that attendant decomposition made impossible the determination of the relative amounts of the two reactions.

Product distributions for the oxygen-catalyzed chlorinations of ethylene and propylene are given in Table VII. With the ethylene mixture in the

absence of oxygen, addition, according to titration analysis, amounted to 25% and substitution to 13%; with oxygen the corresponding figures were 4% and 88% of the halogen. Oxygen in the propylene reaction-mixture increased substitution from 55 to 73%, and apparently reduced addition from 25% to 15% of the chlorine. The significant finding is that of the increased yields of unsaturated chlorides, especially with ethylene.

This catalysis of substitution by oxygen is confined to olefins. Despite extensive tests over a considerable range of operating conditions, no similar effect for paraffins was found; only inhibition of chlorination was observed.

Chlorination of Olefin-Oxygen-Paraffin Mixtures. Ethane is a powerful inhibitor of oxygen-catalyzed chlorine substitution into olefins. This paraffin in a mole concentration of *ca.* 15% suppressed substitution in one case from 95% to 13%. The effect of larger concentrations of ethane is

TABLE VIII

CHLORINATION OF ETHANE-ETHYLENE IN THE PRESENCE OF OXYGEN AT 327°. EFFECT OF ETHANE CONCENTRATION

Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 220 (N_2 + C_2H_6); 7.5 air

cc. C_2H_6/MIN.	% Cl_2 REACTED	% Cl_2 SUBSTITUTED
0	95.2	95.2
50	14.8	12.8
100	16.8	14.8
160	18.6	15.6

also shown by Table VIII. It is to be noted that beyond a certain value, reaction is almost independent of the amount of paraffin.

With a reaction-mixture corresponding to the following flow (cc./min.): 50 Cl_2; 100 C_2H_4; 100 C_2H_6; 7.5 air (1.5 O_2); 45 CO_2, it was necessary to go to 336° to obtain an amount of reaction equivalent to that obtainable at *ca.* 265° in the absence of paraffin. By titration analysis, substitution amounted to 98.4%. The product distribution, Table IX, is striking in that it indicates that the ethylene was participating only slightly in the reaction. Yet if the olefin is replaced with nitrogen, the oxygen inhibits the reaction of chlorine and ethane to reduce substitution below 10% (see Figure 4 of Reference 20).

This interesting result is further demonstrated by the following data for a mixture corresponding to flows of 50 cc./min. chlorine, 100 ethylene, 100 ethane, and 50 oxygen. With this greatly increased amount of oxygen the reaction was remarkably easy to control, and substitution rose from 10.5% at 343° to 72.0% at 404°. Illustrative of the effect of the olefin is

an experiment made at 374° with the above mixture in which 60% of the halogen reacted; when the olefin was replaced by carbon dioxide, reaction dropped to only 4%. Despite the fact that chlorination under these conditions is dependent upon the presence of olefin, analysis of the product made at 414° shows that ethyl chloride was the principal constituent. There was very little increase in the proportion of vinyl chloride formed when the oxygen input was increased from 1.5 cc. per minute (see Table

TABLE IX

CHLORINATION OF ETHANE-ETHYLENE IN PRESENCE OF OXYGEN AT 336°

Flow (cc./min.): 50 Cl_2; 100 C_2H_4; 100 C_2H_6; 7.5 air; 45 CO_2

	mole per cent
Vinyl chloride	12
Ethyl chloride	60
1,1-Dichloroethane	16
1,1,1-Trichloroethane and 1,2-Dichloroethane	12

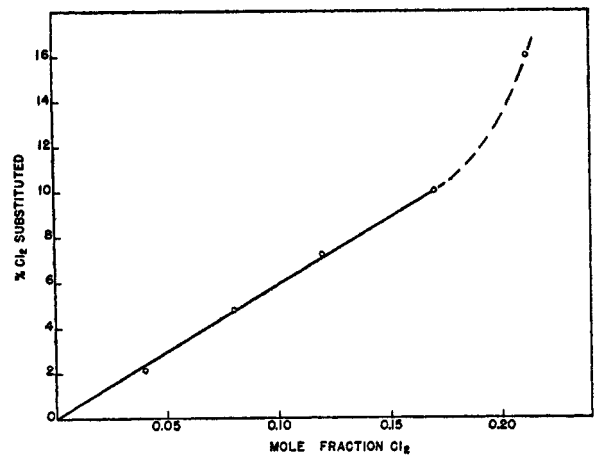

FIG. 15. OXYGEN-CATALYZED CHLORINATION OF ETHANE-ETHYLENE AT 340°C. VARIATION OF CHLORINE INPUT

Flow (cc./min.): (12.5–62.5) Cl_2; 50 C_2H_4; 50 C_2H_6; 7.5 air (1.5 O_2); (180–130) N_2

IX) to the 50 cc. per minute used in this experiment. Of course, the two sets of data are not strictly comparable, as the former experiment was carried out at 336° and the latter at 414°, the higher temperature being necessary to overcome the inhibiting effect of the excessive amount of oxygen.

The inhibition by paraffins of oxygen-catalyzed substitution of chlorine into olefins permits the determination of the rate dependencies for the

over-all formation of hydrogen chloride, as the amount of reaction can be controlled so as to show variation with concentrations. Without the paraffin, the chlorine is almost completely consumed. Although in such mixtures the paraffin is the principal reactant, Table VIII shows that

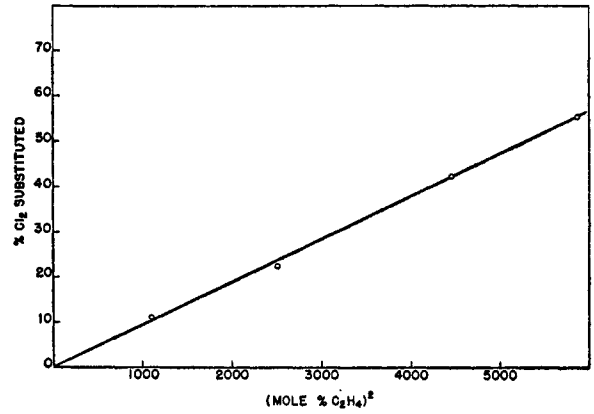

FIG. 16. OXYGEN-CATALYZED CHLORINATION OF ETHANE-ETHYLENE AT 327°C. VARIATION OF ETHYLENE INPUT WITH $[C_2H_4] > [Cl_2]$
Flow (cc./min.): 12.5 Cl_2; (100–230)C_2H_4; 50 C_2H_6; 7.5 air (1.5 O_2); (130-0)N_2

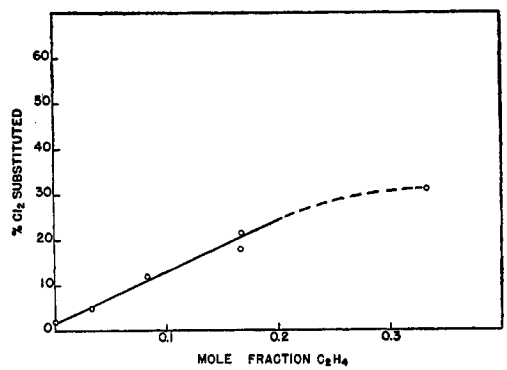

FIG. 17. OXYGEN-CATALYZED CHLORINATION OF ETHANE-ETHYLENE AT 327°C. VARIATION OF ETHYLENE INPUT WITH $[C_2H_4] \leq [Cl_2]$
Flow (cc./min.): 50 Cl_2; (0–100)C_2H_4; 50 C_2H_6; 7.5 air (1.5 O_2); (195–95)N_2

variation in its concentration has relatively little effect. The catalysis is dependent upon the presence of both oxygen and olefin, and the following functions bear some relation to the interaction of these compounds, as this apparently initiates the over-all reaction. Figure 15 indicates that

the amount of substitution is directly proportional to the halogen concentration; the curve deviates from linearity at the higher chlorine inputs, probably because of onset of thermal chains. When the olefin is present in greater amount than the chlorine, the rate is proportional to the square of the mole-fraction of ethylene (see Figure 16). When chlorine exceeds the amount of olefin, the rate varies linearly with the concentration of the latter (see Figure 17). Figure 18 shows that for very low concentrations of oxygen the amount of substitution in a Cl_2:C_2H_4:N_2 mixture is directly proportional to the mole-fraction of oxygen; with greater increases in the oxygen input the catalysis is less marked, and still greater amounts sharply reduce reaction (see Figures 11 and 12).

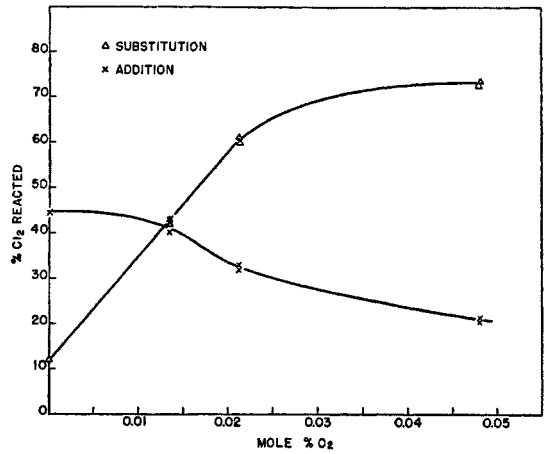

FIG. 18. CHLORINATION OF ETHYLENE AT 315°C. EFFECT OF OXYGEN
Flow (cc./min.): 25 Cl_2; 50 C_2H_4; 225 (N_2 + air)

Discussion of Oxygen-Catalyzed Chlorine Substitution. An explanation of the oxygen-catalysis of substitution of chlorine into olefins must take into consideration several facts, namely:

(A) Chlorine reacts with olefins under conditions heretofore considered unfavorable for such processes, *i.e.*, in the presence of oxygen.

(B) Chlorine reacts principally by substitution under conditions of temperature, some of which, at least, in the absence of oxygen favor addition.

(C) Paraffins (*e.g.*, ethane) inhibit the reaction with the olefin and react with the chlorine themselves. Yet, no oxygen-catalysis of paraffin chlorination is known.

(D) Higher concentrations of oxygen strongly inhibit substitution.

(E) The rate of production of hydrogen chloride by substitution seems to vary linearly,
  (a) with the square of the ethylene concentration
  (b) with the chlorine concentration
  (c) with the oxygen concentration (for very small amounts of oxygen).

These points can be formally correlated by postulating that the over-all rate-determining step is the interaction of an oxygen molecule with ethylene (one or two molecules). This process apparently gives rise to extremely reactive centers which can initiate a chain reaction involving substitution. The formation of a highly reactive intermediate complex which itself reacts substitutively with chlorine might explain the absence of addition by "protection" of the double bond, but it seems inconceivable that the small amounts of oxygen used, which show such pronounced catalysis, could so influence the large number of olefin molecules present. Further, it has been shown that the amount of vinyl chloride produced from an ethane-ethylene mixture was not increased by an increase in the oxygen input from 1.5 cc. to 50 cc. per minute; this finding is contrary to expectations based on the premise of formation of an intermediate complex, since the concentration of the latter should be increased by an increase in the oxygen mole-fraction. Likewise, the astonishingly sudden onset of catalysis with rise of temperature rules out the possibility that reaction originates in the interaction of a complex with chlorine, as the onset would necessitate an anomalous temperature coefficient for the production of the intermediate.

Lenher (13), in his studies of the oxygen-ethylene reaction, postulated that one of the primary steps was the formation of an association complex which could react with another ethylene molecule to give two molecules of ethylene oxide, or with oxygen to give water and carbon monoxide. At higher temperatures he also found polymerization products, butenes, propylene, and amylenes. The formation of the last two led to the suggestion that the association complex was capable of rapid dissociation into oxygen and methylene radicals; the latter could react with ethylene or its dimer. He discussed the energetics of the process of disruption. Lenher (14) also came to similar conclusions regarding higher olefins formed at high temperatures from oxygen-propylene mixtures. In the present instance, a similar development of radicals must be occurring, giving rise to centers which initiate chlorination chains. We have shown that very small amounts of tetraethyl lead will cause reaction of chlorine with saturates (20) and olefins under conditions of temperature where ordinarily thermal reaction does not occur. This catalysis was attributed to the production of centers for chain propagation by interaction of the

alkyl with chlorine. Thus, both addition and substitution are promoted in the case of olefins.

The oxygen catalysis leads to a generalization regarding the relative reactivities of various radicals in their vulnerability to oxygen. In short, radicals containing an ethylenic linkage seem to be more stable toward oxygen than those which have only single C—C bonds. Ethane markedly inhibits the oxygen-catalyzed reactions of chlorine with ethylene, propylene, and 2-butene. What reaction does take place involves principally (though not exclusively) the paraffin. In effect, two competing chains for substitution can occur, and the one involving the paraffin is the predominant one. [Ethane can be made almost the sole reactant in an ethane-ethylene mixture (20).] The radicals produced by interaction of olefin and oxygen initiate chains which immediately involve the paraffin. However, these chains are short because the ethyl radicals are more susceptible to elimination by oxygen than are the ethylenic ones. In the absence of the paraffin, the "catalytic" radicals initiate a chain of the type:

$$R + Cl_2 \longrightarrow RCl + Cl$$
$$Cl + C_2H_4 \longrightarrow C_2H_3 + HCl$$
$$C_2H_3 + Cl_2 \longrightarrow C_2H_3Cl + Cl$$

wherein R is the "catalytic" radical. Free vinyl is apparently less susceptible to removal by oxygen (possibly as a consequence of stabilization by resonance) and the chain can be of considerable length. Similarly, allyl (from propylene) and crotyl (from 2-butene) can persist even in the presence of oxygen.

If the oxygen-catalyzed substitution is actually a consequence of chains initiated by radicals, it is to be supposed that chain addition should also be promoted. However, under the most favorable circumstances for catalysis, such addition is almost non-existent. Chain addition, as has been shown, involves a radical of the type $Cl—\overset{H}{\underset{H}{C}}—\overset{H}{\underset{H}{C}}.$ According to the above postulate, this radical should be highly susceptible to attack by oxygen, and therefore chains involving it alone should be of very short length. Figure 19 bears on this point. In the chlorination of propylene in the presence of a high concentration of oxygen, it may be assumed that radical chains are considerably shortened. It is seen that all reaction is eliminated by the large amount of oxygen until a temperature of about 300° is reached, where both addition and substitution set in. However, with a slight further rise in the temperature, the unsuppressed addition is the same as that found in the absence of oxygen. Thus it would seem that

chain addition is almost non-existent, that is, at this temperature, 330°, at which the oxygen-catalysis first appears for *lower concentrations* of oxygen, oxygen-vulnerable links in the chain, such as $\begin{matrix} H & H & H \\ HC & -C & -CCl \\ H & & H \end{matrix}$, are

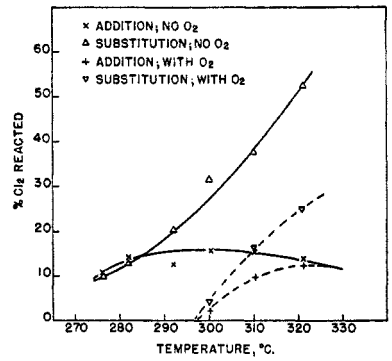

FIG. 19. CHLORINATION OF PROPYLENE IN THE PRESENCE OF OXYGEN. TEMPERATURE PROFILES; PACKED REACTOR

Flow (cc./min.): 25 Cl_2; 50 C_3H_6; 225 N_2; or 25 Cl_2; 50 C_3H_6; 200 N_2; 25 O_2

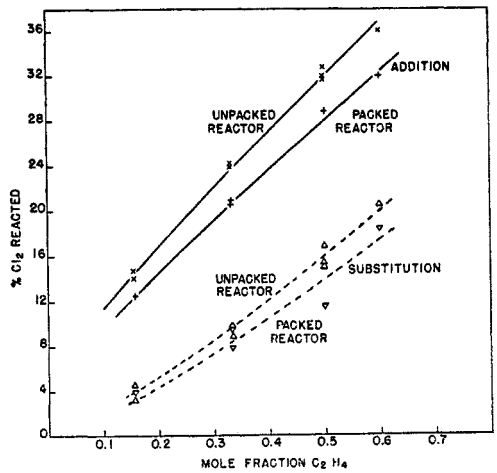

FIG. 20. CHLORINATION OF ETHYLENE AT 348°C. IN PRESENCE OF EXCESS OXYGEN

Flow (cc./min.): 25 Cl_2; (50–180) C_2H_4; (200–70)N_2; 25 O_2

practically eliminated. However, ethylenic radicals, such as allyl, persist as chain carriers for substitution.

The nature of the addition occurring in the presence of the large amount

of oxygen is probably a straightforward, gas-phase, bimolecular association, rather than a surface reaction. Figure 20 shows that at 348°, both the unsuppressible addition and substitution with ethylene are little affected by a 2.8-fold increase in surface. The addition, it is worth noting, is actually the dominant reaction, whereas in the absence of oxygen under these conditions, addition is subordinate to chain substitution. The amounts of both processes are nearly proportional to the olefin concentration.

The foregoing is offered as an explanation of the oxygen catalysis of substitutive chlorination, and the evidence would indicate that the mechanism is one of chain initiation by radicals produced by interaction of olefin and oxygen, rather than reaction of an association complex itself with chlorine.

III. INHIBITION OF HYDROCARBON CHLORINATION BY OLEFINS

It was observed in the course of the study of the chlorination of *n*-propyl chloride (see Figure 9 of ref. 20) that, whereas at lower temperatures the rate was very similar to that of propane, above 260° the rate of reaction was markedly less. This was attributed to inhibition of the chain substitution by propylene produced by induced decomposition of the chloride. Further, the substitutive chlorination of propylene itself (Figure 7) has a lower temperature coefficient than the reactions with ethane or propane (Figure 9 of ref. 20).

That the inhibition is well defined is shown by Figures 21 and 22, which show the effects of propylene and 2-butene on the thermal chlorination of ethane. For example, replacement of 20 cc. of nitrogen per minute in a flow of 50 Cl_2; 100 C_2H_6; 150 N_2 by an equal amount of propylene reduced the amount of reacted chlorine at 261° from 75% to 65%, and at 247° from 96% to 83%. The corresponding values for suppression by 2-butene are practically the same. The decreases, it should be noted, take place despite an increase in the actual amount of hydrocarbon present and the introduction of a simultaneous addition-reaction which consumes *ca.* 8% of the chlorine.

In order to investigate more fully the factors influencing the inhibition, an apparatus was designed which permitted study of photochlorinations to temperatures as high as 200° under easily controllable conditions. Approximately equal amounts of substitution for the "standard" reaction could be readily obtained simply by control of the light intensity, which compensates for other variables. The apparatus consisted essentially of a glass reactor of the usual size (45 × 1.3 cm.) housed within a metal jacket through which paraffin oil was circulated at constant temperature from a thermostated reservoir. The reactor was illuminated through a slit in the jacket.

The relative efficiencies of ethylene, propylene, 2-butene, and isobutylene as inhibitors of ethane chlorination were investigated at 75°, 115°, 134°, and 175°, and the data were compared by means of an arbitrary

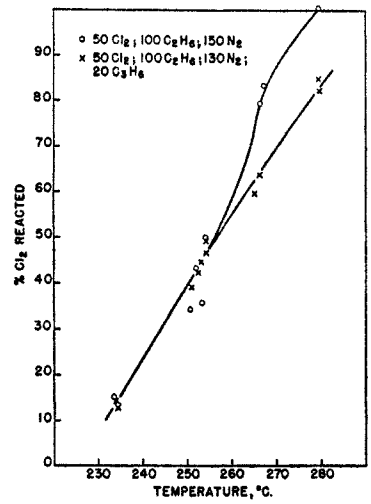

FIG. 21. CHLORINATION OF ETHANE. INHIBITION OF PROPYLENE

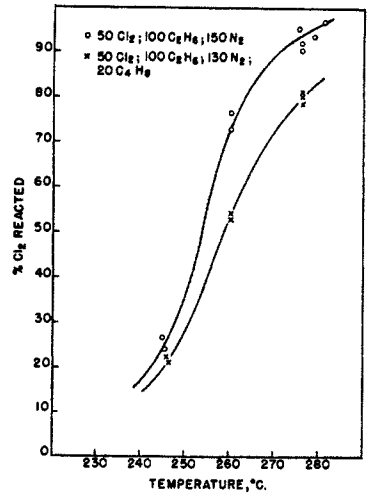

FIG. 22. CHLORINATION OF ETHANE. INHIBITION BY BUTENE-2

"inhibition factor." It is necessary to introduce this factor in order to compensate for the amount of chlorine reacting by addition with the olefins themselves; such a side-reaction, varying in extent from compound

TABLE X

Inhibition of Ethane Chlorination by Olefins

Flows (cc./min.): 50 Cl_2; 100 C_2H_6; 150 N_2; and 50 Cl_2; 100 C_2H_6; 130 N_2; 20C_nH_{2n}

	C_2H_6	C_2H_6 + C_2H_4	C_2H_6 + C_3H_6	C_2H_6 + 2-C_4H_8	C_2H_6 + iso-C_4H_8
75°					
(1) % Cl_2 substituted	73.9	57.1	40.2	45.1	46.3
(2) % Cl_2 added		15.7	18.4	24.3	18.1
(3) $\frac{\%\ Cl_2\ \text{subs.} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		67.7	49.6	59.6	55.7
(4) Inhibition factor 73.9 − (3)		6.2	24.3	14.3	18.2
115°					
(1) % Cl_2 substituted	(a) 72.7	(c)	(a) 36.8	(b)	(a) 46.8
	(b) 79.0		(b) 41.7	47.6	
	(c) 76.3	62.3			
(2) % Cl_2 added		13.0	(a) 14.4	16.3	17.0
			(b) 16.7		
(3) $\frac{\%\ Cl_2\ \text{subs.} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		71.6	(a) 43.0	56.9	56.5
			(b) 50.1		
(4) Inhibition factor					
(a) 72.7 − (3)			(a) 29.7		16.2
(b) 79.0 − (3)			(b) 28.9	22.1	
(c) 76.3 − (3)		4.7			
134°					
(1) % Cl_2 substituted	(a) 74.5	(a) 61.5	(d)	(a) 45.5	(b)
	(b) 73.5				45.1
	(c) 73.2			(c) 42.1	
	(d) 72.3		37.6		
(2) % Cl_2 added		11.8	14.4	(a) 14.3	17.5
				(c) 18.3	
(3) $\frac{\%\ Cl_2\ \text{subs.} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		69.7	43.9	(a) 53.1	54.7
				(c) 51.5	
(4) Inhibition factor					
(a) 74.5 − (3)		4.8		(a) 21.4	
(b) 73.5 − (3)					18.8
(c) 73.2 − (3)				(c) 21.7	
(d) 72.3 − (3)			28.4		
175°					
(1) % Cl_2 substituted	(a) 72.4	(a) 63.4	(a) 39.6	(a) 45.6	(b)
	(b) 76.5				50.4
(2) % Cl_2 added		7.4	14.5	15.3	13.3
(3) $\frac{\%\ Cl_2\ \text{subs.} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		68.3	46.4	53.2	58.2
(4) Inhibition factor					
(a) 72.4 − (3)		4.1	26.0	19.2	
(b) 76.5 − (3)					18.3

The letters (a), (b), (c) and (d) at any one temperature indicate corresponding sets of data.

to compound, obviously alters the concentration of the chlorine available for the principal substitution process, that with ethane. The effective quantity of chlorine is obtained by deducting the amount of "chlorine added" from the "chlorine input." The amount of substitution is expressed as a percentage of this amount of chlorine theoretically available for such reaction. No distinction is made between the substitution into paraffin and that into olefin, since our studies have indicated that the mechanism of substitution is, under these conditions, the same for both types of compound. Moreover, in the present cases, because the concen-

TABLE XI

INHIBITION OF ETHANE CHLORINATION BY CHLOROÖLEFINS

Flows (cc./min.): 50 Cl_2; 100 C_2H_6; 150 N_2; and 50 Cl_2; 100 C_2H_6; 130 N_2; 20 $C_nH_{2n-1}Cl$

	C_2H_6	$C_2H_6 + C_3H_5Cl$	$C_2H_6 + C_3H_5Cl$
		(a)	(b)
134°			
(1) % Cl_2 substituted	(a) 74.0	50.5	
	(b) 67.7		35.0
(2) % Cl_2 added		13.6	8.5
(3) $\frac{\%\ Cl_2\ \text{substituted} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		58.5	38.3
(4) Inhibition factor			
(a) 74.0 − (3)		15.5	
(b) 67.7 − (3)			29.4
175°			
(1) % Cl_2 substituted	72.4	52.0	
(2) % Cl_2 added		6.8	
(3) $\frac{\%\ Cl_2\ \text{substituted} \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$		55.8	
(4) Inhibition factor			
72.4 − (3)		16.6	

tration of olefin is small compared with that of the paraffin, substitution into the olefins may be considered of minor importance. The "inhibition factor," which indicates the amount of suppression, is merely the numerical difference between the percentage of substitution, as determined above, and the percentage of chlorine reacting with ethane in the absence of unsaturates, but under otherwise strictly comparable conditions.

The data on the olefins are given in Table X, and similar findings for vinyl and allyl chlorides as inhibitors are shown in Table XI. The duplicate values give a good idea of the reproducibility of the effect, despite considerable variation in the amount of reaction. It is also noteworthy

that temperature has very little effect on the magnitude of the inhibition. The exception to this, with 2-butene at 75°, is probably only apparent, and is due to the large amount of addition. Propylene and allyl chloride are the most effective inhibitors, and ethylene the least.

Figure 23 illustrates the effect at 138° of variation of the concentration of the most powerful inhibitor, propylene. While substitution decreases regularly, the addition rises.

It is logical to attribute the effect of the olefins in suppressing reaction to an interaction of these substances with radicals produced in the chains involving substitution. This association process would result in the formation of larger radicals which, by reason of orientation requirements for

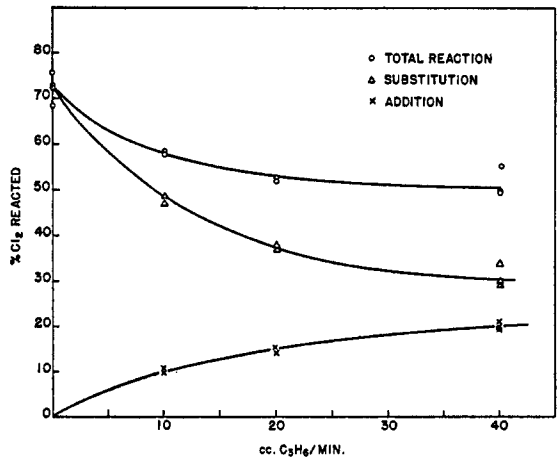

FIG. 23. PHOTOCHLORINATION OF ETHANE AT 138°C. INHIBITION BY VARYING AMOUNTS OF PROPYLENE

Flow (cc./min.): 50 Cl_2; 100 C_2H_6; (150–110)N_2; (0–40)C_3H_6

successful collision, react less readily with chlorine than do the smaller ones. The magnitude of the inhibition is most likely dependent upon two factors, (a) the reactivity of the olefinic bond, and (b) the sizes and configurations of both of the hydrocarbon reactants which form the complex. Thus the data of Tables X and XI probably represent the consequences of reaction of ethyl radicals with the various unsaturates. This interpretation is substantiated by the finding that propane chlorination is less affected by propylene than is ethane chlorination. Thus the "inhibition factor" for the former reaction is 26.0 (see Table XII) as compared to 29.0 for the equivalent ethane-propylene mixture.

Another line of attack was also used. The suppression by the highly reactive olefin, propylene, of the chlorinations of a number of compounds

should afford a measure of the reactivities of the various radicals involved in the chains. Methyl, ethyl, propyl, butyl, β-chloroethyl (Cl—C—C), and α-chloroethyl (C—CH) have been produced by photochlorination of methane, ethane, propane, *n*-butane, ethylene, and ethyl chloride. The results are condensed in Table XII. To determine the various inhibition factors, the compounds were caused to react by adjusting the light intensity until 70–75% of the chlorine was consumed. Methane was found

TABLE XII

INHIBITION OF VARIOUS CHLORINATION REACTIONS BY PROPYLENE AT 135°

Flows (cc./min.): 50 Cl_2; 100 compound; 150 N_2; and 50 Cl_2; 100 compound; 130 N_2; 20 C_3H_6

COMPOUND CHLORINATED	CH_4[a]	C_2H_6	C_3H_8	n-C_4H_{10}	C_2H_4	C_2H_5Cl
(*1*) % Cl_2 substituted when no C_3H_6 present	67.4	73.5	74.3	72.4	74.7[b]	72.6
(*2*) % Cl_2 substituted in the presence of C_3H_6	21.4	37.3	43.9	42.4	57.9[b]	22.1
(*3*) % Cl_2 addition to C_3H_6	39.0	16.3	9.3	6.8	16.8[c]	24.3
(*4*) $\frac{\%\ Cl_2\ \text{subs.}\ (2) \times 100}{Cl_2\ \text{input}\ (100\%) - \%\ Cl_2\ \text{added}}$	35.1	44.5	48.3	45.5	49.4[d]	29.2
(*5*) Inhibition factor (*1*) − (*4*)	32.3	29.0	26.0	26.9	25.3	43.4

[a] Experiments at 172°.

[b] % Cl_2 reacted.

[c] % Cl_2 added to propylene (est.).

[d] $\frac{(\%\ Cl_2\ \text{reacted}\ (2) - 16.8\%) \times 100}{100\% - 16.8\%}$; 57.9 − 16.8 = % Cl_2 added to C_2H_4.

to be unusually difficult to chlorinate—only two-thirds of the halogen substituted at 172° even under the highest intensity of light available. From the values of the inhibition factors, propylene seems to have the greatest effect upon methane and ethyl chloride chlorinations. Although at first sight, the latter with the very high inhibition factor of 43.4 would seem to be most affected, one must consider the fact that under the rigorous conditions required for methane chlorination, the small amount of admixed propylene becomes an important reactant. The inhibiting double bonds become saturated with chlorine and are thus rendered ineffective. The true order of reactivity, therefore, cannot be given at present.

A comparison of the effect of location of the free valency in the radical

is, however, worth noting. By chlorinating ethylene, the β-chloroethyl radical would be expected.

$$H_2C{=}CH_2 + Cl \longrightarrow Cl{-}\overset{H\ H}{\underset{H\ H}{C{-}C}}$$

Ethylene itself has been shown to be of practically no consequence in suppressing reaction. The inhibition factor for the photochlorination of this olefin in the presence of propylene was 25.3. The α-chloroethyl radical is by comparison surprisingly reactive. At 135° its inhibition factor with propylene was 43.4, the highest factor yet obtained. Its mode of formation from ethyl chloride would be:

$$H{-}\overset{H\ H}{\underset{H\ H}{C{-}C}}{-}Cl + Cl \longrightarrow H{-}\overset{H\ H}{\underset{H\ Cl}{C{-}C}} + HCl$$

It has been shown [see Table I of (20)] that the α-position is the principal point of attack.

When different hydrocarbons are photochlorinated, comparisons of the reactivities of various radicals derived from them become much more complicated. In order to obtain comparable amounts of reaction, differing light intensities must be employed. This means that both rate of chain initiation and the chain lengths are variables. Furthermore, the rate of saturation of the inhibiting double bond, and therefore its average concentration, becomes variable. Allowance must be made for all of these complications and until more data are available to make these corrections, these present inhibition factors can only be arbitrary.

The inhibition by olefins of high-temperature chlorination reactions apparently has not been observed previously. However, Groll and Burgin (9) noted that isobutylene inhibited the photochlorination of butane at temperatures below 100°. Also, several workers have observed that propylene suppresses other reactions in which it is suspected that radical chain mechanisms play an important role. Thus, Echols and Pease (6) have found that the thermal decomposition of *n*-butane is inhibited by one of the products, propylene. The rate of dehydrogenation of ethane to form ethylene is decreased in proportion to the amount of added propylene up to concentrations of 14% (4). The pyrolyses of *n*-hexane and *n*-octane are retarded by the products of reaction, such as olefins (5). Snow and Frey (19) have found that the liquid-phase formation of resinous materials from olefins and sulfur dioxide is inhibited by isobutylene. To explain the inhibition by propylene of the thermal decompositions of paraffins and of some other compounds, Rice and Polly (17) postulate that the olefin destroys the radicals R of the chain by forming RH and allyl; the latter

combines with itself to terminate the chain. On the basis of the present data, no distinction between this or any other mechanism can be offered.

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SUMMARY

1. The high-temperature chlorination of olefins has been studied. It seems likely that under certain conditions, both addition- and substitution-reactions occur by radical chain mechanisms. However, reactions at surfaces and gas-phase bimolecular associations and metatheses also play a part.

2. It has been found that under carefully controlled conditions it is possible to catalyze strongly the substitutive chlorination of olefins by inclusion of oxygen in the input gases. The effect occurs with low concentrations of oxygen; larger amounts give the expected inhibition.

The presence of paraffin hydrocarbons in an olefin-oxygen mixture greatly retards the rate of chlorination. The reaction which does occur is chiefly one of substitution of hydrogen atoms on saturated carbon atoms.

3. Olefins act as inhibitors of high-temperature chlorination reactions. Of those tested, propylene seems the most effective.

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THE FATTY CONSTITUENTS OF CALIFORNIA VALENCIA ORANGE PULP (*Citrus Aurantium sinensis L.*)

M. B. MATLACK

Received May 2, 1940

Although the fatty constituents of sweet orange peel (1) have been the subject of investigation, no systematic study of this type of substance has been made on the pulp of any variety of citrus. Rygh, Rygh, and Laland (2) report the presence of "hydrocarotin" in the juice of the orange and lemon. From the data given it would appear that the substance obtained by them was sitosterol. Zechmeister and Tuzson (3) mention colorless impurities which separated during their study of the pigments of the fruit flesh of the mandarin.

EXPERIMENTAL

When the study of the peel (1) was made, all inner locular membrane and fruit flesh was removed and freed from albedo. Some of the juice had been squeezed out previously for other purposes but enough pulp remained for a sufficient yield of fatty material. Since the present study covered only the identification of the constituents and not their quantitative relations, the material at hand was considered suitable for their identification as it represented that portion of the orange ordinarily eaten. The carefully dried material was then ground and extracted with petroleum ether. On evaporation of the petroleum ether a dark reddish-brown fatty residue remained.

Saponification of the Fat and Separation of the Unsaponifiable from the Fatty Acids

The dark reddish-brown material was dissolved in methyl alcohol and hydrolyzed with sodium methoxide. After hydrolysis, the alcohol was removed, the soaps mixed with water and shaken with ether. The unsaponifiable matter was obtained by evaporation of the ethereal solution. The aqueous layer was acidified with dilute sulfuric acid and shaken with ether in order to remove the fatty acids. Separation of the unsaturated from the saturated fatty acids was accomplished by the lead salt-ether method of Gusserow-Varrentrapp (4).

Examination of the Unsaturated Fatty Acids

The unsaturated fatty acids were separated by the bromination method (4). The hexabromides which were obtained melted at 183.5° after two recrystallizations from benzene. The filtrate from which the hexabromides were obtained was nearly freed from ether and poured into water. The material which separated was washed with water and dried. It was then treated with a large volume of petroleum ether. A dark brown resinous solid remained which was soluble in ether. It was not further examined. From the petroleum ether solution crystals were obtained. To the ethereal solution of the crystals petroleum ether was added until precipitation just

began; on standing in the refrigerator the solution deposited pearly white crystals which melted at 113–113.5°. This method of purifying tetrabromides has proved very satisfactory. The average of two bromine determinations (Pregl) on the hexabromides was 63.28%; calculated for linolenic hexabromide, 63.3%. On the tetrabromides the average was 53.38%; calculated for linoleic tetrabromide, 53.27%.

The light brown oily residue remaining after evaporation of the petroleum ether solution from which the tetrabromides were obtained was debrominated with granular zinc. The acids thus liberated had an iodine value of 94.6; calculated for oleic acid, 90.07.

Examination of the Saturated Fatty Acids

The solid fatty acids obtained from the lead salt-ether separation melted at 54–56° after one crystallization from glacial acetic acid. They were then methylated with methyl alcohol and dry hydrogen chloride. The methyl esters, recrystallized once from acetone, melted at 57.5–58°. Chilling in a refrigerator produced a second crop of crystals. The two lots of crystals and the solids from the mother liquors were saponified and the three lots treated with charcoal and crystallized from acetone.

	M.p., °C.	*Neutralisation value*	*Molecular weight*
Fraction I	75.5–76	152.87	366.9
" II	59–59.5	212.44	234.5
" III	56	226.00	242.7

The preceding fractions of solid fatty acids, which were quite small in quantity were fractionally crystallized; the results are shown in Figure I.

A comparison of the neutralization values obtained with those of known fatty acids indicates that the mixture consists chiefly of palmitic and stearic acids (n.v. 219.1 and 197.5 respectively). There is also present a small amount of one or more higher acids, since some material was obtained with a melting point within the range reported for "cerotic acid" (77.5–82.5) and a neutralization value of 145 which is between that of hexa- and penta-cosanic acids (141.4 and 152.3 respectively).

Identification of Glycerol

From the aqueous solution which remained after the fatty acids had been removed by extraction with ether, a small quantity of glycerol was isolated. Identification was made by heating with potassium bisulfate and the reduction of Fehling's solution by the acrolein thus produced.

Examination of the Unsaponifiable Portion

The unsaponifiable material was dissolved in petroleum ether and shaken with 80% alcohol. Crystals separated in both layers. Both sets of crystals gave the Hesse-Salkowski and Liebermann-Burchard sterol reactions, and were combined. After treatment with activated carbon and several recrystallizations from alcohol-ethyl acetate mixture, the crystals melted at 139°. An acetyl derivative melted at 127.5–128°. These tests indicate the presence of a phytosterol consisting largely of sitosterol.

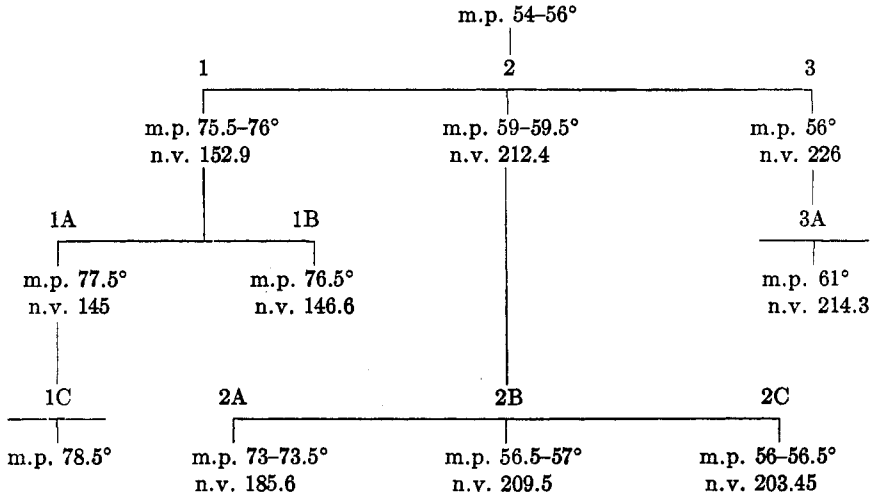
Some viscous material separated between the soap and ether layers at the time when the unsaponifiable fraction was being extracted from the soaps of the original saponification. This was separated by filtration, boiled with alcohol, and the residue washed with ether. After treatment with "Suchar" in pyridine and two recrystalli-

zations from the same diluted solvent, white needle crystals were obtained which melted at 250–255° and gave both the Salkowski and Liebermann-Burchard color tests for sterol as well as the Molish test for carbohydrates thus showing the presence of a phytosterolin.

The residues left after removal of the sterols were taken up in a small amount of carbon disulfide and several volumes of absolute alcohol added. A precipitate was obtained. This was dissolved in acetone and treated with "Suchar." From the cooled solution, crystals were obtained which melted at 45–50°. After two treatments with concentrated sulfuric acid at 104°, crystals were obtained which melted at 51°. Pentacosane melts at 54–55°. X-ray spacing was 34.30 ∓ .20Å. $C_{25}H_{52}$ has

FIGURE I

Solid Fatty Acids



a spacing of 34.7Å. Combustion averages of two determinations were: carbon, 85.24%, hydrogen, 14.86%; calculated for $C_{25}H_{52}$, 85.13% and 14.87%. It would appear from the foregoing that the substance is slightly impure pentacosane.

The mother liquors from the pentacosane yielded a small amount of a colorless oily liquid which did not solidify on cooling. This appeared to be composed of a mixture of saturated and unsaturated substances but the amount was too small for further study.

SUMMARY AND CONCLUSIONS

The pulp and locular tissue of the sweet orange have been examined for their fatty constituents. Oleic, linoleic, linolenic, palmitic, and stearic acids have been found. Also the presence of an acid with a chain of 26 carbon atoms has been indicated, probably mixed with one containing 24 carbon atoms. This would constitute what has been frequently reported as "cerotic acid."

Glycerol, a phytosterol (sitosterol), a phytosterolin, and a hydrocarbon which appeared to be only slightly impure pentacosane were isolated.

It was noted both in this work and in that on the peel (1) that the amount of glycerol appeared too small to combine with all the acids psesent, but that the amount of phytosterol was relatively large. This suggests that the fatty acids may exist in part in combination with the sterols. The composition of the fat of the pulp is quite similar to that of the peel, with the exception that ceryl alcohol was found in the peel but not in the pulp and pentacosane in the pulp but not in the peel.

The writer wishes to express his thanks to Mrs. Mildred S. Sherman for the analyses, and to Dr. Sterling B. Hendricks for the x-ray data reported in this paper.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF THE SCHOOL OF PHARMACY, PURDUE UNIVERSITY]

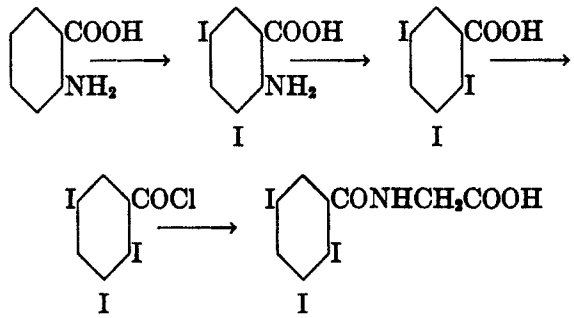
SYNTHESIS OF IODOHIPPURIC ACIDS. II. 2,3,5- AND 3,4,5-TRIIODOHIPPURIC ACIDS[1]

CARL J. KLEMME AND JAMES H. HUNTER

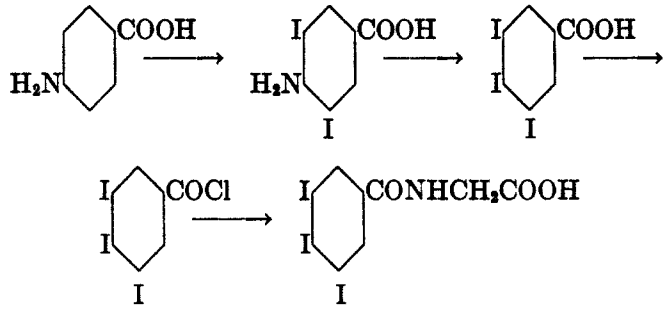
Received May 2, 1940

With the ultimate aim of studying the efficacy of certain iodohippuric acids as contrast agents for clinical radiography, we have recently described the syntheses of three diiodohippuric acids (1). In this second communication we wish to report the syntheses of two more highly iodinated derivatives, *viz.*, 2,3,5- and 3,4,5-triiodohippuric acids.

As indicated below, 2,3,5-triiodohippuric acid was synthesized from *o*-aminobenzoic acid:



and the 3,4,5-triiodo derivative was prepared from *p*-aminobenzoic acid in a similar fashion:



[1] From a portion of a thesis submitted by James H. Hunter in partial fulfillment for the degree of Doctor of Philosophy, August, 1938.

2-Amino-3,5-diiodobenzoic acid was prepared by the action of iodine monochloride on *o*-aminobenzoic acid according to the previously described modification (1) of the procedure of Wheeler and Johns (2). This acid, upon diazotization and treatment with aqueous potassium iodide, gave 2,3,5-triiodobenzoic acid (2). When this acid was warmed with thionyl chloride it readily yielded the corresponding benzoyl chloride. Conversion of the latter into 2,3,5-triiodohippuric acid was effected by treatment with glycine in the presence of dilute sodium hydroxide and subsequent acidification with hydrochloric acid.

Michael and Norton (3), in 1879, described the preparation of 4-amino-3,5-diiodobenzoic acid by the action of iodine monochloride on *p*-aminobenzoic acid. In 1909, Wheeler and Liddle (4) identified 4-amino-3,5-diiodobenzoic acid among the acid hydrolysis products of 4-acetamino-3-iodobenzoic acid. In the same report these authors gave details for the preparation of 4-amino-3,5-diiodobenzoic acid by oxidation of the corresponding acetylated toluide. In our studies we have used an acid prepared by modifying the procedure of Michael and Norton. 4-Amino-3,5-diiodobenzoic acid, when diazotized and treated with aqueous potassium iodide, gave 3,4,5-triiodobenzoic acid as described by Wheeler and Liddle (4). The preparation of 3,4,5-triiodobenzoyl chloride and, from it, 3,4,5-triiodohippuric acid followed the procedure outlined for the foregoing 2,3,5-triiodo derivative.

EXPERIMENTAL

2-Amino-3,5-diiodobenzoic acid was prepared from anthranilic acid and iodine monochloride according to the detailed procedure formerly reported (1).

2,3,5-Triiodobenzoic acid was prepared from the above 2-amino-3,5-diiodobenzoic acid according to the method of Wheeler and Johns (2). It was found to be somewhat more advantageous to purify this compound by dissolving the crude acid, which had been dissolved in dilute alkali and precipitated with dilute hydrochloric acid, in one and one-half volumes of acetone, boiling with a little decolorizing charcoal, filtering, and diluting with water until crystallization began. After thoroughly chilling, eighty per cent recovery was thus obtained.[2] The purified acid melted at 223–224°.[3] Wheeler and Johns reported the melting point as 224–226°.

2,3,5-Triiodobenzoyl chloride. Two and five-tenths grams (0.005 mole) of pure 2,3,5-triiodobenzoic acid (m.p. 223–224°) was gently refluxed with 5 cc. of thionyl chloride (Eastman's "Practical") for forty-five minutes. The excess thionyl chloride was distilled from a steam-bath. The crystalline mass, formed by chilling the residual liquid, was crystallized from carbon tetrachloride; yield, 2.3 g. (85.4%) of a dull yellow solid melting at 85–86° after sintering at 80–84°.

Anal. Calc'd for $C_7H_2ClI_3O$: Cl, 6.84; I, 73.47.
Found: Cl, 7.17; I, 72.01.

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[2] Wheeler and Johns (2) crystallized the crude acid from strong alcohol.

[3] All melting points are uncorrected.

2,3,5-Triiodohippuric acid. One and three-tenths grams of glycine was dissolved in 22 cc. of approximately 3% sodium hydroxide. The solution was warmed to about 85° and treated with 0.9 g. (0.00173 mole) of 2,3,5-triiodobenzoyl chloride. The mixture was shaken until most of the acid chloride had dissolved. The amber colored supernatant liquid was filtered, the residue washed with a little water, and the combined filtrate acidified with concentrated hydrochloric acid. The bulky, white precipitate was collected, washed with water, and dried in air; yield, 0.9 g. (93.3%). The crude, dry product was repeatedly extracted with ether to remove any 2,3,5-triiodobenzoic acid present. The ether-insoluble residue weighed 0.72 g. (74.5%). Crystallization from a mixture of 50 cc. of acetone and 80 cc. of water gave 0.32 g. (33.2%) of white platelets melting at 255.5–257° after darkening at 250–255°.

Anal. Calc'd for $C_9H_6I_3NO_3$: I, 68.38; N, 2.51; M.w. 556.8.

Found: I, 66.80; N, 2.70; M.w. 580.3.

4-Amino-3,5-diiodobenzoic acid. With efficient mechanical stirring, 10 g. (0.073 mole) of recrystallized *p*-aminobenzoic acid (m.p. 184°) (5) was dissolved in 450 cc. of warm (75°) 12.5% hydrochloric acid contained in a 2 l. beaker. Forty-eight grams (0.295 mole) of iodine monochloride (6) in 40 cc. of 25% hydrochloric acid was added, and the mixture stirred for one minute. During this time a yellow precipitate began to appear. The reaction-mixture was then diluted with 1 l. of water, whereupon a copious precipitate was deposited. The temperature of the well-stirred mixture was raised gradually, and held at about 90° for fifteen minutes. After the contents of the beaker had cooled to room temperature, the precipitate was collected, thoroughly washed with water and dried in air; yield, 24.0 g. (84.5%).[4] Purification by dissolving in dilute sodium hydroxide and precipitating with dilute hydrochloric acid gave 22.8 g. (82.4%) of a product of sufficient purity for the preparation of 3,4,5-triiodobenzoic acid. The product was not crystallized because of its slight solubility. Its melting point lies above 350° (4).

3,4,5-Triiodobenzoic acid was prepared according to the procedure of Wheeler and Liddle (4). The crude product was directly crystallized from dilute alcohol. The purified acid melted at 289–290°. Wheeler and Liddle found 288°.

3,4,5-Triiodobenzoyl chloride. Five grams (0.01 mole) of 3,4,5-triiodobenzoic acid (m.p. 289–290°) was gently refluxed for two hours with 10 cc. of thionyl chloride. Excess thionyl chloride was distilled from a steam-bath, and the residue crystallized from a carbon tetrachloride-petroleum ether mixture with the use of a little decolorizing charcoal. The bright yellow needles thus obtained weighed 3.8 g. (73.4%) and melted at 136–138°. Recrystallization from the carbon tetrachloride-petroleum ether mixture gave 2.7 g. (52.1%) of yellow needles melting at 138–139°.

Anal. Calc'd for $C_7H_2ClI_3O$: Cl, 6.84; I, 73.47.

Found: Cl, 7.05; I, 72.28.

3,4,5-Triiodohippuric acid. Two and nine-tenths grams of glycine (Eastman) was dissolved in 50 cc. of 1% sodium hydroxide and the solution warmed to 90°. Two grams (0.00386 mole) of 3,4,5-triiodobenzoyl chloride was added and the temperature held at 90–100° for about ten minutes with frequent shaking. The clear, yellow solution was cooled slightly, acidified with concentrated hydrochloric acid, and again cooled. The somewhat yellow precipitate was collected, washed with water and air-dried; yield, 2.2 g. (quantitative). The crude compound was freed from any 3,4,5-triiodobenzoic acid by repeated extraction with ether. The dry,

[4] The yield obtained by Michael and Norton (3) was not reported.

ether-insoluble residue weighed 1.95 g. (90.6%). One crystallization from dilute alcohol gave pure, white crystals melting at 242–243°.

Anal. Calc'd for $C_9H_6I_3NO_3$: I, 68.38; N, 2.51; M.w. 556.8.
Found: I, 66.76; N, 2.85; M.w. 580.1.

SUMMARY

Details are given for a four-step synthesis of 2,3,5-triiodohippuric acid, and its isomer, the 3,4,5-triiodo derivative, from *o*- and *p*-aminobenzoic acids, respectively.

LAFAYETTE, IND.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY AND CHEMICAL ENGINEERING OF THE UNIVERSITY OF PENNSYLVANIA]

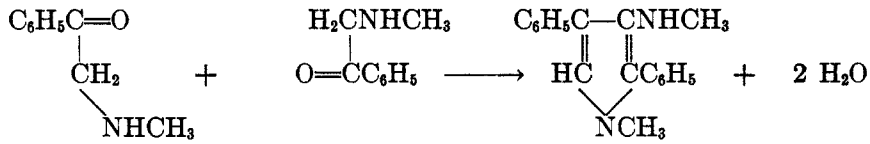
β-NAPHTHYL DERIVATIVES OF ETHANOLAMINE AND N-SUBSTITUTED ETHANOLAMINES

TONY IMMEDIATA AND ALLAN R. DAY

Received May 13, 1940

A survey of the literature disclosed the fact that very few investigations have been carried out on the subject of naphthyl substituted ethanolamines, where the naphthyl radical is in the β-position to the nitrogen. A very large volume of work, however, has been published on the corresponding phenyl derivatives and their esters, particularly the benzoates. Hartung (1), and Alles and Knoefel (2) have published excellent reviews of this work.

One of the widely used methods for the preparation of the phenyl derivatives involved the condensation of a phenacyl halide with an amine. The resulting amino ketone was then reduced to the corresponding amino alcohol. The first step in this reaction, when primary amines were used, was complicated by the formation of substituted pyrroles, which greatly reduced the yields of the desired products. The amino ketones were shown to be stable only in the form of their salts, and attempts to prepare the free bases from the salts usually resulted in the formation of pyrroles. Gabriel (3) proposed the following mechanism to account for this reaction.



Tutin, Caton, and Hann (4) succeeded in isolating ω-amino-*p*-hydroxyacetophenone from its hydrochloride, although they mentioned the fact that it was difficult to obtain a pure product. No attempt has been made to relate the tendency to form pyrroles with the type of phenacyl halide used or with the type of primary amine involved.

It appeared reasonable to believe that the substitution of a larger aryl radical for the phenyl group might reduce pyrrole formation. Similarly it might be expected that as the alkyl group attached to nitrogen increased in size, the tendency to undergo ring closure would be diminished. To test these possibilities, ω-bromo-β-acetonaphthone was condensed with several primary amines.

Difficulties were encountered in the condensation of primary amines with ω-bromo-β-acetonaphthone. The condensations were carried out in ether, alcohol, dioxane, or mixtures of these solvents. Two equivalents of amine were used in every case. That the desired reaction:

$$C_{10}H_7COCH_2Br + 2RNH_2 \rightarrow C_{10}H_7COCH_2NHR + RNH_2 \cdot HBr$$

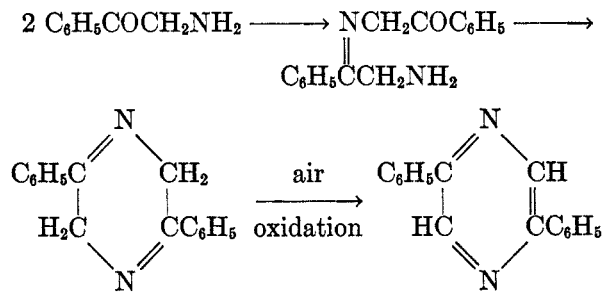
took place was evidenced by the formation of an equivalent quantity of the starting amine as its hydrobromide. The color of the mixtures changed from yellow to dark red on standing. When the filtrate from the hydrobromide was treated with hydrogen chloride, the hydrochloride of the condensation-product was precipitated as expected, but in low yields in some cases, and always contaminated with a dark, gummy material. When the reactions were carried out in oxygen-free solvents and in an atmosphere of nitrogen, similar results were obtained. The reactions were carried out with somewhat greater success by allowing them to proceed for a definite period of time, rather than permitting them to go to completion. In this way fair amounts of the desired products were obtained and the gummy materials arising from subsequent reactions were materially decreased. Even under these conditions, only the reactions carried out in dry ether at 0–5° were satisfactory. The condensation with methylamine proved to be the most difficult, with ethylamine, *n*-butylamine, and benzylamine next, in the order given. The condensation with cyclohexylamine was much easier to carry out. In this case the reaction-mixture, after standing for twenty-four hours, still gave a fourteen per cent yield of the condensation-product, while the methylamine reactions that were allowed to proceed for longer than one hour were complete failures.

The isolation of the free bases of the amino ketone compounds was troublesome and in some cases impossible, as would be expected from a consideration of the difficulties encountered in the preparation of their hydrochlorides. Where the N-alkyl group was the methyl radical, the free base could not be isolated. The free bases of the corresponding ethyl, *n*-butyl, benzyl, and cyclohexyl derivatives were obtained by the addition of sodium bicarbonate solution to well-cooled aqueous solutions of the hydrochlorides. The bases precipitated as almost colorless solids, which when rapidly removed by filtration and quickly dried, could be kept for a day or two. On longer standing they became very dark. With the exception of the cyclohexyl derivative, they could not be recrystallized without further changes occurring.

The results of this series of condensations indicated that the substitution of the naphthyl radical for the phenyl group did not reduce the formation of pyrroles, but the size of the alkyl group attached to nitrogen did

affect this reaction. As the size of this group increased, the tendency to form pyrroles decreased. This effect was most pronounced with the cyclohexyl derivative, and in this case the free base could be kept for longer periods of time without any decomposition. The other free bases, with the exception of the N-methyl derivative, were isolated, although on standing they became dark brown or red. These dark products could not be obtained pure enough for analysis, but they did give certain qualitative tests for the pyrrole ring, such as the formation of addition-products with acetone and the color test with hydrochloric acid.

Attempts to condense ω-bromo-β-acetonaphthone with ammonia were unsuccessful. Red solids were always obtained, but the desired condensation-product, ω-amino-β-acetonaphthone, could not be isolated. The hydrobromide of the latter was finally prepared by the method of Mannich and Hahn (5). Efforts to isolate the free base from this salt resulted in failure. A reddish-brown powder was formed in every attempt. Analysis of this powder suggested that the compound was 2,5-dinaphthylpyrazine, similar to the diphenylpyrazine noted by Gabriel (6). Gabriel reported that when ω-aminoacetophenone hydrochloride was treated with sodium hydroxide, sodium carbonate, or ammonium hydroxide solutions, the product isolated was 2,5-diphenylpyrazine. He formulated the reaction as follows:



Hartung (7) reported the formation of 2,5-diphenylpyrazine when isonitrosoacetophenone was catalytically reduced in a neutral solution.

$$C_6H_5COCH{=}NOH \xrightarrow{H_2} C_6H_5COCH_2NH_2 \xrightarrow[\text{condensation}]{\text{spontaneous}}$$

$$\text{2,5-diphenyldihydropyrazine} \xrightarrow[\text{oxidation}]{\text{air}} \text{2,5-diphenylpyrazine.}$$

It would appear, therefore, that amino ketones, of the type $ArCOCH_2NH_2$ tend to undergo self condensation to pyrazines, while the type $ArCOCH_2NHR$ tend to condense to pyrroles.

Several secondary amines were likewise condensed with ω-bromo-β-acetonaphthone. Good yields of the ω-dialkylamino-β-acetonaphthone hydrochlorides were obtained. These condensations were not complicated by side-reactions such as those noted in the primary amine series. The free bases of the dimethylamino and diethylamino derivatives could not be prepared. They separated as viscous, brown oils which appeared to decompose rapidly. Since these compounds carried no hydrogen attached to nitrogen, it did not seem probable that pyrazines or pyrroles could have been formed. These oils could not be purified without further changes and consequently the analytical results were meaningless. The free bases of the higher molecular weight secondary amine derivatives were quite stable.

The amino ketone hydrochlorides were hydrogenated to the corresponding amino alcohols, in the presence of palladium as the catalyst. Amino alcohols of the following types were obtained:

$C_{10}H_7CHOHCH_2NH_2$ $C_{10}H_7CHOHCH_2NHR$ $C_{10}H_7CHOHCH_2NR_2$

They were insoluble in water but formed hydrochlorides which were fairly soluble in water.

Gabriel (8) noted in 1915 that the addition of a base to an aqueous solution of ethanolamine benzoate hydrochloride yielded N-β-hydroxyethylbenzamide as the sole product. This rearrangement apparently is characteristic of all compounds which have the grouping $-\underset{\displaystyle OCOC_6H_5}{\overset{\displaystyle |}{C}}HCH_2NH_2$ or $-\underset{\displaystyle OCOC_6H_5}{\overset{\displaystyle |}{C}}HCH_2NHR$. This reaction has been observed by other workers. Hartung and Munch (9) pointed out the fact that esters of this type were only stable in solution in the form of their salts. That such rearrangements can be reversed was shown by Kanao (10) who reported that the N-benzoyl derivative of a phenylpropanolamine could be rearranged to the hydrochloride of the O-benzoyl derivative by treatment with strong hydrochloric acid.

Since this rearrangement has not been reported for the benzoates of naphthyl derivatives of ethanolamine and substituted ethanolamines, it seemed desirable to determine the ease with which this reaction occurred in this series. The benzoates of the amino alcohols were prepared as their hydrochlorides. This series of compounds, $C_{10}H_7\underset{\displaystyle OCOC_6H_5}{\overset{\displaystyle |}{C}}HCH_2NHR\cdot HCl$, offered some interesting possibilities: (a) the adjacency of the relatively large naphthyl radical to the ester grouping might retard or prevent the rearrangement; and (b) the size of the N-alkyl group might affect the

reaction in the same way. Neither of these possibilities was realized. The products isolated from the benzoate hydrochlorides of the above type, by the addition of bases, were N-substituted benzamides in every case. The reversal noted by Kanao has been confirmed in the course of the present work and the following relationship has been noted:

$$\underset{\displaystyle|\atop\displaystyle OCOC_6H_5}{C_{10}H_7CHCH_2NH_2} \cdot HCl \;\underset{\text{alcoholic}\atop HCl}{\overset{OH^-}{\rightleftarrows}}\; C_{10}H_7CHOHCH_2NHOCC_6H_5$$

In general the amides were easily distinguished from the true esters by their insolubility in dilute hydrochloric acid.

The esters of the type, $\underset{\displaystyle|\atop\displaystyle OCOC_6H_5}{C_{10}H_7CHCH_2NR_2}$ were stable both in the form of salts and as free bases.

EXPERIMENTAL

Analysis. The semi-micro Kjeldahl method or semi-micro Dumas method was used for the nitrogen determinations. The distillate was absorbed in 4% boric acid solution, and titrated to a methyl red end-point according to the method of Meeker and Wagner (11). The Volhard method was used for the determination of chlorine in the hydrochlorides. Redistilled nitrobenzene was used to coagulate the silver chloride before titrating the excess silver nitrate with potassium thiocyanate. The solution of the more difficultly soluble hydrochlorides was effected by the addition of alcohol.

Preparation of the catalyst. The catalyst used was 10% palladium on charcoal, prepared according to the method of Hartung (12). In all cases the catalyst was shaken under an atmosphere of hydrogen until no more gas was absorbed, immediately before the introduction of the sample.

β-Acetonaphthone. The Friedel-Crafts procedure described by St. Pfau and Ofner (13) for the preparation of this compound did not prove satisfactory. The reaction-mixture became thick and tarry before the complete addition of the aluminum chloride, and efficient stirring was not possible. Their method of separating the α- and β-forms, fractional crystallization of the picrates, also proved tedious and troublesome. After considerable preliminary work, the following procedure was adopted. Thirty grams (0.243 mole) of naphthalene and 23 g. (0.29 mole) of acetyl chloride were dissolved in 250 cc. of pure nitrobenzene. Thirty-five grams (0.26 mole) of aluminum chloride was added to the cold, rapidly stirred solution. The addition was completed in 30 minutes and stirring and cooling were continued for 6 hours. The dark, viscous liquid was then poured over crushed ice and strongly acidified with concentrated hydrochloric acid. The nitrobenzene layer was washed with water, sodium hydroxide solution, and again with water. The solvent was removed by distillation under reduced pressure and the residue then distilled at 3 mm. The fraction distilling at 131–145° was collected. The separation of the α- and β-forms was easily effected by recrystallization from alcohol in which the β-form was less soluble. A second recrystallization gave the pure β-compound in the form of colorless needles, in yields of 35–40%; m.p. 53° (corr.), picrate, m.p. 82° (corr.).

ω-Bromo-β-acetonaphthone. The method of Radcliffe, Sherwood, and Short (14) was first used. The reaction was carried out in carbon tetrachloride solution and the bromine added gradually. Although the method gave good yields (70–73%), it proved to be rather tedious and so the following method was finally adopted. Fifty grams (0.3 mole) of β-acetonaphthone was dissolved in 100 cc. of glacial acetic acid. A solution of 48 g. (0.3 mole) of bromine in 25 cc. of glacial acetic acid was then added all at once. The solution became straw colored within a few minutes and was then poured onto crushed ice, with stirring. After standing overnight, the product was removed by filtration and washed with sodium bicarbonate solution. It was obtained as colorless needles by recrystallization from alcohol. Yields 73–80%; m.p. 80° (corr.), picrate m.p. 93° (corr.).

I. *ω-Amino-β-acetonaphthone hydrobromide.* This compound was prepared by the method of Mannich and Hahn (5). Twenty grams (0.08 mole) of ω-bromo-β-acetonaphthone in 50 cc. of chloroform was added to a solution of 11.3 g. (0.08 mole) of hexamethylenetetramine in 100 cc. of chloroform. The mixture solidified in a few minutes with the evolution of heat. After standing for 5 days, the addition-product was filtered and dried. This material was dissolved in 250 cc. of ethyl alcohol, 30 cc. of concentrated hydrochloric acid added, and the solution allowed to stand for 4 days. The precipitated ammonium chloride was removed by filtration and the filtrate evaporated under reduced pressure. The crude residue was recrystallized from alcohol; yields 40–44%.

All attempts to isolate the free base, ω-amino-β-acetonaphthone, were unsuccessful. A brown powder was obtained in every case. The analysis suggested that the compound might be a dinaphthyl pyrazine (similar to the diphenyl pyrazine reported by Gabriel (8)).

Anal. Calc'd for $C_{24}H_{16}N_2$: N, 8.43. Found: N, 8.20.

Efforts to obtain an oxime directly from ω-amino-β-acetonaphthone hydrobromide were also unsuccessful. Only brown, amorphous powders were obtained which could not be purified. The analyses on this material did not conform to any definite compound.

II. *ω-Methylamino-β-acetonaphthone hydrochloride.* A solution of 8.6 g. (0.08 mole) of methylamine in 30 cc. of dry ethyl alcohol was added gradually to a cooled solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 100 cc. of dry ether. After 1 hour, 25 cc. of dry ether was added to complete the precipitation of the methylamine hydrobromide. The latter was removed by filtration, and dry hydrogen chloride was passed slowly over the ice-cooled filtrate. A large amount of red, gummy material was precipitated along with the crystalline hydrochloride. Purification was difficult and recrystallization from absolute alcohol gave only low yields of the hydrochloride. Yields 12–15%.

Attempts to isolate the free base were unsuccessful, as with ω-aminoacetonaphthone. The material isolated was not uniform and could not be purified.

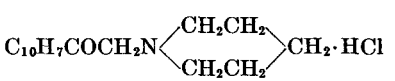
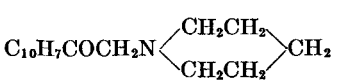
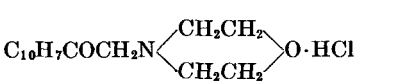
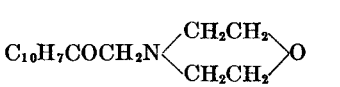
An oxime was obtained directly from the hydrochloride. It separated as an oil, but was finally obtained in crystalline form from an alcohol-ether solution; m.p. 143° (corr.).

Anal. Calc'd for $C_{13}H_{14}N_2O$: N, 13.08. Found: N, 12.88.

III. *ω-Ethylamino-β-acetonaphthone hydrochloride.* A solution of 5.1 g. (0.12 mole) of ethylamine in 60 cc. of dry alcohol was added gradually to a cooled solution of 15 g. (0.06 mole) of ω-bromo-β-acetonaphthone in 150 cc. of dry ether. After 4 hours, 100 cc. of dry ether was added and the precipitated ethylamine hydrobromide removed by filtration. The condensation-product was isolated from the filtrate in the manner described for the methylamino derivative (II). Yields 20–30%.

TABLE I

ω-AMINO AND ALKYLAMINO-β-ACETONAPHTHONES AND HYDROCHLORIDES

NO.	FORMULA	M.P., °C. CORR.	CRYST. FORM	EMPIRICAL FORMULA	NITROGEN %		HALOGEN %	
					Calc'd	Found	Calc'd	Found
I	$C_{10}H_7COCH_2NH_2 \cdot HBr$	213	plates	$C_{12}H_{11}ON \cdot HBr$	5.26	5.34	30.75	30.52
II	$C_{10}H_7CO \cdot CH_2 \cdot NHCH_3 \cdot HCl$	208–209	plates	$C_{13}H_{13}ON \cdot HCl$	5.95	5.86	15.05	15.04
III	$C_{10}H_7 \cdot COCH_2NHC_2H_5 \cdot HCl$	220–222	prisms	$C_{14}H_{15}ON \cdot HCl$	5.61	5.58	14.24	14.20
	$C_{10}H_7COCH_2NHC_2H_5$	68	powder	$C_{14}H_{15}ON$	6.57	6.71		
IV	$C_{10}H_7COCH_2NHC_4H_9 \cdot HCl$	208	plates	$C_{16}H_{19}ON \cdot HCl$	5.04	5.00	12.77	12.58
	$C_{10}H_7COCH_2NHC_4H_9$	82	powder	$C_{16}H_{19}ON$	5.81	5.61		
V	$C_{10}H_7COCH_2NHCH_2C_6H_5 \cdot HCl$	207–208	needles	$C_{19}H_{17}ON \cdot HCl$	4.49	4.38	11.37	11.24
	$C_{10}H_7COCH_2NHCH_2C_6H_5$	84	powder	$C_{19}H_{17}ON$	5.09	5.32		
VI	$C_{10}H_7COCH_2NHC_6H_{11} \cdot HCl$	209–210	needles	$C_{18}H_{21}ON \cdot HCl$	4.61	4.42	11.69	11.51
	$C_{10}H_7COCH_2NHC_6H_{11}$	125	powder	$C_{18}H_{21}ON$	5.24	5.00		
VII	$C_{10}H_7COCH_2N(CH_3)_2 \cdot HCl$	216–217	prisms	$C_{14}H_{15}ON \cdot HCl$	5.52	5.60	14.00	14.21
VIII	$C_{10}H_7COCH_2N(C_2H_5)_2 \cdot HCl$	199	prisms	$C_{16}H_{19}ON \cdot HCl$	5.05	5.06	12.81	12.70
IX	$C_{10}H_7COCH_2N(CH_2C_6H_5)_2 \cdot HCl$	sublimes at 198	plates	$C_{26}H_{23}ON \cdot HCl$	3.48	3.45	8.84	8.74
	$C_{10}H_7COCH_2N(CH_2C_6H_5)_2$	109	needles	$C_{26}H_{23}ON$	3.83	3.86		
X		232	prisms	$C_{17}H_{19}ON \cdot HCl$	4.82	4.70	12.25	12.22
		84	needles	$C_{17}H_{19}ON$	5.52	5.39		
XI		234	needles	$C_{16}H_{17}O_2N \cdot HCl$	4.81	4.67	12.16	12.18
		99	prisms	$C_{16}H_{17}O_2N$	5.49	5.46		

The free base, ω-ethylamino-β-acetonaphthone, was prepared by treating an aqueous solution of the hydrochloride, at 0°, with an ice-cold solution of sodium bicarbonate. The free base precipitated as a yellowish, crystalline powder. This product was dried in a vacuum over sodium hydroxide; m.p. 68° (corr.). The base was relatively unstable and darkened on standing.

The oxime, prepared from the hydrochloride, was obtained as colorless plates by recrystallization from 50% alcohol; m.p. 121° (corr.).

Anal. Calc'd for $C_{14}H_{16}N_2O$: N, 12.28. Found: N, 12.06.

IV. *ω-n-Butylamino-β-acetonaphthone hydrochloride.* A solution of 5.85 g. (0.08 mole) of *n*-butylamine in 50 cc. of dry ether was added gradually to a cooled solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 100 cc. of dry ether. After 1.5 hours, the butylamine hydrobromide was removed by filtration and the condensation-product was precipitated from the cold filtrate by the addition of dry hydrogen chloride. The crude product, which was contaminated with a tarry material, was boiled with water and filtered. The hydrochloride, obtained by evaporation of the filtrate, was recrystallized from alcohol. Yields 36–40%.

The free base was isolated in the same way as ω-ethylamino-β-acetonaphthone. It was unstable and could not be purified by recrystallization. It was dried over sodium hydroxide and analyzed at once.

The oxime, prepared from the hydrochloride, was obtained as colorless plates by recrystallization from alcohol; m.p. 113° (corr.).

Anal. Calc'd for $C_{16}H_{20}N_2O$: N, 10.94. Found: N, 10.64.

V. *ω-Benzylamino-β-acetonaphthone hydrochloride.* A solution of 8.56 g. (0.08 mole) of benzylamine in 10 cc. of dry ether was added gradually to a cold solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 100 cc. of dry ether. After 2 hours, the benzylamine hydrobromide was removed by filtration. The addition of dry hydrogen chloride to the filtrate produced a gummy solid. The latter was washed with dry acetone to remove the gum and then recrystallized from alcohol. Yields 30–32%.

The free base was obtained by the method described for ω-ethylamino-β-acetonaphthone. It could not be recrystallized without decomposition. The reddish powder was carefully washed, dried over sodium hydroxide and immediately analyzed.

The oxime, prepared from the hydrochloride, was obtained as colorless prisms from 50% alcohol; m.p. 116.5° (corr.).

Anal. Calc'd for $C_{19}H_{18}N_2O$: N, 9.66. Found: N, 9.40.

VI. *ω-Cyclohexylamino-β-acetonaphthone hydrochloride.* A solution of 8 g. (0.08 mole) of cyclohexylamine in 25 cc. of dry ether was added all at once to an ice-cooled solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 150 cc. of dry ether. One hundred and fifty cubic centimeters of dry ether was added and the mixture allowed to stand for 4 hours. The cyclohexylamine hydrobromide was removed by filtration and the condensation-product isolated from the filtrate and purified by the method described for the methylamino derivative (II). Yields 30–32%.

The free base was prepared by the method described for ω-ethylamino-β-acetonaphthone. It was recrystallized from alcohol but could not be obtained in a colorless form, the crystals having a light yellow color. This keto base, however, was more stable than the others previously described.

The oxime of the free base could not be isolated in pure form, but its hydrochloride was readily prepared. The oxime prepared in the usual manner separated as a gummy solid, which resisted all attempts at purification. This material was dis-

solved in dry ether and the hydrochloride precipitated in the form of needles, by the addition of dry hydrogen chloride; m.p. 201–202° (corr.).

Anal. Calc'd for $C_{18}H_{22}N_2O \cdot HCl$: N, 8.78. Found: N, 8.56.

VII. *ω-Dimethylamino-β-acetonaphthone hydrochloride.* A solution of 3.6 g. (0.08 mole) of dimethylamine in 10 cc. of dry alcohol and 25 cc. of dry ether was added gradually to an ice-cooled solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 150 cc. of dry ether. After 3 hours the dimethylamine hydrobromide was removed by filtration and the condensation-product was precipitated from the cold filtrate by treatment with dry hydrogen chloride. It was recrystallized from a mixture of alcohol and acetone. Yields 75–80%.

The free base could not be isolated. When a solution of sodium bicarbonate was added to an aqueous solution of the hydrochloride, a viscous brown oil separated, which appeared to decompose rapidly.

The oxime, prepared from the hydrochloride, was obtained as colorless plates by recrystallization from alcohol; m.p. 148° (corr.).

Anal. Calc'd for $C_{14}H_{16}N_2O$: N, 12.28. Found: N, 12.38.

VIII. *ω-Diethylamino-β-acetonaphthone hydrochloride.* A solution of 5.84 g. (0.08 mole) of diethylamine in 5 cc. of dioxane was added gradually to an ice-cooled solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 25 cc. of dioxane. After the solution had stood overnight, 25 cc. of dry ether was added and the diethylamine hydrobromide was removed by filtration. The hydrochloride of the condensation-product was precipitated from the cold filtrate with dry hydrogen chloride and recrystallized from alcohol. Yields 65–70%. This condensation did not proceed smoothly in alcohol or ether solution and very low yields were obtained.

Attempts to isolate the free base were unsuccessful, as with the dimethylamino derivative.

The oxime, prepared from the hydrochloride, was obtained as colorless plates by recrystallization from 60% alcohol; m.p. 121.5° (corr.).

Anal. Calc'd for $C_{16}H_{20}N_2O$: N, 10.93. Found: N, 10.60.

IX. *ω-Dibenzylamino-β-acetonaphthone hydrochloride.* A solution of 10.32 g. (0.08 mole) of dibenzylamine in 100 cc. of dry ether was added gradually to a cold solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 125 cc. of dry ether. After the solution had stood overnight, the dibenzylamine hydrobromide was removed by filtration and the hydrochloride of the condensation-product isolated from the filtrate in the usual manner. It was recrystallized from alcohol. Yields 90–95%. The pure compound sublimed at 198° without melting.

The free base was prepared by the addition of sodium bicarbonate solution to a cold 50% alcohol solution of the hydrochloride. It was recrystallized from ether.

The oxime, prepared from the hydrochloride, was recrystallized from 50% alcohol; m.p. 114° (corr.).

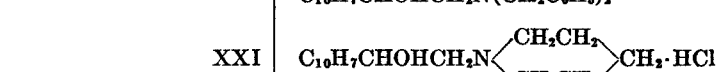
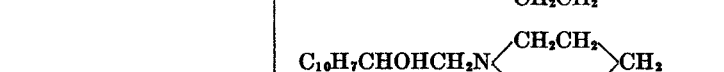
Anal. Calc'd for $C_{26}H_{24}N_2O$: N, 7.37. Found: N, 7.20.

X. *ω-Piperidino-β-acetonaphthone hydrochloride.* A solution of 6.6 g. (0.08 mole) of piperidine in 50 cc. of dry ether was added gradually to a cold solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 150 cc. of dry ether. After the solution had stood overnight, the piperidine hydrochloride was removed by filtration and the hydrochloride of the condensation-product isolated from the filtrate in the usual manner. It was recrystallized from alcohol. Yields 90–95%.

The free base was prepared by the addition of ammonium hydroxide to an aqueous solution of the hydrochloride. The oil which separated was evaporated several times with dry alcohol, or until solidification occurred. The product was then recrystallized from alcohol.

TABLE II

1-β-NAPHTHYL-2-AMINO AND ALKYLAMINOETHANOLS AND HYDROCHLORIDES

NO.	FORMULA	M.P., °C. CORR.	CRYST. FORM	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
					Calc'd	Found	Calc'd	Found
XII	$C_{10}H_7CHOHCH_2NH_2 \cdot HCl$	186	plates	$C_{12}H_{13}ON \cdot HCl$	6.26	6.22	15.88	15.94
	$C_{10}H_7CHOHCH_2NH_2$	113.5	needles	$C_{12}H_{13}ON$	7.48	7.51		
XIII	$C_{10}H_7CHOHCH_2NHCH_3 \cdot HCl$	152	needles	$C_{13}H_{15}ON \cdot HCl$	5.90	5.90	14.94	14.84
	$C_{10}H_7CHOHCH_2NHCH_3$	109	prisms	$C_{13}H_{15}ON$	6.97	7.00		
XIV	$C_{10}H_7CHOHCH_2NHC_2H_5 \cdot HCl$	189.5	needles	$C_{14}H_{17}ON \cdot HCl$	5.57	5.49	14.10	14.00
	$C_{10}H_7CHOHCH_2NHC_2H_5$	110.5	needles	$C_{14}H_{17}ON$	6.51	6.48		
XV	$C_{10}H_7CHOHCH_2NHC_4H_9 \cdot HCl$	190	plates	$C_{16}H_{21}ON \cdot HCl$	5.01	5.00	12.71	12.76
	$C_{10}H_7CHOHCH_2NHC_4H_9$	95.6	plates	$C_{16}H_{21}ON$	5.76	5.69		
XVI	$C_{10}H_7CHOHCH_2NHCH_2C_6H_5 \cdot HCl$	194.5	plates	$C_{19}H_{19}ON \cdot HCl$	4.47	4.36	11.32	11.24
	$C_{10}H_7CHOHCH_2NHCH_2C_6H_5$	136.5	prisms	$C_{19}H_{19}ON$	5.05	4.87		
XVII	$C_{10}H_7CHOHCH_2NHC_6H_{11} \cdot HCl$	224	plates	$C_{18}H_{23}ON \cdot HCl$	4.58	4.60	11.63	11.55
	$C_{10}H_7CHOHCH_2NHC_6H_{11}$	98	needles	$C_{18}H_{23}ON$	5.20	5.18		
XVIII	$C_{10}H_7CHOHCH_2N(CH_3)_2 \cdot HCl$	143.5	prisms	$C_{14}H_{17}ON \cdot HCl$	5.57	5.50	14.11	14.10
	$C_{10}H_7CHOHCH_2N(CH_3)_2$	53	plates	$C_{14}H_{17}ON$	6.51	6.44		
XIX	$C_{10}H_7CHOHCH_2N(C_2H_5)_2 \cdot HCl$	142.5	granules	$C_{16}H_{21}ON \cdot HCl$	5.01	5.00	12.70	12.64
	$C_{10}H_7CHOHCH_2N(C_2H_5)_2$	42	plates	$C_{16}H_{21}ON$	5.76	5.70		
XX	$C_{10}H_7CHOHCH_2N(CH_2C_6H_5)_2 \cdot HCl$	210	needles	$C_{26}H_{25}ON \cdot HCl$	3.47	3.36	8.80	8.70
	$C_{10}H_7CHOHCH_2N(CH_2C_6H_5)_2$	132	needles	$C_{26}H_{25}ON$	3.81	3.70		
XXI		213	plates	$C_{17}H_{21}ON \cdot HCl$	4.79	4.64	12.17	12.00
		98.5	prisms	$C_{17}H_{21}ON$	5.49	5.40		
XXII		223–224	plates	$C_{16}H_{19}O_2N \cdot HCl$	4.77	4.72	12.09	11.86
		120.5	needles	$C_{16}H_{19}O_2N$	5.45	5.32		

The oxime, prepared from the hydrochloride, was recrystallized from 50% alcohol; m.p. 122° (corr.).

Anal. Calc'd for $C_{17}H_{20}N_2O$: N, 10.45. Found: N, 10.41.

XI. *ω-Morpholino-β-acetonaphthone hydrochloride.* A solution of 6.97 g. (0.08 mole) of morpholine in 50 cc. of dry ether was added gradually to a cold solution of 10 g. (0.04 mole) of ω-bromo-β-acetonaphthone in 150 cc. of dry ether. After the mixture had stood overnight, the morpholine hydrobromide was removed by filtration and the hydrochloride of the condensation-product isolated from the filtrate in the usual way. It was recrystallized from alcohol. Yields 85–90%.

The free base, obtained by the addition of ammonium hydroxide to an aqueous solution of the hydrochloride, was recrystallized from ether.

The oxime was prepared from the hydrochloride and recrystallized from 75% alcohol; m.p. 154–155° (corr.).

Anal. Calc'd for $C_{16}H_{18}N_2O_2$: N, 10.37. Found: N, 10.18.

XII. *1-β-Naphthyl-2-aminoethanol hydrochloride.* Ten grams (0.0375 mole) of ω-amino-β-acetonaphthone hydrobromide was dissolved in 250 cc. of ethyl alcohol and hydrogenated at atmospheric pressure using 10% palladium on charcoal as the catalyst. When the theoretical amount of hydrogen had been absorbed, the mixture was heated and filtered while hot. Several extractions of the catalyst with hot alcohol were necessary to recover the reduced product completely. The hydrobromide, recovered from the combined alcohol solutions, was converted to the hydrochloride by liberating the base with sodium bicarbonate solution, extracting with ether, and saturating the dry ether solution with hydrogen chloride. It was recrystallized from alcohol. Yield, practically quantitative.

The free base, 1-β-naphthyl-2-aminoethanol, was prepared by treating an aqueous solution of the hydrochloride with ammonium hydroxide and recrystallizing the product from alcohol.

This general method, with slight modifications, was used for the other alcohols in this series.

XIII. *1-β-Naphthyl-2-methylaminoethanol hydrochloride.*

XIV. *1-β-Naphthyl-2-ethylaminoethanol hydrochloride.*

XV. *1-β-Naphthyl-2-*n*-butylaminoethanol hydrochloride.* This hydrochloride was recrystallized from warm, absolute alcohol by the careful addition of dry ether.

The remaining amino alcohol hydrochlorides in this series were purified in the same manner.

XVI. *1-β-Naphthyl-2-benzylaminoethanol hydrochloride.*

XVII. *1-β-Naphthyl-2-cyclohexylaminoethanol hydrochloride.*

XVIII. *1-β-Naphthyl-2-dimethylaminoethanol hydrochloride.*

XIX. *1-β-Naphthyl-2-diethylaminoethanol hydrochloride.* The free base of this compound was purified by dissolving in a small amount of ethyl alcohol and allowing the solution to evaporate at room temperature until crystallization appeared to be complete.

XX. *1-β-Naphthyl-2-dibenzylaminoethanol hydrochloride.*

XXI. *1-β-Naphthyl-2-piperidinoethanol hydrochloride.*

XXII. *1-β-Naphthyl-2-morpholinoethanol hydrochloride.*

XXIII. *1-β-Naphthyl-2-aminoethanol benzoate hydrochloride.* Two and one-half grams (0.0112 mole) of 1-β-naphthyl-2-aminoethanol hydrochloride was treated with 7 g. (0.049 mole) of benzoyl chloride for 2 hours at 100°. The pasty mass finally liquified to a clear yellow solution. It was cooled, dry ether was added to the reaction-mixture, and the oil slowly solidified. It was recrystallized from hot absolute alcohol by the careful addition of dry ether. Yields 65–70%.

It was not possible to obtain the free base because of its tendency to rearrange to the corresponding N-substituted benzamide XXIV. The amide, isolated by neutralizing an aqueous solution of the hydrochloride, was recrystallized from alcohol and finally from ether. This compound was not soluble in hydrochloric acid. However, when treated with dry alcoholic hydrogen chloride, the amide slowly rearranged to form the hydrochloride of the corresponding ester, m.p. 206° (corr.). The latter was soluble in dilute hydrochloric acid, as well as in water. These facts confirm the statement of earlier workers that esters of this type normally exist only in the form of salts, and attempts to prepare the free bases have resulted in the isolation of the corresponding amides.

XXV. *1-β-Naphthyl-2-methylaminoethanol benzoate hydrochloride.* This ester-hydrochloride was prepared by the method described for 1-β-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 45 minutes at 105–110°. After the addition of dry ether, it was allowed to stand for several days in the cold. The solid which separated was recrystallized from dry alcohol. Yields 28–31%.

Attempts to obtain the free base from the hydrochloride resulted in the isolation of the corresponding N-substituted benzamide XXVI, which was recrystallized from alcohol. This product was insoluble in water and dilute hydrochloric acid (difference from the benzoate hydrochloride).

XXVII. *1-β-Naphthyl-2-ethylaminoethanol benzoate hydrochloride.* It was prepared by the method used for the preparation of 1-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 2 hours at 115°. It was cooled, dry ether was added, and the mixture allowed to stand overnight. It was recrystallized from a hot absolute alcohol solution by the careful additon of dry ether. Yields 50–56%.

The corresponding N-substituted benzamide XXVIII, was obtained by neutralizing an aqueous solution of the ester hydrochloride. It was recrystallized from alcohol. It was insoluble in water and dilute hydrochloric acid, unlike the benzoate hydrochloride.

XXIX. *1-β-Naphthyl-2-butylaminoethanol benzoate hydrochloride.* This compound was prepared by the method described for 1-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 2 hours at 105°. It was cooled, dry ether was added, and the mixture allowed to stand overnight. The solid was recrystallized from a mixture of absolute alcohol and dry ether. Yields 45–48%.

The corresponding N-substituted benzamide (XXX) was obtained by neutralizing an aqueous solution of the ester hydrochloride. It was recrystallized from benzene. It was insoluble in water and dilute hydrochloric acid.

XXXI. *1-β-Naphthyl-2-benzylaminoethanol benzoate hydrochloride.* It was prepared by the method used for 1-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 2 hours at 110°. After it had stood overnight with dry ether, the product was recrystallized from a mixture of absolute alcohol and dry ether. Yields 32–37%.

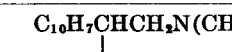
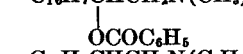
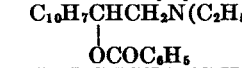
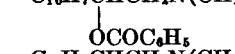
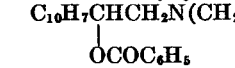
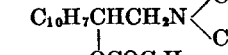
The corresponding N-substituted benzamide, XXXII, was obtained by neutralizing an aqueous solution of the ester hydrochloride. It was recrystallized from alcohol, and like the other amides in this series it was insoluble in water and dilute hydrochloric acid.

XXXIII. *1-β-Naphthyl-2-cyclohexylaminoethanol benzoate hydrochloride.* It was prepared by the method used for 1-β-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 4 hours at 110°. Dry ether was

TABLE III

BENZOYL DERIVATIVES OF 1-β-NAPHTHYL-2-AMINO AND 2-ALKYLAMINOETHANOLS AND HYDROCHLORIDES

NO.	FORMULA	M.P., °C. CORR.	CRYST. FORM	EMPIRICAL FORMULA	NITROGEN %		CHLORINE %	
					Calc'd	Found	Calc'd	Found
XXIII	$C_{10}H_7CHCH_2NH_2 \cdot HCl$ $OCOC_6H_5$	206–206.5	needles	$C_{19}H_{17}O_2N \cdot HCl$	4.27	4.20	10.83	10.97
XXIV	$C_{10}H_7CHOHCH_2NHOCC_6H_5$	207.8	needles	$C_{19}H_{17}O_2N$	4.81	4.72		
XXV	$C_{10}H_7CHCH_2NHCH_3 \cdot HCl$ $OCOC_6H_5$	193–194	needles	$C_{20}H_{19}O_2N \cdot HCl$	4.05	4.00	10.27	10.26
XXVI	$C_{10}H_7CHOHCH_2NOCC_6H_5$ CH_3	134.5	needles	$C_{20}H_{19}O_2N$	4.53	4.54		
XXVII	$C_{10}H_7CHCH_2NHC_2H_5 \cdot HCl$ $OCOC_6H_5$	178–179	powder	$C_{21}H_{21}O_2N \cdot HCl$	3.93	3.79	9.98	9.84
XXVIII	$C_{10}H_7CHOHCH_2NOCC_6H_5$ C_2H_5	125	needles	$C_{21}H_{21}O_2N$	4.39	4.37		
XXIX	$C_{10}H_7CHCH_2NHC_4H_9 \cdot HCl$ $OCOC_6H_5$	151	needles	$C_{23}H_{25}O_2N \cdot HCl$	3.65	3.65	9.25	9.20
XXX	$C_{10}H_7CHOHCH_2NOCC_6H_5$ C_4H_9	126–127	prisms	$C_{23}H_{25}O_2N$	4.04	4.00		
XXXI	$C_{10}H_7CHCH_2NHCH_2C_6H_5 \cdot HCl$ $OCOC_6H_5$	208	needles	$C_{26}H_{23}O_2N \cdot HCl$	3.35	3.26	8.50	8.53
XXXII	$C_{10}H_7CHOHCH_2NOCC_6H_5$ $CH_2C_6H_5$	82	needles	$C_{26}H_{23}O_2N$	3.67	3.65		
XXXIII	$C_{10}H_7CHCH_2NHC_6H_{11} \cdot HCl$ $OCOC_6H_5$	192–193	needles	$C_{25}H_{27}O_2N \cdot HCl$	3.42	3.38	8.67	8.77
XXXIV	$C_{10}H_7CHOHCH_2NOCC_6H_5$ C_6H_{11}	68	needles	$C_{25}H_{27}O_2N$	3.75	3.66		

XXXV		225	prisms	$C_{21}H_{21}O_2N \cdot HCl$	3.93	3.62	9.98	9.97
		69	plates	$C_{21}H_{21}O_2N$	4.39	4.22		
XXXVI		178	granules	$C_{23}H_{25}O_2N \cdot HCl$	3.65	3.54	9.26	9.06
		84	prisms	$C_{23}H_{25}O_2N$	4.03	3.87		
XXXVII		205–206	needles	$C_{33}H_{29}O_2N \cdot HCl$	2.75	2.80	6.99	6.90
		111.2	needles	$C_{33}H_{29}O_2N$	2.97	2.90		
XXXVIII		209	prisms	$C_{24}H_{25}O_2N \cdot HCl$	3.54	3.49	8.97	8.92
		69	prisms	$C_{24}H_{25}O_2N$	3.89	3.82		
XXXIX		204–205	needles	$C_{23}H_{23}O_3N \cdot HCl$	3.52	3.48	8.93	9.00
		105	needles	$C_{23}H_{23}O_3N$	3.88	3.92		

added and the mixture allowed to stand until the oil solidified. The solid was then recrystallized from absolute alcohol. Yields 40–45%.

An aqueous solution of this salt, on neutralization, likewise yielded the corresponding N-substituted benzamide, XXXIV. The latter was recrystallized from alcohol.

XXXV. *1-β-Naphthyl-2-dimethylaminoethanol benzoate hydrochloride.* This ester hydrochloride was prepared as above, except that the reaction was carried out in xylene solution. The solution was refluxed for 3 hours, cooled, and the product removed by filtration. It was recrystallized from a mixture of absolute alcohol and dry ether. Yields 50–60%.

The free base was readily obtained by the addition of ammonium hydroxide to an aqueous solution of the hydrochloride. It was recrystallized from alcohol.

XXXVI. *1-β-Naphthyl-2-diethylaminoethanol benzoate hydrochloride.* It was prepared by the method described for 1-β-naphthyl-2-aminoethanol benzoate hydrochloride, except that the mixture was heated for 2.5 hours at 100°. The product was isolated as before and recrystallized from a mixture of dry alcohol and ether. Yields 68–71%.

The free base was liberated from an alcoholic solution of the hydrochloride by the addition of sodium hydroxide, and recrystallized from ether.

XXXVII. *1-β-Naphthyl-2-dibenzylaminoethanol benzoate hydrochloride.* It was prepared in the usual manner except that the mixture was heated for 5 hours at 108–110°. The product was recrystallized from alcohol. Yields 65–70%.

The free base was obtained by the addition of ammonium hydroxide to a dilute alcoholic solution of the hydrochloride, followed by recrystallization from alcohol.

XXXVIII. *1-β-Naphthyl-2-piperidinoethanol benzoate hydrochloride.* In this case the reactants were heated for 3.5 hours at 120–123°. After being washed with dry ether, the oil was dissolved in absolute alcohol and allowed to evaporate at room temperature. Yields 70–72%.

The free base, liberated by the action of ammonium hydroxide on an aqueous solution of the hydrochloride, was recrystallized from alcohol.

XXXIX. *1-β-Naphthyl-2-morpholinoethanol benzoate hydrochloride.* For the preparation of this compound the reactants were heated for 2 hours at 115–117°. The oil was allowed to stand in contact with dry ether until it solidified. It was then recrystallized from dry alcohol. Yields 75–83%.

The free base, which was obtained by the addition of ammonium hydroxide to an alcoholic solution of the hydrochloride, was crystallized from alcohol.

SUMMARY

1. Improved methods are reported for the preparation of β-acetonaphthone and ω-bromo-β-acetonaphthone.

2. A series of eleven new ω-amino and ω-alkylamino-β-acetonaphthone hydrochlorides has been prepared. The free bases were difficult, and in some cases impossible, to isolate, due to their tendency to undergo self condensation to pyrazines or pyrroles.

3. A series of eleven new 1-β-naphthyl-2-amino (or 2-alkylamino) ethanol hydrochlorides has been prepared from the corresponding keto derivatives by means of catalytic hydrogenation. The free bases were also prepared.

4. The benzoate hydrochlorides of the above aminoalcohols were prepared. The free bases were isolated only in those cases where no hydrogen atoms were attached to nitrogen. When hydrogen was attached to nitrogen, the free bases rearranged at once to the corresponding N-substituted benzamide.

PHILADELPHIA, PA.

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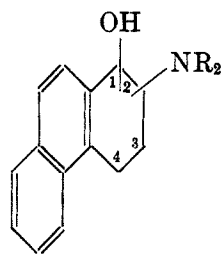
[CONTRIBUTION FROM THE COBB CHEMICAL LABORATORY, UNIVERSITY OF VIRGINIA, AND THE NATIONAL INSTITUTE OF HEALTH]

TETRAHYDROISOQUINOLINO ALCOHOLS DERIVED FROM TETRAHYDRONAPHTHALENE[1]

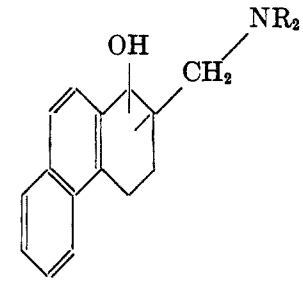
ERICH MOSETTIG AND EVERETTE L. MAY

Received May 31, 1940

Chemical and pharmacological investigations carried out in our laboratories seem to indicate that the phenanthrene nucleus may not be essential in producing a morphine-like, or more specifically, an analgesic action. Several years ago we showed *e.g.* that amino alcohols of the dibenzofuran series exhibit even higher analgesic effects than the corresponding phenanthrylamino alcohols (1, 2). More recently, it was found that this holds true also for the corresponding derivatives of the carbazole series (3, 2). From these results it appears possible that a certain arrangement of the functional groups attached to any ring skeleton of adequate size may bring about the desired physiological effects. Among our phenanthrylamino alcohols, the so-called cyclic amino alcohols of type A and B, and the analogous "3,4 derivatives" (4, 5) were found to be most promising (2), and we decided therefore to synthesize corresponding compounds derived from tetrahydronaphthalene.



Type A



Type B

We employed in these syntheses α-tetralone (I), its methoxy and acetoxy derivatives carrying the substituent in position 6 or 7 (VI, XI), and as

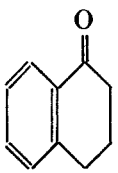
[1] The work reported in this paper is part of a unification of effort by a number of agencies having responsibility for the solution of the problem of drug addiction. The organizations taking part are: The Rockefeller Foundation, the National Research Council, the U. S. Public Health Service, the U. S. Bureau of Narcotics, the University of Virginia, and the University of Michigan. Publication authorized by the Surgeon General U. S. P. H. S.

basic components, tetrahydroisoquinoline and 6-methoxytetrahydroisoquinoline. The amino ketones, except VII-b, were prepared according to the method of Mannich, Borkowsky, and Wan Ho Lin (6), employing aqueous formaldehyde, which proved to be superior to the Mannich procedure with paraformaldehyde (7)[2]. In two instances, namely in the preparation of XII-b and XIII-b, a yellow, crystalline, non-basic by-product was isolated. It probably was formed by the condensation of two moles of the cyclic ketone with two moles of formaldehyde. It was impossible to effect condensation of β-tetralone, formaldehyde, and tetrahydroisoquinoline by either of the above-mentioned Mannich procedures. Almost immediately a viscous resin-like substance was formed, and the secondary amine was recovered unchanged.

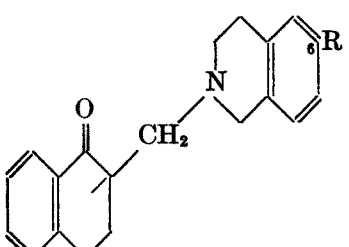
The catalytic reduction of the amino ketones to the corresponding amino alcohols did not offer any particular difficulties. The hydrochlorides, dissolved or suspended in aqueous ethanol, usually absorbed ten to twenty per cent in excess of the calculated amount of hydrogen, the reduction coming to a standstill at this point. In accordance with our previous analogous experiments only one of the two possible diastereoisomeric amino alcohols was obtained. When the catalytic reduction of the amino ketones II and XII-b in the form of base was attempted, hydrogenolysis took place, with the formation of tetrahydroisoquinoline and the respective α-tetralone derivatives. The tendency of the amino alcohols IX-a and X-b to lose the elements of water with the formation of an alicyclic double bond, when dissolved in alcoholic hydrogen chloride, is noteworthy. Amino alcohol X-a was stable in alcoholic hydrogen chloride, but lost a molecule of water when dissolved in a mixture of pyridine and acetic anhydride. The resulting dihydronaphthalene derivatives (from IX-a and X-b) absorbed *two* moles of hydrogen rapidly in the catalytic reduction, yielding by hydrogenolysis 2-methyltetralines and tetrahydroisoquinoline derivatives.

Of amino alcohols having the basic group attached directly to the tetrahydronaphthalene nucleus, only the simplest member, namely XVII, could be prepared by exchange of the bromine atom of XVI with the tetrahydroisoquinolino group. Since, in the formation of XVII, the addition of tetrahydroisoquinoline to an intermediate ethylene oxide

[2] We believe that we can safely exclude the possibility that the tetrahydroisoquinolinomethyl group $RC_9H_9NCH_2$- has entered a position of the unsaturated benzene nucleus of the methoxy- or acetoxy-α-tetralones (*cf.* Auwers and Dombrowski, 8). In order to support this view, we attempted to condense 1- and 2-methoxy-naphthalene with formaldehyde (and paraformaldehyde) and tetrahydroisoquinoline under the conditions imposed in the syntheses of the amino ketones. We recovered practically the whole amount of methoxynaphthalenes unchanged.

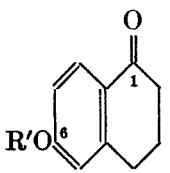


I.

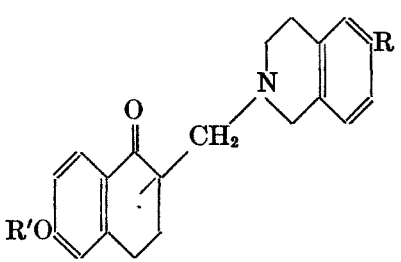


II. R = H

III. R = OCH_3

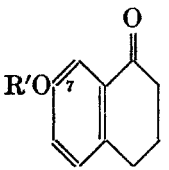


VI.
a R′ = H
b R′ = CH_3
c R′ = $COCH_3$

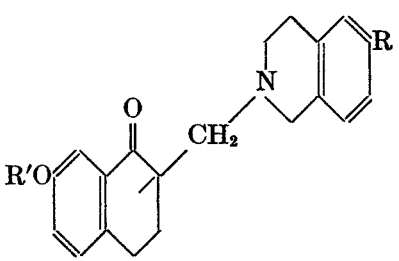


VII.
a R′ = H, R = H
b R′ = CH_3, R = H
c R′ = $COCH_3$, R = H

VIII.
b R′ = CH_3, R = OCH_3
c R′ = $COCH_3$, R = OCH_3



XI.
a R′ = H
b R′ = CH_3
c R′ = $COCH_3$



XII.
b R′ = CH_3, R = H
c R′ = $COCH_3$, R = H

XIII.
b R′ = CH_3, R = OCH_3
c R′ = $COCH_3$, R = OCH_3

IV. R = H

V. R = OCH_3

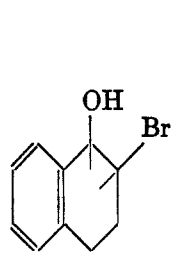
IX.
a R′ = H, R = H
b R′ = CH_3, R = H
c R′ = $COCH_3$, R = H

X.
a R′ = H, R = OCH_3
b R′ = CH_3, R = OCH_3
c R′ = $COCH_3$, R = OCH_3

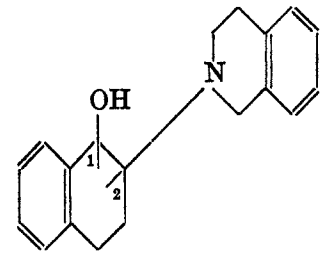
XIV.
a R′ = H, R = H
b R′ = CH_3, R = H
c R′ = $COCH_3$, R = H

XV.
a R′ = H, R = OCH_3
b R′ = CH_3, R = OCH_3
c R′ = $COCH_3$, R = OCH_3

derivative may be involved, a structural formula with the substituents occupying the inverted positions (the hydroxyl in position 2 and the basic group in position 1) must also be taken into consideration (9). Attempts to prepare other amino alcohols of this type *via* the corresponding amino ketones were unsuccessful. The oily 2-bromo-1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene was quite unstable. When it was brought into reaction with tetrahydroisoquinoline in dry ether, a mixture resulted which soon became dark red, and no homogeneous or crystalline products could be isolated. The isomeric 7-methoxybromo ketone is a crystalline compound of moderate stability in the atmosphere, but when mixed in ethereal or benzene solutions with bases, it seemed to lose hydrogen bromide readily, and the desired exchange of the bromine with the tetrahydroisoquinolino group could not be effected.



XVI.



XVII. (?)

The tetrahydroisoquinolino alcohols IV, V, IX-a, IX-b, X-a, X-b, XIV-a, XIV-b, XV-a, XV-b, and XVII were investigated pharmacologically by Dr. Eddy at the University of Michigan (10). All of the group except X-a and XVII are very convulsant and toxic, and sub-convulsant doses produced little or no analgesic effect. Coincidentally with convulsions, sensibility was reduced. Compound XVII had little effect of any kind. Compound X-a showed a brief analgesic effect at 75 mg. per kg., and was not convulsant up to 100 mg. per kg. All members of this group were emetic, and although this effect varied considerably, no relationship between it and any structural characteristics was apparent. In spite of the marked convulsant action and the absence of a definite quieting effect, a moderate fall in body temperature followed the administration of each compound of the group except XVII.

EXPERIMENTAL

1-Keto-1,2,3,4-tetrahydronaphthalene (I) was prepared according to Martin and Fieser (11). The Clemmensen reduction of β-benzoylpropionic acid (12) was carried out according to Martin (13).

1-Keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (VI-b) was prepared according to Robinson and Schlittler (14).

1-Keto-6-hydroxy-1,2,3,4-tetrahydronaphthalene (VI-a). The above compound was demethylated according to Haberland (15); yield of hydroxy ketone, 65%.

1-Keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene (VI-c). A mixture of 6.5 g. of ketone VI-a, 15 cc. of pyridine, and 10 cc. of acetic anhydride was allowed to stand for twenty-four hours at room temperature. The solvent was evaporated in a vacuum and the crystalline residue was recrystallized from dilute ethanol; colorless stout prisms, m.p. 61–62° (corr.), yield 92%. The analytical sample was purified by sublimation.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93.
Found: C, 70.04; H, 6.14.

1-Keto-7-methoxy-1,2,3,4-tetrahydronaphthalene (XI-b) was prepared according to Haworth and Sheldrick (16). The reduction of β-(4-methoxybenzoyl)propionic acid was carried out according to Martin (13).

1-Keto-7-hydroxy-1,2,3,4-tetrahydronaphthalene (XI-a). Five grams of XI-b was dissolved in a mixture of 25 cc. of glacial acetic acid and 50 cc. of 48% aqueous hydrobromic acid. The solution was boiled for two hours and poured into cold water. The precipitate was filtered and dissolved in dilute sodium hydroxide, avoiding an excess. The solution was decolorized with carbon, filtered, and the hydroxy ketone was precipitated with dilute hydrochloric acid. It was recrystallized from dilute ethanol, yield 70%. The compound sublimed readily in an oil-pump vacuum; m.p. 162–164° (corr.).

Anal. Calc'd for $C_{10}H_{10}O_2$: C, 74.04; H, 6.21.
Found: C, 73.67; H, 6.10.

1-Keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene (XI-c). This compound was prepared like its isomer, VI-c. It crystallized from dilute alcohol in colorless rectangular prisms, m.p. 79–80° (corr.), and could be readily sublimed.

Anal. Calc'd for $C_{12}H_{12}O_3$: C, 70.57; H, 5.93.
Found: C, 70.42; H, 6.06.

2-Bromo-1-keto-7-methoxy-1,2,3,4-tetrahydronaphthalene. To an ethereal solution of 2 g. of XI-b was added rapidly 2 g. of bromine in 10 cc. of dry ether. The reaction-mixture became colorless almost immediately. The ethereal solution was washed with water and dried. The oily residue left on evaporation soon became crystalline, and was purified by recrystallization from 80% ethanol; colorless leaflets, m.p. 78–80° (corr.), yield 72%. The substance is highly lachrimative, and irritating to the skin.

Anal. Calc'd for $C_{11}H_{11}BrO_2$: C, 51.78; H, 4.35.
Found: C, 51.27; H, 4.27.

Attempts to exchange the bromine atom with the tetrahydroisoquinolino or piperidino group were unsuccessful.

6-Methoxy-1,2,3,4-tetrahydroisoquinoline was prepared according to Helfer (17), without, however, isolating the formaldehyde condensation-product of β-(*m*-methoxyphenyl)ethylamine. The hydrochloride melted at 233–234°.

Amino ketones and Amino alcohols

1-Keto-2-[(1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1,2,3,4-tetrahydronaphthalene (II). A mixture of 5 g. of α-tetralone (I), 4 g. (1.2 molecular equivalents) of 30% aqueous formaldehyde solution, and 6.1 g. (1.05 molecular equivalents) of tetrahydroisoquinoline hydrochloride was heated for one-half hour on the steam-bath in an atmosphere of nitrogen (mechanical stirring). The resulting brown, viscous mass was dissolved in water, and the solution was extracted with ether. The amino ketone was liberated by addition of ammonia to the aqueous layer, and was ex-

tracted with ether. The oily residue from the ethereal solution became crystalline (7.4 g., m.p. 86–91°) on treatment with 95% ethanol. It crystallized from 95% ethanol in the form of large rhombic plates of m.p. 90–91° (corr.), yield 6.6 g. (66%).

Anal. Calc'd for $C_{20}H_{21}NO$: N, 4.81. Found: N, 5.01.

The *picrate* was formed by mixing the components in warm ethanolic solution. It crystallized from ethanol in yellow rectangular prisms that softened at 86° and melted at 118–120°.

Anal. Calc'd for $C_{26}H_{24}N_4O_8$: N, 10.77. Found: N, 10.51.

1 - Hydroxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4 - tetrahydronaphthalene (IV). Catalytic reduction of base II. A mixture of one part of II (1–5 g.) and one-twentieth part of platinum oxide in thirty parts of absolute ethanol absorbed fairly rapidly 1.25 molecular equivalents of hydrogen. The catalyst was filtered, the solvent evaporated, and aqueous dilute hydrochloric acid was added to the oily residue, whereby a part remained undissolved. This non-basic product was extracted with ether and distilled in an oil-pump vacuum. It gave readily a semicarbazone (of 1-keto-2-methyl-1,2,3,4-tetrahydronaphthalene), which crystallized from 95% ethanol in plates melting at 198–200°.

Anal. Calc'd for $C_{12}H_{15}N_3O$: N, 19.35. Found: N, 19.41.

From the aqueous acid layer pure tetrahydroisoquinoline was obtained by making the solution alkaline and extracting it with ether. It was characterized as the hydrochloride (m.p. 196–198°). The mixture melting point with an authentic sample gave no depression. The ketone (as semicarbazone) was obtained in a yield of approximately 50%. The tetrahydroisoquinoline was formed nearly quantitatively.

Catalytic reduction of the hydrochloride of II. This salt proved to be hygroscopic, and could be obtained crystalline but once. Therefore the following procedure was adopted: Two grams of the amino ketone was dissolved in dilute ethanolic hydrogen chloride, and the solvent and excess of hydrogen chloride were removed in a vacuum desiccator over calcium chloride and potassium hydroxide. The amorphous solid was hydrogenated in 80 cc. of 95% ethanol with 0.1 g. of platinum oxide. The hydrogen absorption proceeded slowly, and usually it was necessary to add new catalyst. As a rule, about 1.5 moles of hydrogen was absorbed. The amino alcohol hydrochloride crystallized from an absolute ethanol-acetone-ether mixture in colorless small leaflets that melted with decomposition at 202–203°; yield, 0.9 g., 44%.

Anal. Calc'd for $C_{20}H_{24}ClNO$: C, 72.81; H, 7.33; Cl, 10.75.
Found: C, 73.19; H, 6.95; Cl, 10.81.

The *base* crystallized from 95% ethanol in colorless prisms of m.p. 94.5–95° (corr.).

Anal. Calc'd for $C_{20}H_{23}NO$: C, 81.87; H, 7.90.
Found: C, 82.10; H, 7.59.

1 - Keto - 2 - [(6 - methoxy - 1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4 - tetrahydronaphthalene (III). This amino ketone was prepared like amino ketone II but the time of heating was extended to 40 minutes, and 20% aqueous formaldehyde solution was employed. Four grams of α-tetralone (I), 5 g. of formaldehyde solution, and 5.7 g. of 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride gave 6 g. (68% yield) of amino ketone of m.p. 95°. It was converted to the hydrochloride in acetone solution. The salt crystallized from an ethanol-ether mixture in the form of glittering leaflets with a buff tint. These softened at 146° and melted with decomposition at 219–221°.

Anal. Calc'd for $C_{21}H_{24}ClNO_2$: N, 3.91. Found: N, 3.83.

1 - Hydroxy - 2 - [(6 - methoxy - 1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4-tetrahydronaphthalene (V). Four and five-tenths grams of the hydrochloride of

amino ketone III with 0.15 g. of platinum oxide in 140 cc. of 95% ethanol absorbed the required amount of hydrogen in six to ten hours. The resulting hydrochloride of the amino alcohol was converted to the base, the latter was extracted with ether and reconverted to the hydrochloride; m.p. 182.5–184°, yield, 3.4 g. (75%). It crystallized from absolute ethanol in colorless leaflets of m.p. 185–186°.

Anal. Calc'd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28.
Found: C, 69.96; H, 6.96.

The *amino alcohol* crystallized from 95% ethanol in the form of prisms of m.p. 95.5–96° (corr.).

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.79.
Found: C, 77.72; H, 7.86.

1 - Keto - 6 - methoxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4 - tetrahydronaphthalene (VII-b). A mixture of 5 g. of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene (VI-b), 2.2 g. of paraformaldehyde, 5.2 g. of tetrahydroisoquinoline hydrochloride, and 25 cc. of isoamyl alcohol was rapidly heated to boiling. The solution was kept boiling under reflux for eight minutes. A few drops of alcoholic hydrogen chloride was added in order to depolymerize the excess of paraformaldehyde. The cooled solution was diluted with water and non-basic material was extracted with ether. The aqueous layer was made ammoniacal and was again extracted with ether. The oily ethereal residue was dissolved in the minimum amount of alcoholic hydrogen chloride. By slow alternate additions of ether and acetone, the amino ketone hydrochloride was obtained in crystalline form (7.4 g., m.p. 142–145°). It crystallized from absolute ethanol in small, colorless leaflets and melted at 146–147°; yield, 6.3 g. (63%).

Anal. Calc'd for $C_{21}H_{24}ClNO_2$: N, 3.91. Found: N, 4.14.

1 - Hydroxy - 6 - methoxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4-tetrahydronaphthalene (IX-b). Six grams of the hydrochloride of amino ketone VII-b with 0.25 g. of platinum oxide in 240 cc. of absolute ethanol was hydrogenated until the absorption came to a standstill (in some experiments 0.05 g. of platinum oxide was added in order to bring the reduction to completion). The amino alcohol hydrochloride separated as a white, finely divided precipitate as the reduction proceeded. Ten to twenty per cent in excess of the calculated amount of hydrogen was absorbed. Water was added to the reduction-mixture in order to dissolve the hydrochloride, the solution was filtered, and the alcohol was removed in a vacuum. The base was liberated and extracted with ether. The ethereal solution left on evaporation an oily base. By dissolving this in alcoholic hydrogen chloride, and carefully adding acetone and ether, the hydrochloride was obtained crystalline in a yield of 70% (4.2 g.), and usually needed no further purification. Purification is more conveniently accomplished through the base than by recrystallization of the salt from an ethanol-acetone-ether mixture. The hydrochloride consisted of tiny felted needles that melted with decomposition at 178–179°.

Anal. Calc'd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28.
Found: C, 69.71; H, 7.43.

The oily *base* became crystalline after some time, and crystallized from 95% ethanol in white plates, m.p. 125.5–126° (corr.).

Anal. Calc'd for $C_{21}H_{25}NO_2$: C, 77.98; H, 7.80; N, 4.33.
Found: C, 77.52; H, 7.71; N, 4.43.

1 - Keto - 6 - methoxy - 2 - [(6 - methoxy - 1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] 1,2,3,4-tetrahydronaphthalene (VIII-b). This compound was prepared like amino ketone III. Three grams of 1-keto-6-methoxy-1,2,3,4-tetrahydronaphthalene

(VI-b), 3 g. of 20% formaldehyde, and 3.8 g. of 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride gave 5.8 g. (88% yield) of amino ketone hydrochloride melting at 126–127°. It crystallized from an absolute ethanol-ether mixture in colorless warts which melted at 127–128°, evolved gas at 160°, resolidified and melted again at 218° with decomposition.

Anal. Calc'd for $C_{22}H_{26}ClNO_3$: N, 3.61. Found: N, 3.44.

The base was oily.

1 - Hydroxy - 6 - methoxy - 2 - [(6 - methoxy - 1,2,3,4 - tetrahydro - 2 - isoquinolyl) - methyl]-1,2,3,4-tetrahydronaphthalene (X-b). Four grams of the hydrochloride of amino ketone VIII-b and 0.15 g. of platinum oxide in 160 cc. of 95% ethanol absorbed ten to twenty per cent in excess of the calculated amount of hydrogen in four to eight hours. The solution was filtered and the solvent evaporated in a water-pump vacuum. The oily hydrochloride was dissolved in a small amount of water, and the base was precipitated with aqueous ammonia. On addition of ether, the base became crystalline. It was filtered and recrystallized from 80% ethanol; tiny felted needles, m.p. 124.5–125° (corr.), yield, 2.5 g. (69%). Sublimation in an oil-pump vacuum at 100–110° did not change the melting point.

Anal. Calc'd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70.
Found: C, 74.77; H, 7.90.

In the attempt to reconvert the base to its hydrochloride by adding ethanolic hydrogen chloride to the acetone solution of the base at room temperature, the amino alcohol lost the elements of one molecule of water. It was converted thereby presumably into *6-methoxy-2-[(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-3,4-dihydronaphthalene hydrochloride.* This crystallized from absolute ethanol in fern-like leaflets melting at 201–202.5°.

Anal. Calc'd for $C_{22}H_{26}ClNO_2$: Cl, 9.53. Found: Cl, 9.92.

The base is decidedly more soluble in ether and less soluble in ethanol than the amino alcohol X-b. It crystallized from 95% ethanol in the form of glittering white leaflets, and melted at 135.5–136° (corr.).

Anal. Calc'd for $C_{22}H_{25}NO_2$: C, 78.77; H, 7.52.
Found: C, 78.29; H, 7.39.

In an attempt to acetylate the amino alcohol X-b in the usual manner (in pyridine solution with acetic anhydride) the same anhydro compound of m.p. 135.5–136° was obtained.

When the hydrochloride of the above base was reduced catalytically (platinum oxide, ethanol), two moles of hydrogen was absorbed. A basic and a non-basic product were separated from the reaction-mixture. The base (yield 75%) could be identified, in the form of its hydrochloride, as 6-methoxytetrahydroisoquinoline (melting point, and mixture melting point with an authentic sample). The non-basic reduction-product, an oil, was purified by distillation in an oil-pump vacuum. It had a fruity odor and was considered to be 6-methoxy-2-methyl-1,2,3,4-tetrahydronaphthalene.

Anal. Calc'd for $C_{12}H_{16}O$: C, 81.78; H, 9.15.
Found: C, 81.44; H, 9.04.

1 - Keto - 6 - acetoxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4 - tetrahydronaphthalene (VII-c). Three grams of 1-keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene (VI-c), 2.75 g. of tetrahydroisoquinoline hydrochloride, and 2.7 g. of 20% formaldehyde were heated on the steam-bath for 15 to 20 minutes in an atmosphere of nitrogen (mechanical stirring). The mixture became homogeneous after five minutes, whereupon it turned increasingly viscous. The crude, semi-solid

amino ketone hydrochloride was dissolved in acetone, from which it crystallized immediately in a pure state (yield, 81%). The salt crystallized from absolute ethanol in colorless needles melting at 151–152°.

Anal. Calc'd for $C_{22}H_{24}ClNO_3$: N, 3.63. Found: N, 3.65.

1 - Keto - 6 - hydroxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 1,2,3,4 - tetrahydronaphthalene (VII-a). Four grams of the hydrochloride of VII-c was boiled in 40 cc. of 8% methanolic potassium hydroxide for three minutes. The precipitated potassium salt was brought into solution by addition of water, and the base was obtained in crystalline form (80% yield) by adding aqueous ammonium chloride dropwise to the solution. The base crystallized from 95% ethanol in colorless leaflets which melted with decomposition at 156–157°.

Anal. Calc'd for $C_{20}H_{21}NO_2$: N, 4.56. Found: N, 4.47.

The *hydrochloride* was obtained by adding ethanolic hydrogen chloride to an acetone solution of the base. It crystallized from absolute ethanol in long needles, m.p. 158–160° (decomp.).

Anal. Calc'd for $C_{20}H_{22}ClNO_2$: N, 4.07. Found: N, 4.23.

1 - Hydroxy - 6 - acetoxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl) methyl] - 1,2,3,4- tetrahydronaphthalene (IX-c). Two grams of the hydrochloride of amino ketone VII-c and 0.15 g. of platinum oxide in 150 cc. of 95% ethanol absorbed the required amount of hydrogen in approximately ten hours. By dissolving the oily reduction-product (freed of catalyst) in acetone and allowing it to crystallize, 1.7 g. (84%) of crystalline hydrochloride, melting at 189–192.5° with decomposition was obtained. It crystallized from an absolute ethanol-ether mixture in the form of small white leaflets, m.p. 194.5–195.5° (decomp.).

Anal. Calc'd for $C_{22}H_{26}ClNO_3$: Cl, 9.14. Found: Cl, 9.41.

1,6 - Dihydroxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl) methyl] - 1,2,3,4- tetrahydronaphthalene (IX-a). A suspension of 2.4 g. of the hydrochloride of VII-a and 0.15 g. of platinum oxide in 200 cc. of 90% ethanol absorbed ten per cent in excess of the calculated amount of hydrogen in 18 hours. The reduction was interrupted, and the oily hydrochloride, after removal of the catalyst and evaporation of the solvent, was dissolved in a small volume of absolute ethanol, from which it crystallized gradually (yield, 1.55 g., 65%). It consisted of leaflets which melted at 105–107° with gas evolution, resolidified and melted again at 190–196° with decomposition. The mother liquor of this hydrochloride yielded, by addition of ether, 0.2 g. of starting material.

Anal. Calc'd for $C_{20}H_{24}ClNO_2 + 0.5\ H_2O$: C, 67.68; H, 7.06; H_2O, 2.54.
Found: C, 67.09; H, 7.10; H_2O, 4.51.

The high value of the water analysis may be accounted for by assuming that under the conditions of the determination of water of hydration (nine hours at 90–100° in a water-pump vacuum) the alcoholic hydroxyl was partially eliminated in the form of water.

The *amino alcohol*, obtained by dissolving the hydrochloride in dilute potassium hydroxide and adding ammonium chloride to the solution, crystallized from 80% methanol in large colorless needles and melted unsharply at 111–121° with evolution of gas.

Anal. Calc'd for $C_{20}H_{23}NO_2 + H_2O$: C, 73.37; H, 7.70.
Found: C, 72.92, 72.85; H, 7.42, 7.47.

In an attempt to determine the water of hydration, the compound was dried in an oil-pump vacuum, but it began to darken at 70–80°, and changed gradually to a dark brown oil.

6 - Hydroxy - 2 - [(1,2,3,4 - tetrahydro - 2 - isoquinolyl)methyl] - 3,4 - dihydronaphthalene. When the amino alcohol IX-c was saponified in methanolic potassium hydroxide solution, as described above in an analogous experiment, the phenolic amino alcohol of 114–120° (decomp.), obviously identical with the base IX-a described in the preceding paragraph, was obtained in nearly quantitative yield. In the attempt to prepare the hydrochloride of this compound by addition of alcoholic hydrogen chloride to its alcoholic solution, a crystalline hydrochloride was obtained that melted at 156–164° with gas evolution. Assuming (from analytical data) that elimination of the alcoholic hydroxyl group had taken place, but perhaps not gone to completion, the product was boiled for five minutes with a solution of 25% methanolic hydrogen chloride. A hydrochloride, which by analysis was shown to lack the elements of one molecule of water, was obtained in the form of triangular prisms melting at 187–188° (decomp.).

Anal. Calc'd for $C_{20}H_{22}ClNO$: C, 73.25; H, 6.76; Cl, 10.81.
Found: C, 72.74; H, 6.66; Cl, 10.36.
(Calc'd for $C_{20}H_{24}ClNO_2$: C, 69.44; H, 6.99.)

When this hydrochloride was recrystallized from methanol a compound was obtained that consisted of white needles, and melted at 126–128.5° with gas evolution. It apparently contained a molecule of methanol of crystallization.

Anal. Calc'd for $C_{20}H_{22}ClNO + CH_3OH$: C, 70.08; H, 7.28.
Found: C, 70.21, 70.28; H, 7.26, 7.05.

The hydrochloride of m.p. 126–128.5° could be reconverted to the hydrochloride of m.p. 187–188° by boiling with methanolic hydrogen chloride. When it was recrystallized from absolute ethanol it consisted of triangular prisms and needles.

Acetyl derivative. The hydrochloride of m.p. 156–164° (from ethanol) was treated with an excess of acetic anhydride in pyridine solution in the usual manner. The resulting hydrochloride crystallized from an absolute ethanol-ether mixture in white clusters, and melted with decomposition at 204–206.5°.

Anal. Calc'd for $C_{22}H_{24}ClNO_2$: Cl, 9.59. Found: Cl, 10.11.

The *dihydro base* itself was obtained either from the hydrochloride of m.p. 156–164° or from the hydrochloride of m.p. 187–188°, or from a mixture of both, by precipitating it from its alkaline solution with ammonium chloride. It crystallized from 95% ethanol in dull, white leaflets melting at 136–137° (corr.).

Anal. Calc'd for $C_{20}H_{21}NO$: N, 4.81. Found: N, 4.65.

By catalytic hydrogenation of the hydrochloride of m.p. 156–164° (0.5 g.) in 95% ethanol (30 cc.) using platinum oxide catalyst (0.025 g.), two moles of hydrogen were absorbed rapidly. The basic reaction-product was identified as tetrahydroisoquinoline hydrochloride of m.p. 194–196°. The non-basic, alkali-soluble reaction-product was purified by sublimation in a vacuum at 80°, and melted at 88–88.5° (corr.).

Anal. Calc'd for $C_{11}H_{14}O$: C, 81.44; H, 8.69.
Found: C, 81.68; H, 8.61.

It was considered to be 6-hydroxy-2-methyl-1,2,3,4-tetrahydronaphthalene.

1-Keto-6-acetoxy-2-[(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (VIII-c). This compound was prepared like the analogous amino ketone VII-c. Three grams of 1-keto-6-acetoxy-1,2,3,4-tetrahydronaphthalene (VI-c), 3 g. of 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride, and 2.5 g. of 20% aqueous formaldehyde were heated for twenty-five minutes, and gave 4.5 g. of amino ketone hydrochloride (74% yield), precipitated in crystalline form from acetone. It crystallized from absolute ethanol in the form of colorless leaflets which softened at 162° and melted at 200–202° with decomposition.

Anal. Calc'd for $C_{23}H_{26}ClNO_4$: N, 3.37. Found: N, 3.61.

1-Hydroxy-6-acetoxy-2- [*(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl*] *-1, 2, 3,4-tetrahydronaphthalene* (X-c). Three grams of the hydrochloride of VIII-c and 0.15 g. of platinum oxide in 100 cc. of 95% ethanol absorbed about 10% less than the required amount of hydrogen in about two hours. The resulting oily hydrochloride was dissolved in acetone, whereby 0.5 g. of a crystalline hydrochloride precipitated immediately. This was found to be 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride (melting point and mixture melting point with an authentic sample). The filtrate was concentrated on the water-bath and allowed to cool. Two and two-tenths grams (73% yield) of the amino alcohol hydrochloride precipitated. It crystallized from an absolute ethanol-ether mixture in the form of small leaflets of m.p. 181.5–183°.

Anal. Calc'd for $C_{23}H_{28}ClNO_4$: Cl, 8.49. Found: Cl, 8.84.

Since in the reduction-mixture no non-basic naphthalene derivatives could be detected, it must be assumed that the 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride did not result from a reductive fission, but must have been present in the sample of amino ketone hydrochloride which was subjected to catalytic reduction, for a slight excess of secondary amine hydrochloride was always used in the preparation of the amino ketone.

1,6-Dihydroxy-2-[*(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl*]*-1, 2, 3, 4-tetrahydronaphthalene* (X-a). The saponification of the hydrochloride of X-c, described above, yielded the phenolic amino alcohol in a yield of 80%. The latter was converted in the usual manner to the hydrochloride, which could be obtained crystalline with difficulty. It crystallized from an absolute ethanol-ether solution in colorless octahedra which melted at 207–208°.

Anal. Calc'd for $C_{21}H_{26}ClNO_3$: C, 67.09; H, 6.97.
Found: C, 67.36; H, 6.56.

The *base* crystallized from 95% ethanol in dull, white leaflets which melted at 145.5–146.5° (corr.).

Anal. Calc'd for $C_{21}H_{25}NO_3$: N, 4.13. Found: N, 4.43.

In an attempt to acetylate the above hydrochloride in pyridine solution with acetic anhydride, the alcoholic hydroxyl group was obviously eliminated, while the phenolic hydroxyl was normally acetylated. The hydrochloride crystallized from absolute ethanol in large white leaflets melting at 203–204.5° with decomposition.

Anal. Calc'd for $C_{23}H_{26}ClNO_3$: C, 69.07; H, 6.55; Cl, 8.87.
Found: C, 68.41; H, 6.84; Cl, 8.95, 8.95.
(Calc'd for the normal diacetyl product $C_{25}H_{30}ClNO_5$: C, 65.26; H, 6.58; Cl, 7.72).

1-Keto-7-methoxy-2-[*(1,2,3,4-tetrahydro-2-isoquinolyl)methyl*]*-1, 2, 3, 4-tetrahydronaphthalene* (XII-b). This compound was prepared like its methoxyl-free analog, the amino ketone II, by employing 9.5 g. of 1-keto-7-methoxy-1,2,3,4-tetrahydronaphthalene (XI-b). The base was purified by one crystallization from 95% ethanol; dull, white hexagonal prisms, m.p. 104–105° (corr.), yield, 13 g. (76%).

Anal. Calc'd for $C_{21}H_{23}NO_2$: OCH_3, 9.65. Found: OCH_3, 9.42.

The hydrochloride became crystalline only after weeks of standing in ethanol. It crystallized from an ethanol-ether mixture in the form of colorless small warts melting at 119–120° (corr.).

Anal. Calc'd for $C_{21}H_{24}ClNO_2$: N, 3.91. Found: N, 3.60.

As by-product in this reaction, a yellow crystalline compound was obtained in yields varying from 5% to 10%. It would not form a semicarbazone under ordinary

conditions. It crystallized from acetone in yellow clusters, and melted at 138–139° (corr.). Analytical data indicated that the compound might have resulted from the condensation of two moles of methoxytetralone with two moles of formaldehyde.

Anal. Calc'd for $2C_{11}H_{12}O_2 + 2CH_2O - 2H_2O = C_{24}H_{24}O_4$: C, 76.57; H, 6.42; M. wt., 376.4.

Found: C, 76.31; H, 6.02; M. wt., 379 (average of 3 micro-Rast determinations).

1-Hydroxy-7-methoxy-2-[(1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XIV-b). Two grams of the hydrochloride of the amino ketone XII-b and 0.1 g. of platinum oxide in 50 cc. of absolute ethanol absorbed one and one-fourth moles of hydrogen. The reduction-mixture yielded 1.4 g. (70%) of pure amino alcohol hydrochloride. It crystallized from absolute ethanol in glittering leaflets, m.p. 207.5–209° (decomp.).

Anal. Calc'd for $C_{21}H_{26}ClNO_2$: C, 70.08; H, 7.28.

Found: C, 69.66; H, 7.56.

The *base* crystallized from 95% ethanol in tiny needles of m.p. 111.5–112° (corr.).

Anal. Calc'd for $C_{21}H_{25}NO_2$: OCH_3, 9.59. Found: OCH_3, 9.19.

The *acetyl derivative* was obtained by dissolving the hydrochloride (0.3 g.) of the amino alcohol in a mixture of 1 cc. of acetic anhydride and 5 cc. of pyridine, and allowing the reaction-mixture to stand for twenty-four hours. The solvent was evaporated in a water-pump vacuum, and the oily residue was dissolved in acetone from which the hydrochloride of the acetyl derivative crystallized eventually in colorless, tiny needles of m.p. 167.5–169.5°. A crystallization from absolute ethanol did not raise the melting point.

Anal. Calc'd for $C_{23}H_{28}ClNO_2$: Cl, 8.82. Found: Cl, 8.95.

When the amino ketone XII-b itself was reduced catalytically, complete reductive fission obviously took place, the tetrahydroisoquinoline being obtained in a nearly quantitative yield (one molecular equivalent).

1-Keto-7-methoxy-2-[(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XIII-b). This compound was prepared like amino ketone III or VIII-b. By employing 4 g. of 7-methoxy-1-keto-1,2,3,4- tetrahydronaphthalene (XI-b), 6 g. of amino ketone hydrochloride (68% yield) was obtained. It crystallized from an absolute ethanol-ether mixture as buff-tinted leaflets that softened at 156° and melted at 220–221° (decomp.). The base was oily.

Anal. Calc'd for $C_{22}H_{26}ClNO_3$: N, 3.61. Found: N, 3.69.

In this experiment the same yellow non-basic compound was isolated as was obtained in the preparation of amino ketone XII-b.

1-Hydroxy-7-methoxy-2-[(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3,4-tetrahydronaphthalene (XV-b). Four grams of the hydrochloride of amino ketone XIII-b and 0.15 g. of platinum oxide in 140 cc. of 95% ethanol absorbed the required amount of hydrogen in seven hours. The amino alcohol, which is sparingly soluble in ether, was obtained from the reduction-mixture like its isomer X-b. It crystallized from 95% ethanol in colorless plates which melted at 135–135.5° (corr.); yield, 2.8 g. (77%). The compound sublimed readily in an oil-pump vacuum at 125°.

Anal. Calc'd for $C_{22}H_{27}NO_3$: C, 74.76; H, 7.70.

Found: C, 74.22, 74.52; H, 7.89, 7.25.

The hydrochloride, prepared in acetone-alcoholic hydrogen chloride, could be obtained only in the form of an amorphous, white, and finely divided precipitate, which could be easily filtered off. It melted without decomposition at 154–163°, and could be reconverted to the pure amino alcohol.

The *picrate* crystallized from 95% ethanol in yellow leaflets, m.p. 150–151.5°.

Anal. Calc'd for $C_{28}H_{30}N_4O_{10}$: C, 57.73; H, 5.19.
Found: C, 57.47; H, 4.78.

The *acetyl derivative* of the amino alcohol was prepared in pyridine with acetic anhydride. Its hydrochloride crystallized from absolute ethanol in short needles, m.p. 182.5–183.5°.

Anal. Calc'd for $C_{24}H_{30}ClNO_4$: Cl, 8.21. Found: Cl, 8.22.

1-Keto-7-acetoxy-2-[(1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XII-c). This amino ketone was prepared like its isomer VII-c, employing 3 g. of 1-keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene (XI-c). The reaction-mixture became entirely solid. The crude hydrochloride was recrystallized from 95% ethanol, whereby it was obtained in colorless leaflets of m.p. 156.5–157.5°; yield, 61%.

Anal. Calc'd for $C_{22}H_{24}ClNO_3$: N, 3.63. Found: N, 3.64.

1-Hydroxy-7-acetoxy-2-[(1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XIV-c). Three grams of the hydrochloride of amino ketone XII-c and 0.1 g. of platinum oxide in 200 cc. of 95% ethanol absorbed one mole of hydrogen in about twenty hours. The catalyst was filtered off and the solvent evaporated in a water-pump vacuum. The remaining oily hydrochloride was dissolved in acetone from which it crystallized almost immediately in a practically pure state; yield, 2.4 g. (80%). It crystallized from an absolute ethanol-ether mixture in trapezoidal plates of m.p. 194–195°.

Anal. Calc'd for $C_{22}H_{26}ClNO_3$: Cl, 9.14. Found: Cl, 9.32.

1,7-Dihydroxy-2-[(1, 2, 3, 4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XIV-a). One and five-tenths grams of the above hydrochloride of XIV-c was boiled for three minutes with 15 cc. of an 8% methanolic potassium hydroxide solution. The phenolic base was precipitated in crystalline form with ammonium chloride. It was dried and converted to the hydrochloride. The salt crystallized from an absolute ethanol-ether mixture as colorless elliptical plates, m.p. 206–207.5° (decomp.); yield nearly quantitative.

Anal. Calc'd for $C_{20}H_{24}ClNO_2$: C, 69.44; H, 6.99.
Found: C, 69.19; H, 6.80.

The base, which was obtained by dissolving the hydrochloride in aqueous potassium hydroxide and adding ammonium chloride, crystallized from 95% ethanol in colorless hexagons of m.p. 205–207° (decomp.).

Anal. Calc'd for $C_{20}H_{23}NO_2$: N, 4.53. Found: N, 4.52.

1-Keto-7-acetoxy-2-[(6-methoxy-1, 2, 3, 4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XIII-c). This compound was prepared like its isomer VIII-c. The mixture of the reactants was heated for thirty minutes. Three grams of 1-keto-7-acetoxy-1,2,3,4-tetrahydronaphthalene (XI-c) gave 3.9 g. (64%) of amino ketone hydrochloride. It crystallized from acetone in colorless leaflets, which softened at 158° and melted with decomposition at 209–211°. A recrystallization from absolute ethanol did not change the melting point of the compound.

Anal. Calc'd for $C_{23}H_{26}ClNO_4$: N, 3.37. Found: N, 3.79.

1-Hydroxy-7-acetoxy-2-[6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XV-c). In the catalytic reduction of the hydrochloride of amino ketone XIII-c (5.8 g.), the same experimental conditions were adhered to, solvent and catalyst being used in the same proportions as in the reduction of the isomeric VIII-c to the amino alcohol X-c. The resulting oily hydrochloride was dissolved in acetone, whereby 1.3 g. of 6-methoxy-1,2,3,4-tetrahydroisoquinoline

hydrochloride precipitated immediately. From the concentrated filtrate, 2.9 g. of the expected amino alcohol hydrochloride crystallized. It was recrystallized from an absolute ethanol-ether mixture; fine, short needles, m.p. 149–160°.

Anal. Calc'd for $C_{23}H_{28}ClNO_4$: Cl, 8.49. Found: Cl, 8.85.

From the mother liquors, 0.9 g. of the phenolic amino alcohol XV-a was recovered by treatment with methanolic potassium hydroxide. Also in this experiment the appearance of the 6-methoxy-1,2,3,4-tetrahydroisoquinoline hydrochloride must be explained by assuming that it was present in the amino ketone hydrochloride subjected to hydrogenation.

1,7-Dihydroxy-2-[(6-methoxy-1,2,3,4-tetrahydro-2-isoquinolyl)methyl]-1, 2, 3, 4-tetrahydronaphthalene (XV-a). The saponification of the acetoxy compound XV-c was carried out as above. The phenolic base was dissolved in the minimum of warm alcohol and when alcoholic hydrogen chloride was added, the hydrochloride precipitated readily in a pure crystalline form (78%). It crystallized from an alcohol-ether mixture in small white plates of m.p. 209°.

Anal. Calc'd for $C_{21}H_{26}ClNO_3$: C, 67.09; H, 6.97.
Found: C, 66.86, 66.72; H, 6.73, 6.73.

The *base* crystallized from 95% ethanol in the form of banana-shaped needles of m.p. 173–174.5° (corr.).

Anal. Calc'd for $C_{21}H_{25}NO_3$: N, 4.13. Found: N, 4.27.

1-Hydroxy-2-(1,2,3,4-tetrahydro-2-isoquinolyl)-1, 2, 3, 4-tetrahydronaphthalene (?) (XVII). To a solution of 5 g. of 2-bromo-1-hydroxy-1,2,3,4-tetrahydronaphthalene (XVI) (18) in 25 cc. of benzene was added 6.5 g. of tetrahydroisoquinoline, and the mixture was boiled under reflux for sixteen to twenty hours. As the reaction proceeded, tetrahydroisoquinoline hydrobromide separated gradually from the solution. The benzene filtrate left on evaporation a brown, viscous oil that solidified slowly. By crystallization from 95% ethanol, 4 g. (66% yield) of an amino alcohol melting at 133–134° was obtained in the form of white, hexagonal prisms. After another recrystallization the compound melted at 133.5–134° (corr.).

Anal. Calc'd for $C_{19}H_{21}NO$: C, 81.67; H, 7.58.
Found: C, 82.02; H, 7.41.

No crystalline hydrochloride or picrate could be obtained.

SUMMARY

The amino alcohol 1-hydroxy-2-[(1,2,3,4-tetrahydro-2-isoquinolyl)-methyl]-1,2,3,4-tetrahydronaphthalene, and various derivatives of it carrying a hydroxyl, or acetoxyl, or methoxyl group in the naphthalene portion, or in the isoquinoline portion, or in both, have been obtained by catalytic reduction of the corresponding amino ketones. The latter were obtained by the Mannich method, condensation of α-tetralone and its proper derivatives with formaldehyde and tetrahydroisoquinoline or 6-methoxytetrahydroisoquinoline.

The lower homologous amino alcohol, 1-hydroxy-(1,2,3,4-tetrahydro-2-isoquinolyl)-1,2,3,4-tetrahydronaphthalene (?) was prepared by exchanging the bromine atom of 2-bromo-1-hydroxytetrahydronaphthalene with tetrahydroisoquinoline.

WASHINGTON, D. C.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. III. PARTIAL OXIDATION OF 3,5,6-TRIOLS AND OXIDATION WITH PERMANGANATE OF 5,6-UNSATURATED STEROIDS[1]

MAXIMILIAN EHRENSTEIN AND MARGUERITE TWADDELL DECKER

Received July 26, 1940

In a preceding publication (1), the transformation of pregnane-20-one-3(β),5,6(*trans*)-triol into pregnane-3,20-dione-5,6(*trans*)-diol 6-monoacetate was discussed. This series of reactions involved the partial saponification of the 3,6-diacetate of the 3,5,6-triol and the subsequent oxidation with chromic acid of the 6-monoacetate. We have been interested in utilizing other methods which lead to the two possible partial oxidation-products of 3,5,6-triols, namely, the corresponding 3-one-5,6-diols or 6-one-3,5-diols. A simple procedure would obviously consist in the partial oxidation by chromic acid of the free 3,5,6-triols. It remains to be shown whether such an oxidation always attacks the same carbon atom preferentially, regardless of the configurations at carbon atoms 3, 5, and 6, or whether the course of this reaction is determined by the stereochemical arrangement at the asymmetric centers mentioned.

Wieland and Dane (2) performed the partial oxidation of hyodesoxycholic acid (3,6-dihydroxycholanic acid) and obtained 3-hydroxy-6-ketocholanic acid. In hyodesoxycholic acid the hydroxyl group at carbon atom 3 possesses the α-configuration and the hydrogen atom at carbon atom 5 is in *cis* position to the methyl group at carbon atom 10. Ellis and Petrow (3) described the partial oxidation of a cholestane-3(β),5,6-(*trans*)-triol (called by these authors "cholestane-3,5,6-triol I") to a cholestane-6-one-3,5-diol. In this triol the hydroxyl group at carbon atom 3 possesses the β-configuration; the hydroxyl group at carbon atom 5 is probably in *trans* position to the methyl group at carbon atom 10 and the hydroxyl groups at carbon atoms 5 and 6 are in *trans* position. In a previous paper (4), androstane-17-one-3(β),5,6(*trans*)-triol (I) was discussed, in which the steric arrangement of the hydroxyl groups at carbon atoms 5 and 6 is probably opposite to that of the cholestane-3,5,6-triol mentioned above; this would imply that the hydroxyl group at carbon

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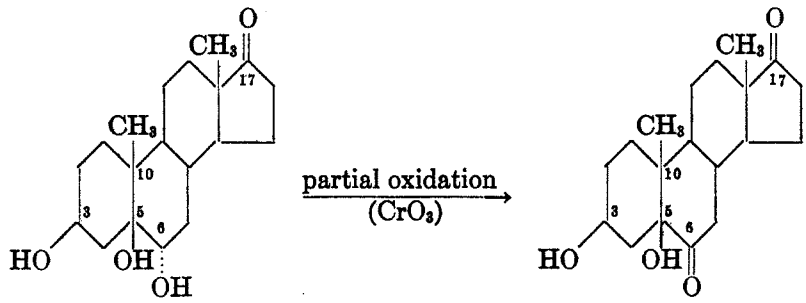
atom 5 and the methyl group at carbon atom 10 are in *cis* position. It was of interest to determine whether the partial oxidation of androstane-17-one-3(β),5,6(*trans*)-triol (I) furnishes also a 6-keto compound, namely, androstane-6,17-dione-3(β),5-diol (II). Experimentally this was shown to be the case. The proof for the chemical structure of the oxidation-product (II) will be discussed below.

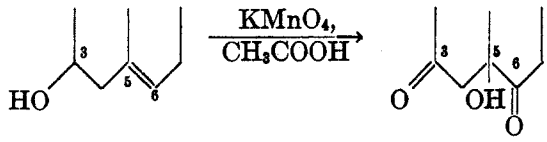


I. Androstane-17-one-3(β),5,6(*trans*)-triol

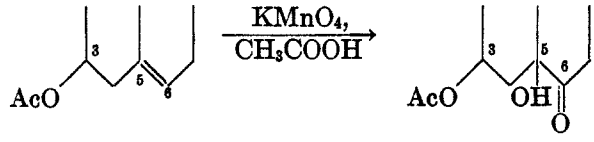
II. Androstane-6,17-dione-3(β),5-diol

In a recent publication, Marker and Rohrmann (5) discussed the action of potassium permanganate in acetic acid on cholesterol and sitosterol compounds. According to their findings, potassium permanganate, which in an alkaline medium merely adds two hydroxyl groups to the 5,6-double bond, carries the oxidation beyond this stage in the medium of acetic acid. If a free sterol is taken, the resulting oxidation-product is a 3,6-dione-5-ol (scheme A). An acetylated sterol furnishes, however, the 3-monoacetate of a 6-one-3,5-diol (scheme B). Our calculations showed that in scheme B, Marker and Rohrmann used an amount of potassium permanganate possessing the oxidation equivalent of 3 gram atoms of oxygen per mole of oxidized substance.

Scheme A

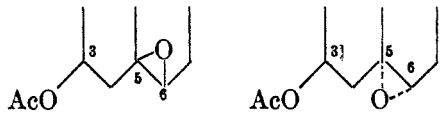


Scheme B



At first glance, it might appear that scheme B represents a simple method for the preparation of a 6-one-3,5-diol, which can otherwise be obtained by a partial oxidation of a 3,5,6-triol. We expected, therefore, that this reaction applied to the acetate of dehydroisoandrosterone (IV) would furnish an androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII). Provided that the previously discussed partial oxidation of androstane-17-one-3(β),5,6(*trans*)-triol (I) had taken place at carbon atom 6, the oxidation-product (II) should be transformable into compound VII by acetylation. Through this series of reactions the structure of compound II might be definitely established.

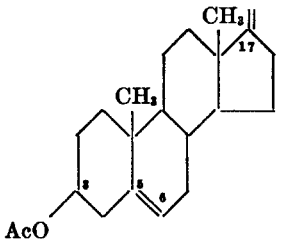
When we subjected the acetate of dehydroisoandrosterone (IV) to an oxidation with potassium permanganate in a solution of acetic acid under conditions analogous to Marker's experiments (amount of permanganate equivalent to 3 gram atoms of oxygen per mole of dehydroisoandrosterone acetate) we were unable to isolate a compound of structure VII. The neutral fraction of the oxidized material was subjected to a separation by chromatographic adsorption. Thereby two isomeric substances (Va and Vb) were obtained, which proved to be oxides of dehydroisoandrosterone acetate. We call the lower-melting (188–190°) isomer α-oxide compound, and the higher-melting (221–222.5°) isomer, β-oxide compound.



α- and β- Oxide Compound
(no definite configuration has been assigned to either stereoisomer)

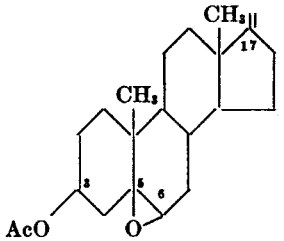
The presence of a compound of structure VII cannot be entirely excluded; appreciable amounts are certainly not present. When the oxide ring of either of the two isolated oxides was ruptured by hydrolysis, two identical substances were obtained (VI). Acetylation of VI furnished the diacetate of androstane-17-one-3(β),5,6(*trans*)-triol (VIII). Because in both oxides the oxygen of the oxide ring must be attached to carbon atoms 5 and 6 in *cis* configuration, the opening of the oxide rings must have been accompanied by an inversion at carbon atoms 5 or 6 respectively. An oxidation of androstane-17-one-3(β),5,6(*trans*)-triol 3-monoacetate (VI) with chromic acid gave androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII), a compound which proved to be identical with the substance obtained by acetylating the material (II) which had been secured by partially oxidizing androstane-17-one-3(β),5,6(*trans*)-triol (I). This transformation proves definitely the structure of compound II.

As is known, the oxidation of 5,6-unsaturated steroids by potassium per-



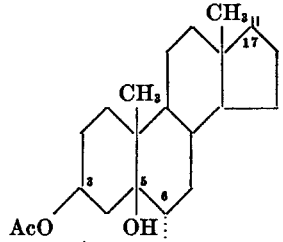
IV. Dehydroisoandrosterone acetate.

$KMnO_4$ (acetic acid)



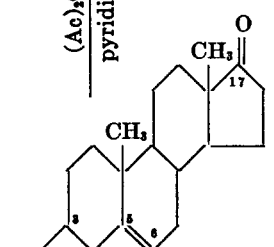
Va. Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate.
Vb. Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate.

$+H_2O$



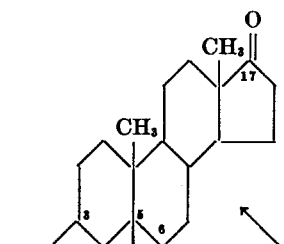
VI. Androstane-17-one-3(β),5,6(*trans*)-triol 3-monoacetate.

$(Ac)_2O$ pyridine



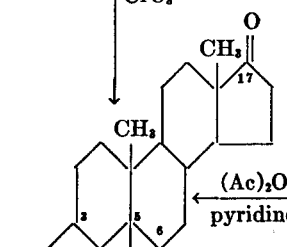
III. Dehydroisoandrosterone.

$(Ac)_2O$



VIII. Androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate.

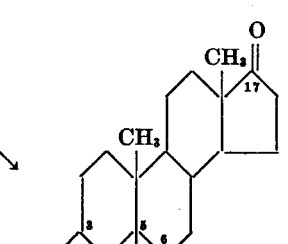
CrO_3



VII. Androstane-6,17-dione-3(β),5-diol 3-monoacetate.

$(Ac)_2O$ pyridine II.

$C_6H_5CO_2H$



IX. Dehydroisoandrosterone oxide.
(Androstane-(5,6)(β)-oxide-17-one-3(β)-ol)

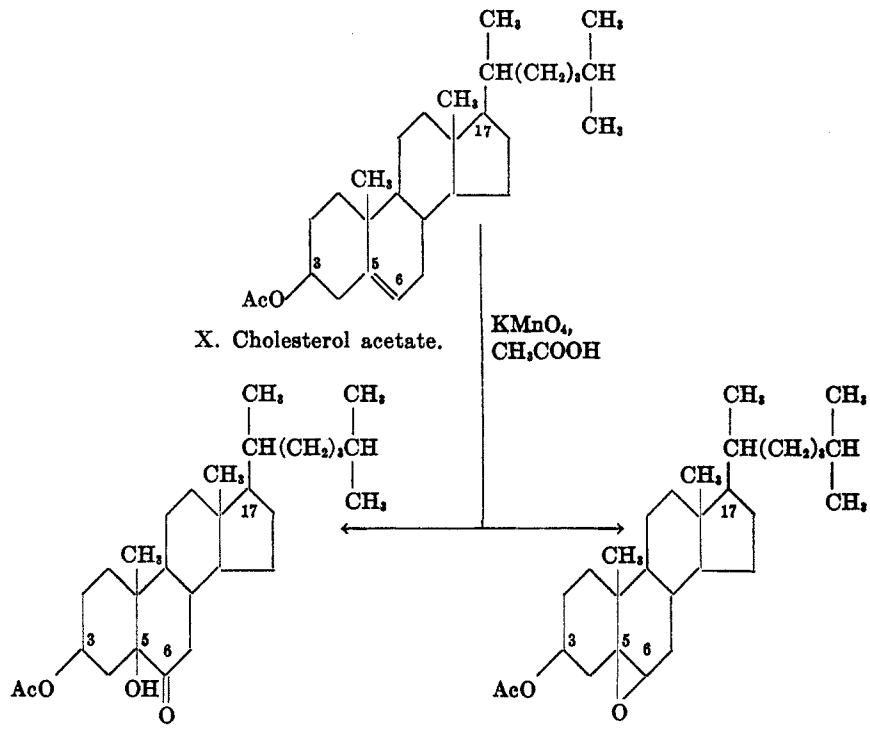
Vb. $(Ac)_2O$

$(Ac)_2O$ I.

manganate in an alkaline medium yields 5,6(*cis*)-diols. There is a possibility that such a diol is formed as an intermediary product in acetic acid and, what is less likely, that in this medium there is a tendency for oxide ring-formation. One may also postulate that a ring-closure can take place under the influence of the aluminum oxide during the procedure of chromatographic adsorption. When androstane-17-one-3(β),5,6(*cis*)-triol was treated under the conditions of the permanganate oxidation in acetic acid but in the absence of potassium permanganate, the unchanged triol was recovered. The unchanged material was also regained after filtering a solution of the triol through an aluminum oxide column.

Ouchakov and Lutenberg (6), as well as Miescher and Fischer (7), treated non-esterified dehydroisoandrosterone (III) with perbenzoic acid and obtained an oxide (IX) with melting points of 227.5–228° and 229–230° respectively. We obtained the same oxide by the prccedure described by Miescher and Fischer. When this compound was acetylated, a substance was obtained which proved to be identical with the higher-melting (β-oxide compound, Vb) of the previously discussed isomeric oxides. In order to give analogous designations to the acetylated and the non-acetylated compounds, we propose to call the compound obtained by the above mentioned authors β-oxide of dehydroisoandrosterone.

The above discussed reactions obtained with dehydroisoandrosterone acetate prompted us to repeat the experiment carried out by Marker and Rohrmann (5) with cholesterol acetate (X). These authors state that cholesterol acetate is oxidized by potassium permanganate in acetic acid to cholestane-6-one-3(β),5-diol 3-monoacetate (XI) (scheme B). No yields of this compound were given. When the neutral fraction of the oxidation was treated with acetone, some crystalline product was obtained which represented about 14% of the weight of the starting material. The melting point indicated that it was largely the substance described by Marker and Rohrmann. For further purification, it was subjected to chromatographic adsorption. By this procedure the cholestane-6-one-3(β),5-diol 3-monoacetate (XI) was secured in a pure form. In addition, a small amount of a substance was obtained which is obviously identical with the acetate of β-cholesterol oxide (XII) (8). It was then decided to investigate the whole non-crystalline material which was contained in the mother liquors. This resin was subjected to chromatographic adsorption, which resulted in several crystalline fractions. A fair amount of the above mentioned acetate of β-cholesterol oxide (XII) was obtained. It can be stated that the total yield of the latter substance is somewhat larger than that of the cholestane-6-one-3,5-diol 3-monoacetate. There was no indication of the presence of the acetate of α-cholesterol oxide, but it may have escaped our notice.

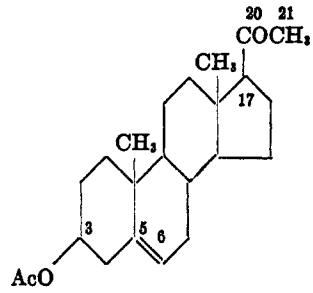


X. Cholesterol acetate.

XI. Cholestane-6-one-3(β),5-diol 3-monoacetate.

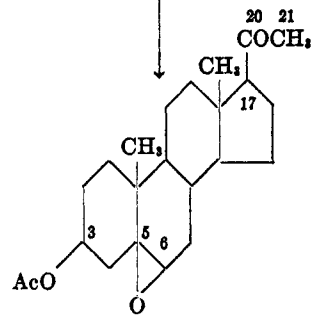
XII. Cholestane-(5,6)(β)-oxide-3(β)-ol acetate.
(Acetate of β-cholesterol oxide)

An orienting experiment was carried out in the pregnane series. When 5-pregnene-20-one-3(β)-ol acetate (XIII) was subjected to an oxidation with potassium permanganate in acetic acid solution, we were able to isolate three different substances in a pure form. The first is doubtless a 5,6-oxide of pregnenonol acetate (XIV); it was obtained from the main fraction of the chromatographic adsorption. The second substance is presumably analogous to the compounds which were isolated by Marker and Rohrmann (5) in the cholestane and sitostane series; hence it represents pregnane-6,20-dione-3(β),5-diol 3-monoacetate (XVI). A small yield of a third compound was obtained which is probably a pregnane-20-one-3(β),5,6-triol 3-monoacetate (XV). By acetylating the latter (XV) a substance was obtained which was not quite pure. It probably represented pregnane-20-one-3(β),5,6(*cis*) 3,6-diacetate which was described in an earlier paper (1). A mixture with an authentic specimen did not give a depression of the melting point. We may therefore suppose that

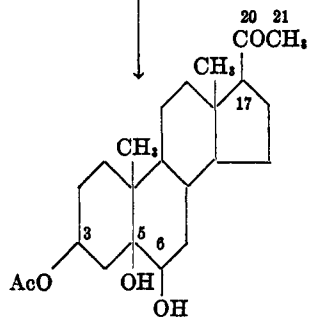


XIII. 5-Pregnene-20-one-3(β)-ol acetate.

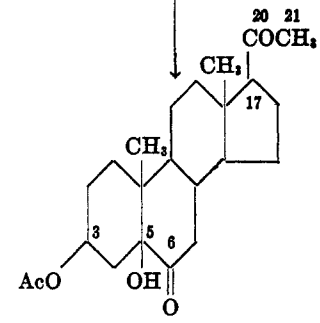
$KMnO_4$,
CH_3COOH



XIV. Pregnane-(5,6)-oxide-20-one-3(β)-ol acetate.



XV. Pregnane-20-one-3(β),5,6-triol 3-monoacetate.



XVI. Pregnane-6,20-dione-3(β),5-diol 3-monoacetate.

compound XV represents the 3-monoacetate of pregnane-20-one-3(β),5,6-(*cis*)-triol.

The observations made on the 5,6-unsaturated steroids discussed above

demonstrate that by the action of potassium permanganate in acetic acid two types of substance result:

1. 5,6-Oxides; the thesis may be advanced that oxygen is directly added to the 5,6-double bond. This may lead to two stereoisomeric oxides. The intermediary formation of 5,6-diols and their subsequent dehydration to 5,6-oxides can be ruled out.

2. 5-Ol-6-ones; it is probable that 5,6-diols are intermediates which, however, because of the excess of permanganate are oxidized to 5-ol-6-ones.

The yields of the possible reaction-products certainly depend on the velocities of the various reactions leading to them. It is probable that these velocities are different depending upon the initial reactant.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company, Pittsburgh, Pa. All microanalyses were carried out by Mr. Lyon Southworth, Harvard University, Cambridge, Mass. The dehydroisoandrosterone and pregnenonol were kindly furnished by Dr. Erwin Schwenk of the Schering Corporation in Bloomfield, N. J.

Androstane-17-one-3(β),5,6(cis)*-triol 3,6-diacetate.* Four hundred milligrams of *cis* triol was refluxed with 4 cc. of acetic anhydride for 1½ hours. After having reached room temperature, the solution was poured into water; the separation of white scales began immediately. The crystalline precipitate was filtered after some standing, washed with water and dried. The yield of crude diacetate was 481 mg. The material was recrystallized from 95% alcohol. The yield of the first crop was 364 mg.; melting point 253–254°; $[\alpha]_D^{26}$ +63.6° (50 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43.
Found: C, 67.93, 67.75; H, 8.36, 8.57.

Androstane-17-one-3(β),5,6(trans)*-triol 3,6-diacetate (VIII) by acetylating the free triol (I).* Four hundred milligrams of triol (I) was refluxed with 4 cc. of acetic anhydride for 1½ hours. After cooling, the solution was poured into water. The oily precipitate became sticky after some standing. By kneading, it assumed a crumbly consistency. It was eventually filtered, washed with water, and dried. Yield: 470 mg. The crude diacetate was dissolved in 95% alcohol; to this solution water was gradually added until the crystallization of needles began. These were filtered after some standing. Yield of first crop: 382 mg.; melting point 214.5–217°. A sample was recrystallized from 95% alcohol for microanalysis. White needles, melting point 216.5–217°; $[\alpha]_D^{26}$ 0.0° (75 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{34}O_6$: C, 67.94; H, 8.43.
Found: C, 68.00, 67.91; H, 8.42, 8.53.

Androstane-6,17-dione-3(β),5-diol (II) by partial oxidation of androstane-17-one-3(β),5,6(trans)*-triol (I).* On a water-bath 200 mg. of pure triol (I) was dissolved in 12 cc. of glacial acetic acid; thereafter 1.8 cc. of water was added. This solution was cooled in an ice-bath and 46 mg. of chromium trioxide (calc'd for 1 atom oxygen: 41.4 mg. CrO_3) dissolved in 3 cc. of 50% acetic acid was added from a microburette over a period of 1½ hours. The mixture was thoroughly agitated after the addition of each drop. Thereafter the solution was kept in the ice-bath for two hours and at room temperature for three more hours. After the addition of 4 cc. of alcohol, the solution was allowed to stand overnight. It was then concentrated *in vacuo* (40–50°)

almost to dryness; to the residue was added some water. After some standing, the white crystalline precipitate was filtered and washed with water; 140 mg. after drying, m.p. 258–264°. By concentrating the mother liquor, 28 mg. more of precipitate could be secured. The combined crude material, 168 mg., was recrystallized from 95% alcohol, whereby several crops, totalling 146 mg. and melting between 270° and 275° were obtained. By recrystallizing these combined crops from acetone, 107 mg. of sparkling crystals, melting between 277° and 280° was obtained. By two more recrystallizations, the melting point was raised to 282–284°. The analysis was performed with samples of two different batches. The substance was very difficultly soluble in the common solvents, hence no optical rotation was determined.

Anal. Calc'd for $C_{19}H_{28}O_4$: C, 71.20; H, 8.81.
Found: C, 71.09, 71.09; H, 9.01, 8.87.

Androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII) by acetylation of the diol (II). On a water-bath 335 mg. of androstane-6,17-dione-3(β),5-diol (II) was dissolved in 2.9 cc. of pyridine. To this solution was added at room temperature 2.9 cc. of acetic anhydride. The mixture was allowed to stand for two days. Then about 20 cc. of water was added, which caused a white crystalline precipitate to appear. It was filtered after two hours and washed with water. The dry weight was 332 mg., the melting point of this crude material was between 180° and 185°. The crude acetate was dissolved in hot alcohol and the solution concentrated to a low volume. While it was still hot, a few drops of water was added, which caused the immediate separation of beautiful white crystals. The crystallization was completed by allowing the mixture to stand in the ice-box over night. After filtering, the dry weight was 245 mg.; the melting point was 190–193°. The material was now taken up in a sufficiently large amount of hot ether. This solution was concentrated to a lower volume and then allowed to stand in the ice-box over night. The first crop of crystals (needles) weighed 84 mg., the melting point was 197–198°. For analysis this material was once more recrystallized from ether, the melting point was practically unchanged (197.5–199°). More material of the same melting point was secured by working up the various mother liquors. The microanalyses were carried out with samples of two different batches. $[\alpha]_D^{28}$ +17.0° (41.8 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{30}O_5$: C, 69.57; H, 8.35.
Found: C, 69.06, 69.10; H, 8.52, 8.64.

Oxidation of dehydroisoandrosterone acetate (IV) by potassium permanganate in acetic acid; preparation of the (5,6)(α)-oxide and of the (5,6)(β)-oxide of dehydroisoandrosterone acetate (Va and Vb). To a solution of 750 mg. of dehydroisoandrosterone acetate (IV) in 94 cc. of glacial acetic acid was added at a temperature of 50°, over a period of thirty minutes, 22.5 cc. of a solution of *N* potassium permanganate (31.6 g. $KMnO_4$ per liter). The reaction-mixture was then kept at a temperature of 50° for thirty more minutes. It was cooled to room temperature, diluted with approximately 360 cc. of water and extracted three times with ample quantities of freshly distilled ether. The combined ether extracts were freed from acid by washing them first with an excess of 2 *N* sodium carbonate solution and finally with water. After drying over sodium sulfate, the ether extract was brought to dryness; 691 mg. of a white residue was obtained. Attempts to recrystallize this residue from a mixture of ether and petroleum ether gave no satisfactory results. Therefore the material was subjected to chromatographic adsorption, for which it was dissolved in 45 cc. of benzene. To this solution 290 cc. of petroleum ether was added. A column (Jena filter tube, with permanently fused-in glass filter disc, No. 15a G 3) of 22 g. of aluminum oxide (aluminium oxide anhydrous, standardized for chromato-

graphic adsorption acc. to Brockmann, E. Merck, Darmstadt) was prepared in the usual way with petroleum ether. The above solution was allowed to drip through this column, and the adsorbed material was eluted with a series of appropriate solvent mixtures (see Table I). Slight suction was applied throughout this process. The solvents were then evaporated and the residues dried in a vacuum desiccator.

The residues of fractions 2–9 were crystalline. In a preliminary experiment it was shown that a fair amount of the balance of the material can be extracted from the aluminum oxide by methanol. The residue of this eluate was an almost colorless glass. The crystalline fractions 2–9 were separately recrystallized from ether.

Androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (Va). The first crops of crystals obtained from fractions 2, 3, and 4 respectively, represented glistening needles melting between 188° and 190°; they consisted of identical material and totalled 114 mg. From the combined mother liquors of fractions 2–4 were secured two more

TABLE I

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)
1	45 cc. benzene + 290 cc. petroleum ether	3.2
2	22 cc. benzene + 145 cc. petroleum ether	26.0
3	35 cc. benzene + 115 cc. petroleum ether	78.1
4	70 cc. benzene + 80 cc. petroleum ether	94.1
5	105 cc. benzene + 35 cc. petroleum ether	55.7
6	150 cc. benzene	57.0
7	150 cc. benzene	24.7
8	105 cc. benzene + 35 cc. ether	46.4
9	70 cc. benzene + 80 cc. ether	51.3
10	35 cc. benzene + 115 cc. ether	4.4
11	150 cc. ether	6.4
12	300 cc. ether	20.8
Total		468.0

crops with the same melting points, totalling 61 mg. The residues 2–4 of the chromatographic treatment consisted therefore of identical and pure material. A solution of the substance in chloroform gave no color with tetranitromethane. $[\alpha]_D^{20}$ +58.4° (50.0 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.
Found: C, 72.53; H, 8.93.

Residue 5 of the chromatographic treatment represented a mixture, as was established by attempts to recrystallize it. It was not further investigated.

Androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (Vb). When the residues 6, 7, and 8 of the chromatographic treatment were separately recrystallized from ether, fair amounts of material melting between 215° and 222° could easily be secured. Residue 6 consisted practically completely of this substance. Only the first crops of the recrystallizations of residues 7 and 8 respectively furnished material melting between 215° and 220°; the mother liquors represented mixtures. The constant melting point of the substance was 221–222.5°. A solution of the substance in

chloroform gave no color with tetranitromethane. $[\alpha]_D^{25}$ +10.0° (20 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{21}H_{30}O_4$: C, 72.78; H, 8.73.
Found: C, 72.57; H, 8.89.

No constant-melting material could be obtained when residue 9 of the chromatographic treatment was subjected to fractional crystallization. All obviously impure fractions from the mother liquors of residues 6, 7, and 8, as well as the whole of residue 9, were combined and subjected to another chromatographic treatment. Excepting a small amount of material melting around 220°, the various fractions consisted of mixtures.

Androstane-17-one-3(β),5,6(trans)-triol 3-monoacetate (VI). A. By hydrolysis of the oxide ring of androstane-(5,6)(α)-oxide-17-one-3(β)-ol acetate (Va). A solution of 80 mg. of the acetate of the α-oxide (m.p. 188–190°) (Va) in 13 cc. of acetone was diluted with 5 cc. of water, and fifteen drops of 10% sulfuric acid was added. This solution was allowed to stand at room temperature for 46 hours. Then 25 cc. of water was added, and the acetone removed *in vacuo*. A white crystalline precipitate was obtained; weight after drying: 46.6 mg. By extracting the aqueous phase with ether, 12.2 mg. of amorphous material was obtained which could not be crystallized. The crystalline precipitate was purified by chromatographic adsorption. For this purpose it was dissolved in 20 cc. of benzene and then 10 cc. of petroleum ether was added. A column (Jena filter tube, with permanently fused-in glass filter disc, No. 12 G 3) of 1.9 g. of aluminum oxide was prepared in the usual way with petroleum ether. The original solution was filtered through the column (fraction 1) and thereafter 10 cc., 15 cc., and 15 cc. of benzene (fractions 2, 3, and 4) respectively. The residues of these first four fractions were traces of resinous material. By eluting with a mixture of 10 cc. of benzene and 5 cc. of ether the main fraction (fraction 5) was obtained which yielded 24.6 mg. of a white crystalline residue. A number of fractions (fractions 6–11) were obtained by eluting with benzene-ether mixtures of increasing ether and decreasing benzene content. Eventually ether alone was taken. The residues of fractions 6–11 were crystalline, and totalled 19.0 mg. All residues were dissolved in comparatively large volumes of ether. By concentrating to lower volumes, beautiful crystals were obtained, which proved to consist of a single substance throughout all fractions. The melting point was 234–235°.

Anal. Calc'd for $C_{21}H_{32}O_5$: C, 69.18; H, 8.85.
Found: C, 69.03; H, 9.03.

B. By hydrolysis of the oxide ring of androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (Vb). A solution of 20 mg. of the acetate of the β-oxide (m.p. 216–220°) (Vb) in 3.5 cc. of acetone was diluted with 1 cc. of water, and four drops of 10% sulfuric acid was added. The mixture was allowed to stand at room temperature for two days and then diluted with 15 cc. of water. On removing part of the acetone *in vacuo*, white crystals (10.0 mg.) settled out, which were recrystallized three times from ether. The melting point of the final material was 231.5–233°. There was no depression of the melting point when the substance was mixed with the substance of m.p. 234–235° described above under caption A.

Androstane-17-one-3(β),5,6(trans)-triol 3,6-diacetate (VIII) by acetylating androstane-17-one-3(β),5,6(trans)-triol 3-monoacetate (VI). A solution of 6.4 mg. of monoacetate (VI obtained from Va) in 0.5 cc. of acetic anhydride was refluxed for 1½ hours. The acetic anhydride was removed *in vacuo* and water was added to the residue. The white precipitate was dissolved by shaking several times with ample quantities of ether. The combined ether phases were washed with *N* sodium carbonate solution and with water. After drying with sodium sulfate, the ether was brought to dryness; the residue was a whitish-yellow film.

Attempts to recrystallize this residue from various solvents were of no avail. Therefore the residue was dissolved in a combination of 1 cc. of ether and 3 cc. of petroleum ether and this solution passed through a column of 0.5 g. of aluminum oxide. The elution was performed with 3 cc. of ether + 0.75 cc. of petroleum ether, 4 cc. of ether, and 4 cc. of ether + 0.1 cc. of methanol, respectively. The major part of the material was found in the last fraction; the residue was 5.4 mg. of a colorless glass. It was recrystallized from alcohol to which a trace of water was added; yield, 2.8 mg. of m.p. 208–210°. Recrystallization from a mixture of ether and petroleum ether raised the melting point to 215–217°. There was no depression of the melting point in mixture with a sample of androstane-17-one-3(β),5,6(*trans*)-triol diacetate (VIII, obtained from I).

Androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII) by oxidation of androstane-17-one-3(β),5,6(trans)*-triol 3-monoacetate (VI).* Twelve milligrams of androstane-17-one-3(β),5,6(*trans*)-triol 3-monoacetate (VI obtained from Va) was dissolved in 2 cc. of glacial acetic acid. To this solution was added 1.2 cc. of a chromic acid solution prepared by dissolving 221 mg. of chromium trioxide in 1 cc. of water and making the volume up to 100 cc. by the addition of glacial acetic acid. One cubic centimeter of the latter solution is the equivalent of one atom of oxygen in this particular oxidation. The reaction-mixture was allowed to stand at room temperature overnight. After addition of 1 cc. of alcohol, the solution was brought almost to dryness *in vacuo*. The addition of some water caused a white crystalline precipitate to appear which was filtered after one-half hour; weight 11.5 mg.; m.p. 186–196°. This crystalline material was dissolved in ether; on concentrating this solution to a small volume and adding petroleum ether, bundles of shining needles appeared; weight 7.5 mg.; m.p. 196–197°; weight after another recrystallization, 6.5 mg.; m.p. 197–198.5°. When this substance was mixed with the acetylation-product of compound II, no depression of the melting point was observed.

Dehydroisoandrosterone oxide (IX) according to the procedures of Miescher and Fischer (7) and Ouchakov and Lutenberg (6); subsequent acetylation to androstane-(5,6)(β)-oxide-17-one-3(β)-ol acetate (Vb). To a solution of 500 mg. of dehydroisoandrosterone (III) in 10 cc. of chloroform was added in the cold-room 24 cc. of a chloroform solution containing 40% excess of perbenzoic acid (335 mg.). The mixture was allowed to stand in the cold-room for 24 hours and thereafter at room temperature for two days. It was then washed with *N* sodium carbonate solution and with water. After drying with sodium sulfate, it was brought to dryness. Because fractional crystallization did not readily furnish the desired substance in a pure form, the residue was subjected to chromatographic adsorption. The procedure employed was similar to that described elsewhere in this paper. The various fractions obtained were recrystallized from ether, and a fair supply of crystals melting at 226–228.5° was obtained. There was an indication of the presence of at least one crystalline by-product.

A solution of 45 mg. of the above oxide melting at 226–228.5° in 2 cc. of acetic anhydride was refluxed for one hour, cooled to room temperature, and 15 cc. of water was added. The crystalline precipitate was filtered after standing overnight. Yield: 45 mg., m.p. 218–220.5°. After recrystallization from ether, 33 mg. of crystals melting at 223–224° was obtained. When mixed with the (5,6)(β)-oxide of dehydroisoandrostane acetate (Vb) described above, there was no depression of the melting point.

Oxidation of cholesterol acetate (X) by potassium permanganate in acetic acid; preparation of cholestane-6-one-3(β),5-diol 3-monoacetate (XI) and of the acetate of β-cholesterol oxide (XII). To a solution of 2.0 g. of cholesterol acetate (X) in 210 cc. of glacial acetic acid was added at a temperature of 50°, over a period of 25 minutes,

50 cc. of *N* potassium permanganate. The mixture was kept at 50° for 30 more minutes. After cooling to room temperature, 1800 cc. of water was added, causing a precipitate to appear. The mixture was extracted four times with ether, and the combined ether phases washed neutral with 4 *N* sodium carbonate solution and water. The ethereal extract was dried with sodium sulfate and then evaporated to dryness; residue: 2.14 g. of a partly crystalline solid mass. The residue was recrystallized from acetone, yielding 0.285 g. of crystalline material melting between 190° and 210°. The mother liquor was brought to dryness and furnished 1.824 g. of a glassy residue. Further recrystallization of the crystalline part from acetone did not yield a sub-

TABLE II

CHROMATOGRAPHIC FRACTIONATION OF CRYSTALLINE PART

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE	M.P., °C.
1	15 cc. benzene + 40 cc. petroleum ether	2.5	Crystalline	
2	15 cc. benzene + 20 cc. petroleum ether	27.7	Glassy and crystalline	
3	20 cc. benzene + 15 cc. petroleum ether	23.9	Crystalline	
4	25 cc. benzene + 10 cc. petroleum ether	31.0	Crystalline	222–225
5	30 cc. benzene + 5 cc. petroleum ether	32.6	Crystalline	226–229
6	35 cc. benzene	27.7	Crystalline	226–228
7	35 cc. benzene	18.5	Crystalline	229–231.5
8	30 cc. benzene + 5 cc. ether	45.0	Crystalline	225–230
9	25 cc. benzene + 10 cc. ether	25.9	Crystalline	200–205
10	30 cc. benzene + 40 cc. ether	8.8	Crystalline	
11	70 cc. ether	1.1	Resinous	
12	30 cc. ether + 5 cc. methanol	20.9	Largely crystalline	
13	35 cc. methanol	6.6	Resinous	
Total		272.2		

stance with a clearly defined melting point. The crystalline material was therefore subjected to chromatographic adsorption, for which it was dissolved in 15 cc. of benzene and 40 cc. of petroleum ether and then filtered through a properly prepared column of 9 g. of aluminum oxide. The adsorbed material was eluted with a series of appropriate solvent mixtures (see Table II).

Cholestane-6-one-3(β),5-diol 3-monacetate (*XI*). Fractions 3–8 furnished by repeated recrystallizations from ether a total of 120 mg. of material melting between 227° and 231°. After crystallization from acetone, the melting point was 226.5–228.5°.

Anal. Calc'd for $C_{29}H_{48}O_4$: C, 75.59; H, 10.51.
Found: C, 75.73; H, 10.69.

Acetate of β-cholesterol oxide (*XII*). The residue of fraction 2 of the above chro-

matographic adsorption was recrystallized from a little 95% alcohol. Two crops, both melting at 114–117° and totalling 16.8 mg., were obtained. When mixed with cholesterol acetate (m.p. 114.5–116°), there was a depression of the melting point of 20°.

Anal. Calc'd for $C_{29}H_{48}O_3$: C, 78.31; H, 10.89.
Found: C, 78.06; H, 11.07.

Non-crystalline part of the oxidized material: The glassy residue (1.824 g.) from the oxidation mentioned above was subjected to chromatographic adsorption for which purpose it was dissolved in 80 cc. of benzene and 240 cc. of petroleum ether; this solution was filtered through a properly prepared column of 54 g. of aluminum oxide. The adsorbed material was eluted as indicated in Table III. No attempt was made to recover from the aluminum oxide the balance of the material.

TABLE III

CHROMATOGRAPHIC FRACTIONATION OF RESINOUS PART

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	80 cc. benzene + 240 cc. petroleum ether	33.7	Crystalline
2	80 cc. benzene + 120 cc. petroleum ether	333.7	Largely crystalline
3	110 cc. benzene + 90 cc. petroleum ether	69.7	Largely crystalline
4	140 cc. benzene + 60 cc. petroleum ether	70.9	Golden resin
5	170 cc. benzene + 30 cc. petroleum ether	86.2	Resinous
6	200 cc. benzene	30.0	Largely crystalline
7	200 cc. benzene	84.5	Largely crystalline
8	170 cc. benzene + 30 cc. ether	183.7	Resinous, trace of crystals
9	140 cc. benzene + 60 cc. ether	98.0	Partly crystalline
10	170 cc. benzene + 240 cc. ether	22.6	Resinous
11	200 cc. ether	6.9	Resinous
12	170 cc. ether + 30 cc. methanol	170.2	Resinous
13	150 cc. methanol	92.0	Mainly resinous
Total		1382.1	

Fractions 1–3 were separately recrystallized from 95% alcohol. Fraction 1 represented obviously a mixture (m.p. between 60° and 75°). From fractions 2 and 3 was obtained an ample supply (294 mg.) of a substance melting at 111–112°, and showing no depression in melting point when mixed with the above described acetate of β-cholesterol oxide (XII). From the mother liquors was secured 44 mg. of somewhat impure material, melting at 100.5–102°.

Attempts to obtain a uniform substance from fractions 6–9 failed. The melting points of the recrystallized material were above 170° and had a very wide range.

Oxidation of 5-pregnene-20-one-3-ol acetate by potassium permanganate in acetic acid; preparation of pregnane-5,6-oxide-20-one-3(β)-ol acetate (XIV), pregnane-6,20-dione-3(β),5-diol 3-monoacetate (XVI), and pregnane-20-one-3(β),5,6-triol 3-monoacetate (XV). To a solution of 1.7 g. of pregnenonol acetate in 226 cc. of glacial acetic acid was added at a temperature of 50°, over a period of 30 minutes, 47.6 cc. of *N* potassium permanganate. The mixture was kept at this temperature for 30

more minutes. After cooling to room temperature, 1800 cc. of water was added, and the solution was extracted four times with ether. The combined ether extracts were washed neutral with 4 *N* sodium carbonate and with water. After drying with sodium sulfate, the ether was brought to dryness. A brittle resinous residue was obtained, weighing 1.366 g. It was subjected to chromatographic adsorption dissolved in a mixture of 65 cc. of benzene and 200 cc. of petroleum ether. This solution was filtered through a properly prepared column of 40 g. of aluminum oxide (acc. to Brockmann). The elution was carried out as indicated in Table IV.

All residues were treated with some ether, as a result of which crystals separated also from fractions 7, 8, and 9. The supernatant ether was decanted after some standing. After a superficial examination of all crystalline residues, it was decided to search for individual substances especially in the crystalline fractions 2, 9, 10, and 12.

TABLE IV

CHROMATOGRAPHIC FRACTIONATION

NO. OF FRACTION	SOLVENT	WEIGHT OF RESIDUE (MG.)	APPEARANCE OF RESIDUE
1	65 cc. benzene + 200 cc. petroleum ether	74.8	Crystalline
2	65 cc. benzene + 95 cc. petroleum ether	408.1	Mainly crystalline
3	90 cc. benzene + 70 cc. petroleum ether	4.9	Resin
4	115 cc. benzene + 45 cc. petroleum ether	1.6	Resin
5	140 cc. benzene + 20 cc. petroleum ether	13.7	Resin
6	160 cc. benzene	49.8	Golden resin
7	160 cc. benzene	51.9	Colorless glass
8	140 cc. benzene + 20 cc. ether	138.9	Colorless glass
9	115 cc. benzene + 45 cc. ether	114.7	Colorless glass
10	130 cc. benzene + 160 cc. ether	72.5	Mostly crystalline
11	160 cc. ether	12.3	Crystalline
12	135 cc. ether + 25 cc. methanol	355.3	Mainly crystalline
13	120 cc. methanol	43.5	Yellow resin; partly crystalline
Total		1342.0	

Pregnane-5,6-oxide-20-one-3(β)-ol acetate (*XIV*). The crystalline fraction 2 (299 mg.) was easily soluble in ether. Recrystallization from a mixture of ether and petroleum ether furnished 143 mg. of big, stout prisms which melted at 163–165°. Renewed crystallization from a mixture of ether and petroleum ether gave beautiful long prisms of the same melting point.

Anal. Calc'd for $C_{23}H_{34}O_4$: C, 73.74; H, 9.16.
Found: C, 73.60; H, 9.35.

Preparation of the oxime: To a solution of 10 mg. of the above described substance in 1 cc. of alcohol was added a concentrated aqueous solution of a mixture of 20 mg. of hydroxylamine hydrochloride and 30 mg. of sodium acetate. After refluxing on a water-bath for 2½ hours, the oxime was precipitated by the addition of water. It was then recrystallized from aqueous alcohol. Yield: 6.9 mg.; melting point, 219–221°.

Pregnane-6,20-dione-3(β),5-diol 3-monoacetate (*XVI*). The crystalline fractions

9 (81 mg.) and 10 (47 mg.) were separately recrystallized from ether. The first crops obtained from both fractions (total: 24 mg.) melted around 220°, and a mixture showed the same melting point. By recrystallizing the combined material from ether the melting point was raised to 222.5–224°. No attempt was made in this instance to secure a quantitative yield of this substance. In a preliminary experiment we had found that a total yield of this compound can be obtained which amounts to about 10% of the weight of the oxidized material.

Anal. Calc'd for $C_{23}H_{34}O_5$: C, 70.72; H, 8.78.
Found: C, 70.48; H, 9.02.

Preparation of the dioxime: To a solution of 10 mg. of the substance described above, in 1 cc. of alcohol, was added a concentrated aqueous solution of a mixture of 20 mg. of hydroxylamine hydrochloride and 30 mg. of sodium acetate. After refluxing on a water-bath for 100 minutes, water was added to this solution until a white precipitate appeared. The crude oxime was recrystallized from aqueous alcohol. Yield: 6.3 mg., melting point, 262–264° (decomp.).

Pregnane-20-one-3(β),5,6-triol 3-monoacetate (XV). Fraction 12 (232 mg) contained a substance which was rather insoluble in ether. The whole of fraction 12 was dissolved in a large volume of ether, which was then concentrated to a somewhat lower volume. A yield of 51.4 mg. of a crystalline powder was obtained; the melting point was 222–226°. An additional recrystallization from ether raised the melting point to 226–228°. When mixed with the substance obtained from fractions 9 and 10 (m.p. 222.5–224°) there was a marked depression of the melting point.

Anal. Calc'd for $C_{23}H_{36}O_5$: C, 70.36; H, 9.25.
Found: C, 70.23; H, 9.46.

Preparation of the oxime: To a solution of 10 mg. of the substance described above was added a concentrated aqueous solution of a mixture of 20 mg. of hydroxylamine hydrochloride and 30 mg. of sodium acetate. After refluxing on a water-bath for 2 hours, water was added. The oxime separated rather slowly from this solution. The crude oxime was recrystallized from aqueous alcohol. Yield: 4.3 mg.; melting point, 221–223°.

Acetylation: A micro-sample of XV was refluxed with acetic anhydride for 1½ hours. The acetate was precipitated with water, filtered and recrystallized from alcohol; m.p. 234–235°. When mixed with a sample of pregnane-20-one-3(β),5,6(*cis*)-triol 3,6-diacetate (m.p. 251.5–252°) the melting point was 251.5–252° with distinct sintering a few degrees below.

SUMMARY

1. By partial oxidation with chromic acid, androstane-17-one-3(β),5,6-(*trans*)-triol (I) was transformed into androstane-6,17-dione-3(β),5-diol (II). By acetylating the latter substance (II), androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII) was obtained.

2. When dehydroisoandrosterone acetate (IV) was oxidized with potassium permanganate in acetic acid, a mixture of substances was obtained from which two isomeric 5,6-oxides were isolated, namely androstane-(5,6) (α)-oxide-17-one-3(β)-ol acetate (Va) and androstane-(5,6) (β)-oxide-17-one-3(β)-ol acetate (Vb). By opening the oxide ring of both compounds, the same androstane-17-one-3(β),5,6(*trans*)-triol 3-monoacetate (VI) was obtained. The latter compound (VI) was transformed

by oxidation into androstane-6,17-dione-3(β),5-diol 3-monoacetate (VII) and, by acetylation, into androstane-17-one-3(β),5,6(*trans*)-triol 3,6-diacetate (VIII).

3. The dehydroisoandrosterone oxide (IX) described by Ouchakov and Lutenberg (6), as well as by Miescher and Fischer (7), was transformed by acetylation into androstane-(5,6) (β)-oxide-17-one-3(β)-ol acetate (Vb).

4. When cholesterol acetate (X) was oxidized with potassium permanganate in acetic acid, a mixture of substances was obtained from which were separated by chromatographic adsorption appreciable amounts of cholestane-6-one-3(β),5-diol 3-monoacetate (XI) and of the acetate of β-cholesterol oxide (XII).

5. The analogous oxidation by potassium permanganate in acetic acid of pregnenonol acetate (XIII) gave a mixture of substances from which was isolated pregnane-5,6-oxide-20-one-3(β)-ol acetate (XIV), pregnane-6,20-dione-3(β),5-diol 3-monoacetate (XVI) and a small amount of a pregnane-20-one-3(β),5,6-triol 3-monoacetate (XV).

6. The mechanism of the permanganate oxidation of 5,6-unsaturated steroids is briefly discussed.

7. The 3,6-diacetate of androstane-17-one-3(β),5,6(*cis*)-triol is described.

PHILADELPHIA, PA.

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(2) WIELAND AND DANE, *Z. physiol. Chem.*, **212**, 41 (1932).
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(4) EHRENSTEIN, *J. Org. Chem.* **4**, 506 (1939).
(5) MARKER AND ROHRMANN, *J. Am. Chem. Soc.*, **62**, 516 (1940).
(6) OUCHAKOV AND LUTENBERG, *Bull. soc. chim.*, [5] **4**, 1394 (1937).
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SOME STRUCTURAL INTERPRETATIONS OF FLAVONE SPECTRA

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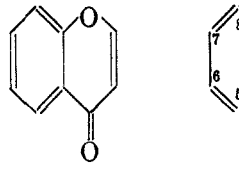
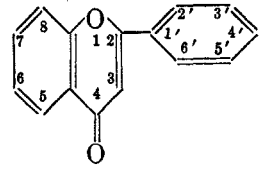
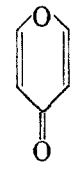
Flavones and flavonols are of widespread occurrence in plants. They are polyhydroxy derivatives of flavone, 2-phenylbenzopyrone, and may occur methylated to varying degrees. The structures for flavone (I), chromone or γ-benzopyrone (II), γ-pyrone (III), flavanone (IV), and 2-hydroxyhydrochalcone (V) are shown below.



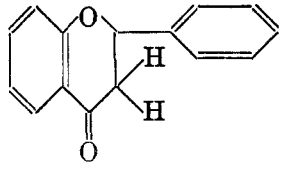
II



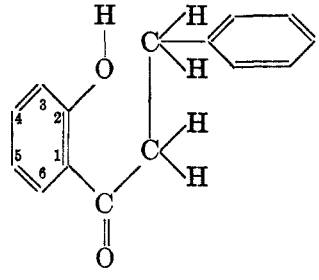
I



III



IV

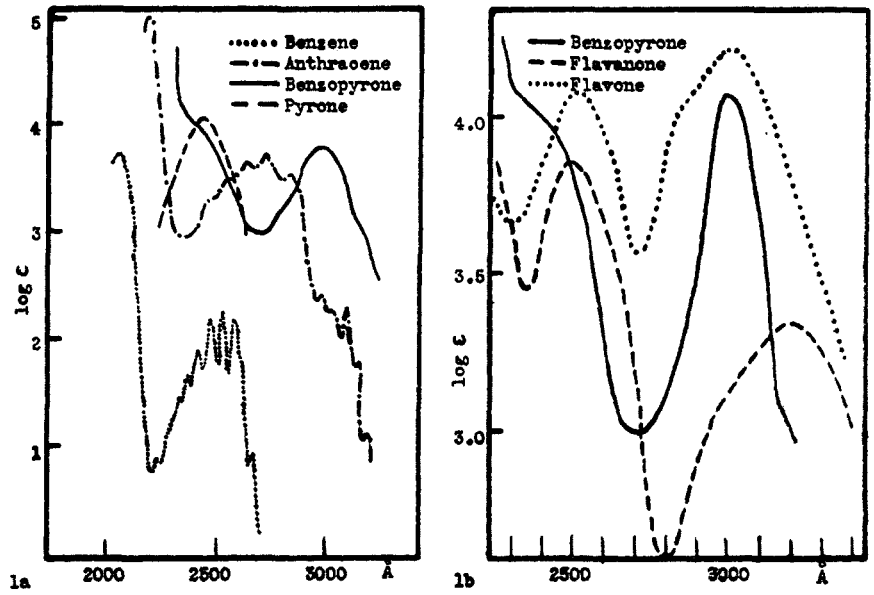


V

Until lately, comprehensive work on flavone spectra had been pursued only by a small group of Japanese workers (1), notably Shibata, Hattori, Tasaki, and Kimotsuki, and by Marchlewski's associates (2). Although the chromic effect of various substitutions in flavone has been recognized empirically, only rarely (as for the 3-hydroxyl position) has correlation between spectrum and molecular configuration been attempted. As a result of Skarżyński's work (2), which had the advantage of better instruments, comparisons may be made and certain errors are to be

noted. Finally, a more or less systematical correlation of the data becomes possible.

(a) The ultraviolet spectrum of flavone shows two well-defined bands at 3000 Å and 2500 Å, though if it were pursued further, a third would



Note on the Curves

It was not feasible to compare directly extinction values in the two sets of data. The Japanese data are plotted as the logarithm of the depth against wave number. Values of ϵ obtained by recalculation did not check sufficiently closely with comparable curves by Skarżyński to make them useful as a basis for comparison.

We may, however, write

$$I/I_0 = F(x) \text{ and}$$

$$\text{lg. } x = \text{constant} = kd \text{ where } d = \text{depth},$$

whence lg. k = constant − lg. d.

To plot ln. d as positive and in terms of lg. k, the curve is simply inverted, and by using the term "relative" lg. k, the constant may be omitted. The curves, then, are simply the inverted originals, maxima becoming minima and vice versa, with the frequency (actually wavenumber) translated as wavelength.

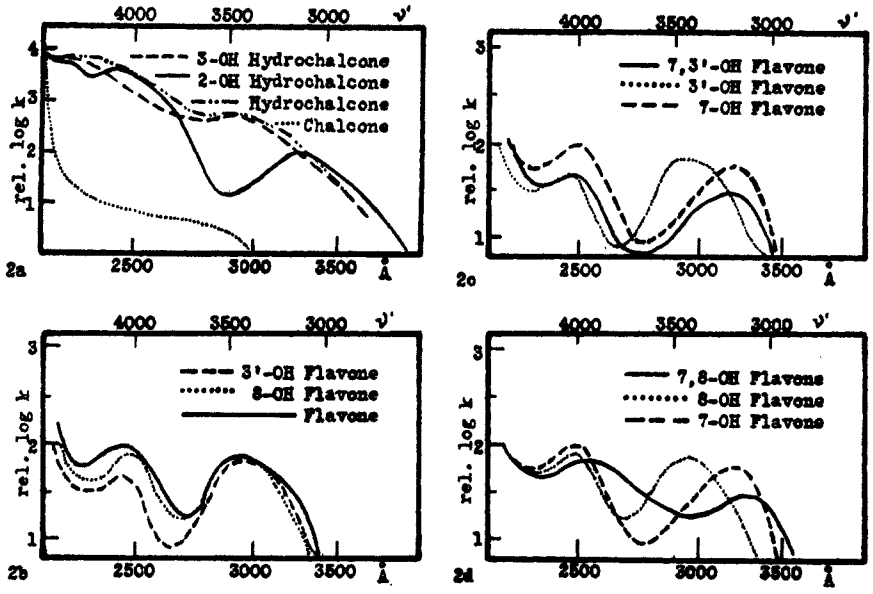
Curves of other authors have simply been drawn to scale.

be present at 2000 Å. At one time, Shibata and Kimotsuki (1) placed the responsibility for the absorption bands on the phenyl group of flavone, while according to Skarżyński, it is due to γ-benzopyrone, or chromone. That neither is entirely the case may be shown as follows: first, the ultraviolet spectrum of benzene (3) consists of a single band at 2000 Å due

to the ethylenic linkages, with a second harmonic series possessing a maximum at 2500 Å. (Fig. 1a.)

(b) The spectrum of pyrone (4) consists of a band at 2500 Å, though another (not shown in the original work), is undoubtedly present at 2000 Å. Thus it is in general similar to benzene. (Fig. 1a.)

(c) The spectrum of benzopyrone (4), however, shows, besides two maxima at 2000 and 2500, a third at 3000 Å. Thus the new molecule, composed of two with identical maxima, produces a new band in addition to the old ones.



(d) The substitution of a phenyl group in the 2 position (Fig. 1b) does not alter basically the position of any of the absorption bands, and thus does not, *per se*, affect the nucleus. The assumption of Shibata and Kimotsuki is therefore incorrect.

(e) The flavanone spectrum (2) shows two bands beyond 2000 Å, one at 2500 and another at 3200. A disruption of the quinoidal structure of the pyrone in benzopyrone shifts one of the bands to the red, so that a quinoidal pyrone structure is not of itself responsible for the two-banded system beyond 2000 Å.

(f) Finally, Tasaki (5) working with acetophenones, showed 2'-hydroxybenzylacetophenone[1] (2-hydroxyhydrochalcone) to have a spectrum

[1] For convenience in discussion, benzylacetophenone notation has been made to conform with that of 2-phenylbenzopyrone derivatives.

similar to flavanone (that is, with maxima at 2500 and 3200). There is only a single band in both benzylacetophenone and its 3′-hydroxy derivative (Fig. 2).

Thus even a chromone structure is not necessary to produce the "characteristic" flavone spectrum, though what does appear involved is an

TABLE I

ABSORPTION MAXIMA FOR MONOHYDROXYFLAVONES IN Å

HYDROXY SUBSTITUENT		BAND				FLAVONE DIFF.	
		Ia	Ib	IIa	IIb	I	II
Flavone	S	2500	—	3000	—	—	—
	H	2470		2910			
8	H	2495		2920		25	10
7	S	2470			3060	−30	60
	H	2495			3115	25	205
6	S		2730	3045		230	45
	H		2815		3470*	345	580*
5	H		2705		3390*	235	480*
3	S	2390*		3050	3415	−110*	50
	H	2490		3035	3335	20	125
2′	H	2470		2875*	3340*	0	430*
3′	S	2410		2980		−90*	−20
	H	2470		2875		0	−35
4′	S	2485			3280	−15	280
	H	2450		2860*	3230	−20	320

* Doubtful values; see text.
S = Skarżyński.
H = Hattori.
a = nominal position of flavone band.
b = shifted position.

oxygen on the phenone capable (either directly or by chelation) of completing a two-ringed system or, more explicitly, of ortho or para resonance. (The meta resonance, as in 3-hydroxybenzylacetophenone is negligible since the bond distances involved are so large as to make that form very unstable and minor.)

The Monohydroxy Substituted Flavones

[There is striking disagreement on the positions and log ϵ values of the maxima for the preparations, so that only qualitative conclusions may be drawn. On the basis of the spectra of benzopyrone and Skarżyński's chromone derivatives, band II of Skarżyński's flavone appears to be closer to that which would be expected. In each case, however, the differences are derived from the values given by the respective authors (Tables I and II).]

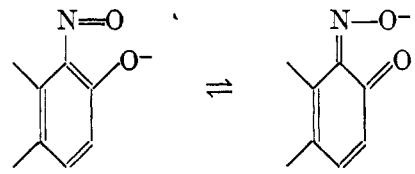
TABLE II

ABSORPTION MAXIMA FOR DIHYDROXYFLAVONES IN Å

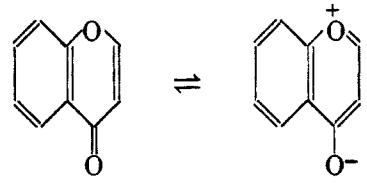
HYDROXY SUBSTITUENTS	TYPE		BAND			
			Ia	Ib	IIa	IIb
7,3′	s	H	2485			3150
3′,4′	s	S	2460		2985*	3480
		H	2470			3370
7,2′	d	H	2480			3180
7,4′	d	H	2470			3510
5,7	d	S		2700		3300
		H		2700		3220
2′,4′	d	H	2470			3340
3,3′	t	S	2365		3030	3500
3,4′	s-t	S	2450		3050	3585
7,3′	s-t	S	2525		3170	3450
7,8′	n	H	2510			3150

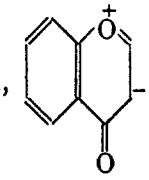
* Doubtful values; see text.
n = non-resonator.
s = single resonator.
d = double resonator.
t = tautomers.
S = Skarżyński.
H = Hattori.

As first proposed by Bury (7), the augmentation of color in a compound may be correlated with a resonance between similar energy forms of the same compound, owing to the inductive polarizability of a substituted group (thereby known as a chromophore). Thus, in the mordant dyes, color is explained by the resonance:



This theory has been expanded by Pauling (8, 9) and by Lewis and Calvin (10). In a similar fashion we may note that among the various ionic resonance forms which benzopyrone may take, the following is probably the most important[2]:



and substituted hydroxyls exert their effect by resonating with one of the two oxygens. Naturally, other forms, *e.g.*,  exist but these are relatively minor.

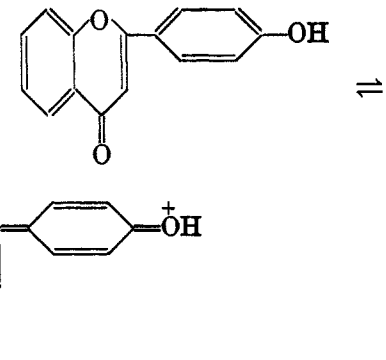
From Table I the following facts are to be noted (regarding qualitative shift from flavone) of substituted hydroxyl groups:

(a) 4′-, 7-, and 2′-Hydroxy substitution shift band II, the order (as given) being proportional to the length of the conjugation chain, one of them affecting band I.

(b) 8- and 3′-Hydroxy substitutions do not shift the spectrum at all.

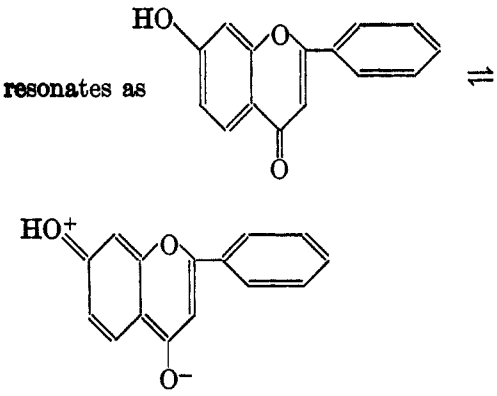
(c) A 3-hydroxy substitution does not shift band I (band II doubtful), but creates a new band beyond I and II.

(d) 5- and 6-Hydroxyflavone shift band I, the former also shifting band II. These may be correlated with the following resonances:

(a) 4′-hydroxy resonates as 

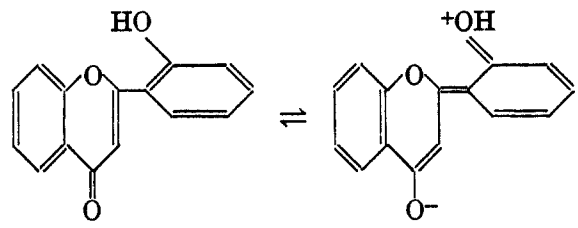
[2] This resonance does not imply a tautomerism but merely shows the various forms which contribute to the actual structure of the molecule.

7-hydroxy resonates as



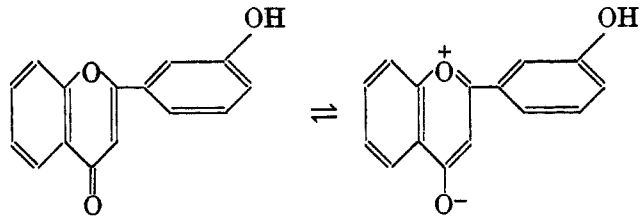
Skarżyński's 7-hydroxy derivatives, differing from Hattori's by 55 Å, are shifted from flavone by 60 Å, while the shift in Hattori's derivative is 205 Å. Since the former's 4′-hydroxyflavone is shifted by 280 Å, and his 5-hydroxy-7-methoxy derivative about 200 Å, it seems reasonable to expect a shift corresponding to that of Hattori, because the methoxyl may be considered non-polarizable here, thus making 5-hydroxy-7-methoxy equivalent to the difficulty obtainable 5-hydroxy derivative.

2′-Hydroxy resonates as



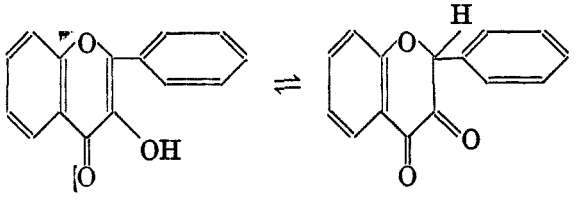
It is interesting to note that in these cases (as contrasted with the more stable anthocyanidins), resonance with the oxonium oxygen is not dynamically stable, *i.e.*, is not a dominant form.

(b) With 3′-hydroxy, however, such a resonance is not possible, the main type of resonance which occurs being, like that of flavone itself:



and the spectrum is not affected. In a similar manner the spectrum of the 8-hydroxy derivative is almost identical with that of flavone.

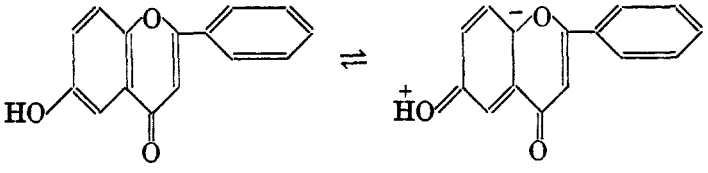
(c) For the formation of a new band with 3-hydroxy (and its derivatives), tautomerism is suggested by Skarżyński, *i.e.*, a rearrangement to a flavanone, in agreement with Hattori (6), who proposed a "quinoid" form, and this seems most probable. As the former notes, however,



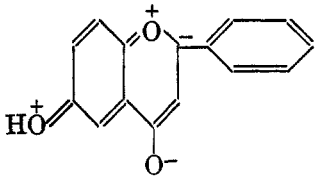
the persistence of the 3050 Å band may be due to the equilibrium mixture of the flavonol and the flavanone. This is, of course, only the normal keto-enol tautomerism, the predominance of the keto form being shown by its much higher log ϵ at 3415 Å as compared with log ϵ at 3050 Å.

Skarżyński's flavonol places band I at 2390 Å while his derivatives have the band at 2500 Å. Since Hattori places the maximum for flavonol at 2490 Å, this value seems more probable.

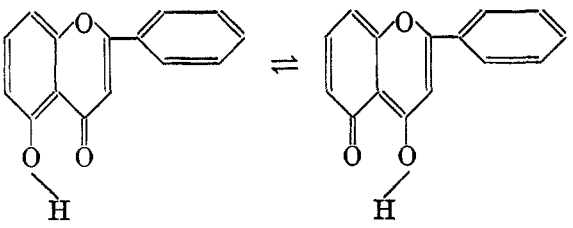
(d) The well-known naphthalene spectrum (Fig. 1a) involves a shift of band I with respect to benzene. If we assume a similar state to exist with regard to the 5-hydroxy and 6-hydroxy, the resonance would be solely of the type:



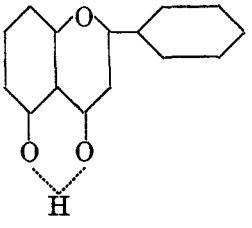
or

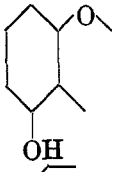
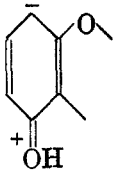
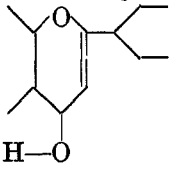


Why this should occur with 5-hydroxy and 6-hydroxy and not, *e.g.*, with 8-hydroxy is not clear at present, and an actual H-shift is therefore suggested, *i.e.*,



This, in essence, is equivalent to hydrogen bond formation, so that the actual molecule might be written:



The position of the H is not, however, necessarily as indicated, nor need it be static. Since  permits formation of  relatively easily, while  would not permit such resonance, the H would, if not in a median position, be closer, actually, to the oxygen on the pyrone. In this case the effect would be a function of distance, almost negligible in the 8-hydroxy derivative. Unfortunately, the data with 6-hydroxy are contradictory. It is interesting to note that with the 5-hydroxy, as a result of a resonance similar to 7-, etc., *both* bands are shifted (though the auxochromic effect is much more pronounced in band I than in band II).

Hattori records an additional though hypochromic band for 6-hydroxyflavone at 3490 Å, while Skarżyński notes the normal extinction value at 3045 Å for the same compound. Since neither Hattori's 3,6-dihydroxy- or 6,7-dihydroxyflavones, nor Skarżyński's derivatives with 6-hydroxy substitution show a bathychromic effect, Hattori may be in error.

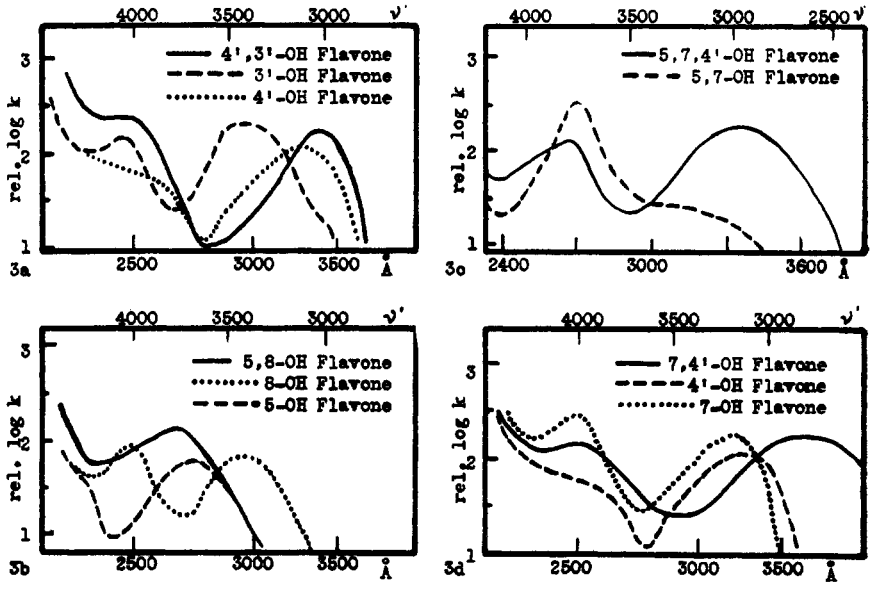
It seems permissible to conclude:

(A) That due to the restriction of the normal resonance of the pyrylium

nucleus by a ketonic oxygen, the additional resonances caused by substitutions follow a path through *this* oxygen, resulting in a shift of one band of the spectrum to the red 4′-, 5-, 7-, or 2′-hydroxy).

(B) Where such resonances cannot occur, two possibilities arise: (a) the resonance is identical with flavone (3′-, 8-hydroxy), or (b) a tautomerism involving much more energy predominates (5-, 6-hydroxy).

(C) An exception is made with 3-hydroxy substitution where, although a resonance form similar to 7-hydroxy etc., does not exist, a rearrangement to a ketonic flavanone occurs most readily.



Polyhydroxy Substituted Flavones

Although the data on dihydroxy compounds are sufficiently extensive to cover all the groups involved, the accuracy and agreement of the data permit only qualitative interpretation.

In general, one notes that except where additional resonance forms may exist, the resultant wavelengths of the absorption bands lie on the maximum position of each band with regard to the substituted hydroxyl group. Thus

$$7,8 \cong 7; \quad 7,3' \cong 7; \quad 6,7 \cong 6\text{II}7\text{II}; \quad 3,3' \cong 3; \quad 5,8 \cong 5.$$

Hattori gives a single-banded curve for 7,8- and a double-banded curve for 6,7-dihydroxy substitution. These are assumed to be reversed. Further evidence is the identity of band II in the supposed 6,7-hydroxy

and 7-hydroxy derivatives, and the lack of hypochromic effect of 6-substitution, an effect present however in the supposed 7,8-derivative.

Hattori records primetin, hitherto considered to be 5,6-dihydroxyflavone as a single-banded structure somewhat similar to 5-hydroxyflavone. Since both 5- and 6-substitution affect band I, one would expect a considerable shift with primetin. Baker (11) has recently shown that primetin is actually 5,8-dihydroxyflavone, and the spectrum should be, as it is, strikingly similar to 5-hydroxyflavone.

In most cases, however, especially those involving 4′-hydroxy, there is a large shift, and here the only interpretation can be that the additional resonance involves a still larger energy absorption. Since the chain length is greatest through 4′, the shift is also proportionately greater with compounds of this derivative. What has been said of dihydroxy applies as well to tri- and tetra- hydroxy substitutions.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY OF THE UNIVERSITY OF BUFFALO]

STUDIES IN SILICO-ORGANIC COMPOUNDS. III. THE PREPARATIONS AND REACTIONS OF SILICON ANALOGS OF CERTAIN ALIPHATIC ORTHOESTERS[1]

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The primary purpose of this investigation was to conduct a more detailed study of the action of the Grignard reagent on ethyl orthosilicate. It was of further interest, however, to study the interchange of alkoxyl groups between two alkyl orthosilicates and the mechanism of the reaction previously presented (1) between silicoorthoesters and the homologous aliphatic alcohols.

In 1908, Khotinsky and Seregenkoff carried out a reaction between phenylmagnesium bromide and ethyl orthosilicate, obtaining ethyl benzeneorthosiliconate (2). These authors also obtained the corresponding products from the Grignard reagents of parabromo-*m*-xylene and α- and β-bromonaphthalene. As a result of their investigation, Khotinsky and Seregenkoff stated that not more than one ethoxyl of any one molecule of ethyl orthosilicate could be replaced by the Grignard.

Although the same Grignard reagents were not used in this investigation, it was found both with methylmagnesium iodide and butylmagnesium bromide that more than one ethoxyl could be replaced. Dimethyldiethoxysilicane and tetrabutylsilicane were prepared by this method. Replacement-products of ethyl orthosilicate are difficult to obtain from its reaction with methylmagnesium iodide. Several attempts were made before any pure products were isolated. It was interesting to note that three products were obtained from the reaction-mixture; ethyl methaneorthosiliconate, dimethyldiethoxysilicane, and ethyl methanesiliconate. The yields of all products were poor.

$$\text{I.} \quad Si(OC_2H_5)_4 + CH_3MgI = C_2H_5OMgI + CH_3Si(OC_2H_5)_3$$

$$\text{II.} \quad CH_3Si(OC_2H_5)_3 + CH_3MgI = C_2H_5OMgI + (CH_3)_2Si(OC_2H_5)_2$$

$$\text{III.} \quad CH_3Si(OC_2H_5)_3 = C_2H_5OC_2H_5 + CH_3SiOOC_2H_5$$

[1] Abstracted from the thesis presented by the second author to the Faculty of the University of Buffalo in partial fulfillment of the requirements for the degree of Doctor of Philosophy.

Ladenburg has twice reported the preparation of ethyl methaneorthosiliconate by the reaction in a closed tube between zinc dimethyl and ethyl orthosilicate in the presence of metallic sodium (3, 4).

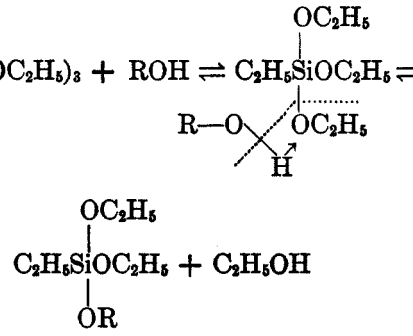
Tseng and Chao reported a 44.5% yield of tetrabutylsilicane from the reaction between butylmagnesium bromide and silicon tetrachloride (5).

The action of the butyl Grignard on ethyl orthosilicate is so vigorous that the former must be added drop by drop if only the mono replacement-product is desired. If the ethyl silicate is added dropwise to an excess of butyl Grignard, the replacement goes still further and gives a 56% yield of tetrabutylsilicane.

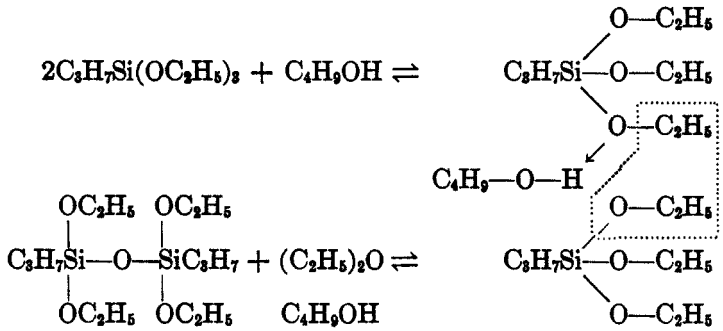
It has been reported previously (1) that the higher homologous alcohols exchange alkoxyl groups with ethyl ethaneorthosiliconate. However, experimental evidence shows that when the alkyl group attached to the silicon is larger than ethyl, exchange takes place only slightly and the silicoorthoesters react to form compounds of higher molecular weights.

In order to devise and propose a mechanism that would take into consideration the known facts concerning the exchange reaction, it is necessary to consider the work of Post and Erickson on the carbon orthoformates and orthoacetates (6). With the orthoformates, exchange of alkoxyl groups with the homologous alcohols would be expected to take place through a mechanism involving the acidic character of the alcohol. The promotion of the ionic nature, as proposed by the above authors, is largely due to the polar nature of the orthoformates. A structure such as that of the orthoformates would allow coordination with an alcohol. With the alkyl group of the alcohol, methyl and successively larger, it would be expected that if the reaction is to continue to occur at all, it should gradually change from an ionic to a coordination mechanism. It is assumed that an investigation of the silicoorthoformates and methane orthosiliconates will prove that the same type of change will occur with the corresponding silicon compounds. That a change does occur is obvious from a comparison of the ethaneorthosiliconates and the propaneorthosiliconates. Ninety-five per cent of the products from the reaction between ethyl propaneorthosiliconate and butyl alcohol have a molecular weight higher than 468. Eighty-five per cent of the products have molecular weights between 468 and 530. Formation of compounds of higher molecular weight may occur as a result of a competition between the alcohol oxygen and the ether oxygen of the silicoorthoester. The larger the groups surrounding the central silicon atom the more difficult it is for the alcohol to penetrate for coordination. As the alkyl groups increase in molecular weight, a certain point is reached at which the above competition favors the formation of the heavy compound rather than the simple orthoester. The formation of the silicon-oxygen-silicon linkage also tends toward the forma-

tion of high molecular weight compounds. It is believed, therefore, that the exchange of alkoxyl groups between the homologous alcohols and the ethane- and propane- orthosiliconates takes place through a coordination mechanism according to the following equation:

IV. 

The coordination of the alcoholic hydrogen results in the creation of a net positive charge on the silicon atom of the molecule, which can then exert an attractive force on the surrounding oxygen atoms. The moving in of any particular oxygen atom aids the splitting off of the other alcohol and results in an exchange. This mechanism makes it possible for heavier compounds to form when the groups are larger. The following equation illustrates this competition.

V. 

Alkoxyl interchange occurring between homologs has been reported by Friedel and Crafts (7). These authors stated that from a stoichiometric mixture of ethyl and methyl orthosilicates, dimethyl diethyl orthosilicate was isolated. It was further stated that none of the 1:3 compounds was formed.

It was believed that in order to form the 2:2 compound the reaction must go through a step where the 1:3 compound is present. The reaction between ethyl and butyl orthosilicates was studied. One-half mole quantities were refluxed for 120 hours. Fractionation at reduced pressures

produced a 22% yield of triethyl butyl orthosilicate, 30.4% yield of diethyl dibutyl orthosilicate as well as a crude yield of ethyl tributyl orthosilicate of *ca.* 25% which was not pure enough for analysis. Traces of the original orthosilicates were identified by their refractive indices. From this experimental evidence it can be seen that a redistribution reaction such as proposed by Calingaert and Beatty (8) may have taken place. It is worthy of mention that analogous silicon and carbon orthoesters and similar compounds have very nearly the same boiling points. The following table is the result of a search of the literature for exact analogs.

SILICON COMPOUND	B.P., °C.	B.P., °C. (CARBON ANALOG)
$HSi(OCH_3)_3$	104–106 (9)	103–105 (10)
		102 (11)
$CH_3SiOOC_2H_5$	73 (12)	77.1 (13)
$C_2H_5Si(OCH_3)_3$	125–126 (4)	126–128 (14)
$(CH_3)_2Si(OC_2H_5)_2$	110–111 (12)	112 (15)
$CH_3Si(OC_2H_5)_3$	145–151 (3)	144–145 (16)
	150–151 (12)	
$C_2H_5Si(OC_2H_5)_3$	158–160 (1)	159–160 (18)
$Si(OC_2H_5)_4$	165.5 (7)	159 (19)
$HSi(OC_3H_7)_3$	191–192 (20)	196–198 (10)
		192–196 (11)
		190–191 (6)
$C_6H_5Si(OC_2H_5)_3$	235–238 (1)	239.5–240.5 (14)
$Si(OC_3H_7)_4$	225–227 (22)	224.2 (19)
$HSi(OC_4H_9\text{-}i)_3$	240–242 (20)	224–226 (10)
$HSi(OC_5H_{11})_3$ °	302 (20)	267–269 (10)
$C_6H_5CH_2Si(OC_2H_5)_3$	245–250 (9)	225–227 (23)

EXPERIMENTAL PART

Ethyl orthosilicate, $Si(OC_2H_5)_4$, was purchased from the Carbide and Carbon Chemicals Corp. Constants found: b.p. 165.5° (760 mm.); $n^{20}D$ 1.3821.

Ethyl propaneorthosiliconate, $C_3H_7Si(OC_2H_5)_3$, was prepared by the method outlined by Post and Hofrichter (1). Constants found: b.p. 179–180° (760 mm.); $n^{25}D$ 1.4076.

Silicon tetrachloride, $SiCl_4$, was a gift of the Niagara Smelting Corp. Constants found: b.p. 57.6° (760 mm.).

Other chemicals were purchased from the Eastman Kodak Co. and the constants found agreed with those appearing in the literature.

Ethyl methaneorthosiliconate, $CH_3Si(OC_2H_5)_3$. Two and one-half moles of methyl iodide were allowed to react in the presence of anhydrous diethyl ether with 68.5 g. of a copper-magnesium alloy containing 24.3 g. of magnesium to 3.1 g. of copper. This mixture was added dropwise to 1.5 moles of ethyl orthosilicate. After the spontaneous reaction had subsided, the mixture was digested on a hot-plate at 150° for three hours. The mixture was cooled and the ether layer separated. Several fractionations of this layer produced three homogeneous products, the highest-boiling

of which was identified as the silicon analog of ethyl orthoacetate. Constants found: b.p. 150–151° (760 mm.); d_4^{20} 0.938; $n^{20}D$ 1.3869; Ladenburg (3), b.p. 145–151°, d^0 0.9283.

Anal. Calc'd: M. w., 178. Found (cryoscopic in benzene): M. w., 174.
Si, 15.74. Found: Si, 15.58, 15.76.

Dimethyldiethoxysilicane, $(CH_3)_2Si(OC_2H_5)_2$, was also isolated from the above reaction-mixture. Constants found: b.p. 110–111° (760 mm.); d_4^{20} 0.890; $n^{20}D$ 1.3839.

Anal. Calc'd: M. w., 148.2. Found (cryoscopic in benzene): M. w., 146.7.
Si, 18.88. Found: Si, 18.55, 18.58.

Ethyl methanesiliconate, $CH_3SiOOC_2H_5$, was also isolated from the above reaction-mixture, but was not conclusively identified, since the nature of the compound made analysis difficult. Constants found: b.p. 73° (760 mm.); d_4^{20} 0.891; $n^{20}D$ 1.3696.

Anal. Calc'd: M. w., 104. Found (cryoscopic in benzene): M. w., 101.

n-*Butyl orthosilicate*, $Si(OC_4H_9)_4$, was prepared by adding 6.56 moles of *n*-butyl alcohol dropwise to 1.5 moles of silicon tetrachloride. An 84.07% yield of *n*-butyl orthosilicate was obtained. Kalinin (24) has reported a similar preparation both with and without benzene as solvent. The yield with benzene as solvent was 82.5% and without the benzene the yield was 61.2%. The table of yields in the Kalinin paper appears in the reverse order to that stated in the text. The simple physical constants found were: b.p. 142–144° (3 mm.); d_4^{20} 0.899; $n^{20}D$ 1.4128.

Anal. Calc'd: M. w., 320. Found (cryoscopic in benzene): M. w., 320.
Si, 8.76. Found: Si, 8.88, 9.01.

Ethyl butaneorthosiliconate, $C_4H_9Si(OC_2H_5)_3$. One mole of butylmagnesium bromide was added dropwise to one mole of ethyl orthosilicate. A 27% yield of the above compound was obtained as well as other higher-boiling products. Constants found: b.p. 190–193° (740 mm.); d_4^{20} 0.895; $n^{20}D$ 1.3976.

Anal. Calc'd: M. w., 220. Found (cryoscopic in benzene): M. w., 219.
Si, 12.74. Found: Si, 12.58, 12.62.

Tetrabutylsilicane, $Si(C_4H_9)_4$, was prepared by adding dropwise 0.825 mole of ethyl orthosilicate to 4 moles of butylmagnesium bromide. Constants found: b.p. 231° (760 mm.); d_4^{22} 0.822; $n^{22}D$ 1.4332; yield 56%.

Anal. Calc'd: M. w., 256.4. Found (cryoscopic in benzene): M. w., 253.3.

Triethyl butyl orthosilicate, $C_4H_9OSi(OC_2H_5)_3$. One-half mole quantities of ethyl and butyl orthosilicates were allowed to reflux together for 120 hours. Fractionation at reduced pressures produced a 22% yield of the triethyl butyl compound as well as other products. Constants found: b.p. 82.5° (15 mm.); d_4^{20} 0.920; $n^{20}D$ 1.3935.

Anal. Calc'd: Si, 11.89. Found: Si, 11.92, 11.93.

Diethyl dibutyl orthosilicate, $(C_2H_5O)_2Si(OC_4H_9)_2$. A 30.4% yield of this product was also obtained from the above reaction-mixture. Constants found: b.p. 100° (15 mm.); d_4^{20} 0.909; $n^{20}D$ 1.4008. Each of the two compounds from this reaction disproportionated on heating to its boiling point at atmospheric pressure.

Anal. Calc'd: Si, 10.62. Found: Si, 10.58, 10.69.

An attempt to prepare butyl propaneorthosiliconate from the reaction between ethyl propaneorthosiliconate and butyl alcohol was unsuccessful. Ethyl propaneorthosiliconate (0.925 mole) was allowed to reflux for 96 hours with 5.05 moles of butyl alcohol. A distillate was obtained, boiling from 30° to 79° at atmospheric pressure, probably containing ethyl ether and ethyl alcohol. Further fractionation produced excess butyl alcohol. After the butyl alcohol had been removed, the mixture was cooled and subsequently fractionated at 7 mm. Four fractions were taken: (a) 105–180°, *ca.* 5%; (b) 180–185°, *ca.* 40%; (c) 185–210°, *ca.* 5%; (d) 210–215°, *ca.* 40%. Obviously little if any of the monomeric exchange-compound was present.

Examination of the major fractions showed them to be fairly simple polymers although their specific identity was not determined. Constants found: (b) d_4^{20} 0.911; $n^{20}D$ 1.4268.

Anal. Found (cryoscopic in benzene): M. w., 468. Si, 13.63.

Fraction (d) showed d_4^{20} 0.925; $n^{20}D$ 1.4300.

Anal. Found (cryoscopic in benzene): M. w., 530. Si, 12.33.

CONCLUSIONS

The statement that no more than one ethoxyl of ethyl orthosilicate can be replaced by means of the Grignard reagent is untenable.

The nature of the reaction between ethane- and propane- orthosiliconates and the homologous alcohols can be explained on the basis of a coordination mechanism, which seems to be the result of a gradual shift from an ionic mechanism due to the shielding of the permanent dipole by larger alkyl groups attached to silicon.

Interchange of alkoxyls between two alkyl orthosilicates necessarily produces all isomers. There is no reason why one isomer should be more stable than another. A random radical distribution would appear to approximate a thermodynamic equilibrium.

SUMMARY

1. The action of the Grignard reagent on ethyl orthosilicate has been investigated and methyl methaneorthosiliconate, dimethyldiethoxysilicane, ethyl methanesiliconate, ethyl butaneorthosiliconate, and tetrabutylsilicane have been prepared by this method. The data covering their simple physical properties are given.

2. The work on alkoxyl exchange between silicoorthoesters and the aliphatic alcohols has been extended. Based on theoretical and experimental evidence, a mechanism for this reaction has been suggested.

3. The alkoxyl interchange between homologous alkyl orthosilicates has been investigated and the formation of the 1:3 compounds definitely ascertained.

4. The yields of the preparations of butyl orthosilicate and tetrabutylsilicane have been improved.

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ORGANIC SELENIUM COMPOUNDS. THEIR DECOMPOSITION IN ALKALINE SOLUTIONS, AND OTHER PROPERTIES RELATED TO THE BEHAVIOR OF SELENIUM COMPOUNDS IN CEREALS[1]

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From the evidence based on the properties of selenium in cereal grains (1, 2), which is supported by feeding trials (3), it has been assumed that selenium is in organic combinations in the protein. Some studies have been made to identify the compounds in the protein hydrolysates, but these have been handicapped by the small amount of selenium present and by our limited knowledge of the properties of organic selenium compounds. Several compounds were therefore prepared to compare their properties with those of the selenium compounds in the cereal proteins, to compare their properties with those of analogous sulfur compounds, and to determine if their physiological action was similar to that of seleniferous cereals or inorganic selenium salts.

Some relationship between the metabolism of selenium and sulfur by the plant has been indicated (4, 5) and the interesting observation has been made by Painter and Franke (6) that nearly the same percentage of total selenium as the percentage of the total sulfur is in the lead sulfide when seleniferous proteins are hydrolyzed in the presence of alkaline plumbite.

Some properties of organic selenium compounds were studied with the view of determining if they have properties similar to those of analogous organic sulfur compounds. In order to compare general properties of different selenium compounds, the diselenide, selenide, and seleninic acid of four radicals were prepared. All selenium compounds were boiled for 6 hours in 5% sodium hydroxide in the presence and absence of lead, and the inorganic selenium cleaved from the organic molecule was determined.

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[2] Taken from part III of a thesis submitted by Edgar Page Painter to the Graduate Faculty of the University of Minnesota in partial fulfillment for the Ph.D. degree.

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For convenience, these alkaline solutions will be referred to as the hydrolysates. The different forms of selenium cleaved from the organic molecule, which are indicated in Tables I and II, can be readily determined. From inorganic selenide (column 5, Table I, and column 2, Table II), metallic selenium precipitates when the solution is acidified. Selenite (columns 3 and 6, Table I, and column 3, Table II) is readily reduced to metallic

TABLE I

EFFECT OF BOILING ORGANIC SELENIUM COMPOUNDS WITH 5% SODIUM HYDROXIDE SOLUTION FOR 6 HRS.

HYDROLYSATE NO.	COMPOUND	PER CENT SELENIUM REDUCED WITH SO_2 + HYDROXYLAMINE HYDROCHLORIDE	6 HRS. IN 5% NaOH + PbO			6 HRS. IN 5% NaOH		
			Per cent selenium in PbSe	Per cent selenium reduced with SO_2 + hydroxylamine HCl after acidified	Per cent selenium recovered as inorganic Se	Per cent selenium separated after acidifying and heating	Per cent selenium reduced with SO_2 + hydroxylamine HCl	Per cent of total selenium recovered as inorganic selenium
		1	2	3	4	5	6	7
29	Diselenodiacetic acid	0	85.5	2.6	88.1	37.6	1.1	38.7
30	β,β'-Diselenodipropionic acid	0	78.5	17.1	95.6	70.3	12.2	82.5
31	n-Propyl diselenide[c]	15.8[b]	23.4	6.0	29.4	14.7	1.1	15.8
32	Benzyl diselenide[c]	trace[a]	53.4	0.0	53.4	71.3	16.4	87.7
33	Selenodiacetic acid	0	<1.0	0.0	<1.0	<1.0	0.0	<1.0
34	β-Selenodipropionic acid	0	97.4	2.3	99.7	34.2	0.0	34.2
35	n-Propyl selenide[c]	0	<2.0	0.0	<2.0	<1.0	0.0	<1.0
36	Benzyl selenide[c]	trace	4.6	0.0	4.6	<2.0	0.0	<2.0
37	Seleninoacetic acid	0	0.0	98.6	98.6	69.9	31.0	100.9
38	β-Seleninopropionic acid	0	34.0	63.1	97.1	37.4	58.4	95.8
39	n-Propylseleninic acid	0	0.0	0.0	0.0	0.0	0.0	0.0
40	Benzylseleninic acid	0	3.0	0.0	3.0	28.3	39.7	68.0

[a] The amount can be increased by adding concentrated sulfuric acid to the hot reducing solution.

[b] Selenium separated when heated in alcohol in an open flask.

[c] Boiled in 71.3% ethyl alcohol.

selenium by sulfur dioxide and hydroxylamine hydrochloride. Selenate is also reduced in this way, but strong oxidizing agents are necessary for its formation. Selenium was determined on all the hydrolysate fractions. A good recovery of selenium was obtained in all cases except with n-propyl diselenide and n-propyl selenide.

The alkaline decomposition of the two diselenides of organic acids was studied by boiling for 6 hours in calcium and barium hydroxides, and in

different concentrations of sodium hydroxide, to see if anomalous results, similar to those with cystine (7, 8, 9, 10) and other disulfides (11), would be obtained. It has been shown that hydroxides of divalent metals have a greater destructive action on the cystine molecule than the monovalent

TABLE II

EFFECT OF BOILING DISELENIDES OF ORGANIC ACIDS IN DIFFERENT ALKALINE SOLUTIONS FOR 6 HRS.

HYDROLYSATE NO.	COMPOUND	ALKALINE SOLUTION USED	PER CENT SELENIUM IN PbSe	PER CENT SELENIUM SEPARATED ON ACIDIFICATION	PER CENT SELENIUM REDUCED	PER CENT SELENIUM IN ORGANIC RESIDUE	PER CENT RECOVERY
			1	2	3	4	5
41	Diselenodiacetic acid	5% NaOH		37.6	1.1	59.5	98.2
42	" "	5% NaOH + PbO	85.5		2.6	4.8	92.9
43	" "	20% NaOH		34.4	1.8	61.0	97.2
44	" "	20% NaOH + PbO	66.9		11.6	19.7	98.2
45	" "	14% $Ba(OH)_2 \cdot 8 H_2O$		46.4	0.0	48.4	94.8
46	" "	14% $Ba(OH)_2 \cdot 8 H_2O$ + PbO	65.4		4.6	30.6	100.6
47	" "	6.5% $Ca(OH)_2$		54.7	<1.0	42.9	97.6
48	" "	6.5% $Ca(OH_2)$ + PbO	64.6		1.8	30.9	97.3
49	β,β'-Diselenodipropionic acid	5% NaOH		70.3	12.2	17.3	99.8
50	" "	5% NaOH + PbO	78.5		17.1	2.4	97.9
51	" "	20% NaOH		80.2	14.4	5.2	99.8
52	" "	20% NaOH + PbO	78.5		18.1	<1.0	96.6
53	" "	14% $Ba(OH)_2 \cdot 8 H_2O$		89.2	0.0	10.0	99.2
54	" "	14% $Ba(OH)_2 \cdot 8 H_2O$ + PbO	92.7		3.9	<1.0	96.6
55	" "	6.5% $Ca(OH)_2$		66.5	<1.0	28.7	95.2
56	" "	6.5% $Ca(OH)_2$ + PbO	67.5		30.5	<1.0	97.9

hydroxides, which are the stronger bases. The results are shown in Table II.

The diselenides resemble the disulfides in their decomposition in alkaline solutions. The selenium compounds show different degrees of selenium lability, and apparently not all of them decompose in the same way (Tables I and II). Schoberl and Wiesner (11), in a study of the decompo-

sition of disulfides of organic acids in alkaline solutions found, as did Gabriel (12) in his studies on isocystine and cystine, that compounds with the sulfur in the α-position are more readily decomposed than dithiodihydracrylic acid, which has sulfur in the β-position. The diselenides did not show the same behavior as the disulfides because β,β'-diselenodipropionic acid is more completely decomposed in most alkaline solutions than is the diselenide of acetic acid. In the present work, however, much more drastic methods of hydrolysis were used. Fruton and Clarke (13) find that dithiodihydracrylic acid slowly gives up its sulfur to form lead sulfide in *N* sodium hydroxide at 25°. They find it less stable than homocystine.

Schoberl and Eck (14) show that the rate of sulfur elimination in alkaline solution is greater when lead is present. Except with benzyl diselenides, there was a greater selenium elimination from the diselenides when lead was present.

Di-*n*-propyl diselenide was found to be the most stable diselenide in alkaline solution. The amount of selenium which appeared as lead selenide was less than 9% of the amount which spontaneously separated from the preparation. Billheimer and Reid (15) found mercaptans of hydrocarbons to be very stable in alkaline solutions. They give three courses for the reaction to follow. In every case sodium sulfide is one of the reaction-products. They recovered 43.4% of the sulfur from *n*-propyl mercaptan (the diselenide would give the analogous selenol by a hydrolytic cleavage between the selenium atoms) as sodium sulfide after heating in 3 *N* sodium hydroxide for 2 hours at 260°.

From the selenide fraction, 71.3% of the selenium from benzyl diselenide was recovered after alkaline hydrolysis. Only 53.4% was found in the lead selenide when lead was present. It is difficult to conceive how the presence of lead could decrease the decomposition of this selenium compound. Price and Twiss (16) have shown that there is a hydrolytic cleavage of benzyl disulfide similar to that shown by Schoberl.

Owing to the similarity between the diselenides and the disulfides in their decomposition in alkaline solutions, it is probable that the mechanism of the removal of selenium is similar to that of the removal of sulfur. Schoberl and co-workers (11, 14) believe that the first step in the decomposition of disulfides of organic acids in alkaline solutions is a hydrolytic cleavage between the sulfur atoms. Sulfide is then removed from the extremely unstable sulfenic acid and an aldehyde is formed:

$$RCH_2SSCH_2R + H_2O \rightleftharpoons RCH_2SH + HOSCH_2R$$

$$RCH_2SOH \longrightarrow RCHO + H_2S$$

In the presence of oxygen the sulfhydryl will be oxidized to the disulfide, where it can repeat the reaction, and the aldehyde may be oxidized to the acid. Schoberl and Wiesner (11) were able to recover 69% of dithiodiacetic acid as oxalic acid by leading a stream of oxygen through the alkaline solution. Schoberl and Hornung (17) have extended their studies to cystine and cystine derivatives and believe the primary step in their degradation is a hydrolytic cleavage between the sulfur atoms. According to this scheme, all of the sulfur eliminated from the disulfide should form lead sulfide, but Schoberl and Eck (14) show that a number of disulfides may also undergo a dismutation similar to that of the action of some heavy metal salts on cystine (18), whereby the sulfenic acid formed by hydrolytic cleavage will give a mercaptan and sulfinic acid.

$$2\ RSOH \longrightarrow RSH + RSO_2H$$

Behaghel (19) and Fredga (20, 21) show that diselenides may undergo a similar dismutation.

$$2\ RSeSeR + 2\ H_2O \longrightarrow 3\ RSeH + RSeO_2H$$

If this reaction occurs, it is probable that there is a hydrolytic cleavage with diselenides, as Schoberl postulates for disulfides.

Clarke and Inouye (9) believe sulfur from cystine is eliminated as disulfide; three-fourths of it appears as lead sulfide, the rest mainly as thiosulfate.

$$4\ Na_2S_2 + 6\ Pb(OH)ONa + 2\ H_2O \longrightarrow 6\ PbS + Na_2S_2O_3 + 12\ NaOH$$

Bergmann and Stather (22) postulate that the primary action of alkalies on cysteine or cystine is the removal of sulfide or disulfides, and the formation of α-aminoacrylic acid. Nicolet (23, 24) gives evidence to support the theory of Bergmann and Stather and suggests that the α-aminoacrylic acid arises by the enolization of the carboxylic carbonyl group, followed by a 1,4 elimination of hydrogen sulfide.

Either reaction mechanism may explain the presence of selenium eliminated from the diselenides which did not form lead selenide. In every case, except with benzyl diselenide, there was more selenite produced when lead was present. This fact may be interpreted as indicating that alkali diselenides became oxidized as in the scheme of Clarke and Inouye. There was, however, neither a consistent ratio of selenite to lead selenide selenium, nor has seleno selenate been described (25). A seleninic acid would form by a dismutation, and seleninic acids cleave in alkaline solutions to give selenite. If a selenol formed (by a dismutation), it would yield lead selenide almost quantitatively as does the sulfhydryl cysteine (9, 10), because when the two diselenides of organic acids were reduced by

boiling with stannous chloride in acid before heating 6 hours in alkaline plumbite, the recovery of selenium as lead selenide was 96.2% and 97.4%.

It must be admitted that the theory of the removal of sulfur from disulfides or sulfhydryls, which has been advanced as a result of studies on cystine and cysteine, is inadequate to explain all the known facts. It does not account for the quantitative removal of sulfur from the sulfhydryl cysteine in alkaline plumbite (9, 10) and the incomplete removal of sulfur from the disulfide cystine (8). It cannot be applied to the decomposition of α-disulfides or sulfhydryls. The hydrolytic cleavage of Schoberl likewise fails to account for the removal of sulfur from sulfhydryl compounds.

The results in Table II are of interest, but no relationship between the efficacy of different alkaline solutions for removal of sulfur from cystine (7, 8, 9, 26), and the removal of selenium from the diselenides, is shown. The high percentage of selenium recovered as lead selenide when β,β'-diselenodipropionic acid was hydrolyzed in barium hydroxide appears inexplicable.

Only one of the selenium ethers, β-selenodipropionic acid, decomposed in alkaline solution to yield selenide. The removal of selenium was almost quantitative in the presence of lead. Selenium ethers, like sulfur ethers, are in general stable in alkaline solutions. Nicolet (23) has shown that certain keto thioethers are converted to mercaptans in alkaline solution. If this selenium ether decomposed according to Nicolet's scheme, it would give rise to selenide.

The seleninic acids (hydrol. 37, 38, 39, 40; Table I) are not equally stable in alkaline solutions. Benzylseleninic acid gives selenide. *n*-Propylseleninic acid was very stable. Benzylseleninic acid, like dibenzyl diselenide, is more stable in the presence of PbO. No analogous sulfur compounds have been studied in alkaline solutions. Sulfinic acids are unstable, hence few have been prepared. Wagner and Reid (27) have shown that sulfonic acids of hydrocarbons are more stable in alkaline solutions than are the mercaptans. Benzyl and *n*-propyl sulfonic acids were only partly decomposed by heating 3 hours in 4 *N* sodium hydroxide at 375°. Clarke and Inouye (28) found that cysteic acid was decomposed when boiled in dilute alkali. The selenium appears to be quantitatively cleaved from seleninoacetic acid and β-seleninopropionic acids. A mechanism for the breakdown of these compounds is difficult to postulate, especially when, with seleninoacetic acid, some selenium precipitated when the hydrolysate was acidified, but in the presence of lead no lead selenide formed. If the decomposition of seleninic acids is similar to that which Wagner and Reid (27), and Clarke and Inouye (28) have shown for sulfonic acids

$$RSO_3Na + NaOH \longrightarrow ROH + Na_2SO_3$$

it would account for some of the results, because selenite is formed.

The percentages of selenium removed from the organic molecules (Table I) does little to simplify the problem of identifying the selenium compounds in cereals. Di-*n*-propyl diselenide and selenino-β-propionic acid lost their selenium to form lead selenide in about the same proportions as the selenium in the proteins. The selenides and diselenides of short-chain hydrocarbons are somewhat volatile, and have strong odors by which they could be detected in very small concentrations. There is nothing abnormal about the odor of any of the many seleniferous grains, proteins, or protein hydrolysates which have been studied. The selenium in the seleninic acids of organic acids appears to be quantitatively removed from the organic molecule in alkaline solutions, but the selenium in proteins and protein hydrolysates has not been completely recovered in inorganic forms, excepting by the action of oxidizing agents. The oxidizing agents used by Westfall and Smith (29) convert diselenides to seleninic acids and selenium ethers to selenoxides. These cleave in acid, as well as in basic, solutions to give inorganic selenium.

Recently Horn and Jones (30) have reported the isolation of a crystalline selenium-containing amino acid. From the structure they suggest from the empirical formula,

$$HO_2CCHCH_2SeCH_2CH_2CHCO_2H$$
$$\quad\;|\qquad\qquad\qquad\;|$$
$$\quad NH_2\qquad\qquad\quad NH_2$$

it would be probable that the compound would give alkali "labile selenium," and could be cleaved after oxidation to a selenoxide. They report that their compound is notably stable.

In general, selenium compounds appear to be less stable in air and in neutral solutions than the corresponding sulfur compounds. Most of the compounds studied were stable in neutral organic solvents. The diselenides of the organic acids decompose slowly to give metallic selenium after they have aged for several days or weeks. The diselenide of acetic acid decomposes much more rapidly than the diselenide of propionic acid. Benzyl diselenide has been kept in the dark for several months, apparently without decomposition. Selenium ethers seem to be stable, for no decomposition has been noted after several months standing. The seleninic acids decompose rapidly in aqueous solution and in air. Both metallic selenium and diselenide are formed, as Fredga (20) has shown.

It can be seen from Table II that the recovery of selenium was fairly good. Most of the values are a little low because there may have not been enough oxygen present to convert all the alkali selenide to metallic selenium on acidification. Repetition of some of these hydrolyses frequently gives slightly different values. This may be due to the varying availability of oxygen during hydrolysis. Judging from the results with disulfides,

different results would have been obtained had hydrolysis been carried out while bubbling a current of either hydrogen or of oxygen through the solution.

Several organic compounds were sent to A. L. Moxon at the South Dakota Experiment Station where they were bio-assayed. These results have been published by Moxon, Anderson, and Painter (31). None of the compounds was found to be as toxic as is inorganic selenite or selenate, either by injection or oral feeding. The symptoms produced by the organic compounds were similar to, but not as acute as, those produced by selenite or selenium as it occurs in natural foodstuffs.

EXPERIMENTAL

One-tenth gram of each selenium compound was boiled 6 hours in 50 ml. of the alkaline solution. After 6 hours boiling in 5% sodium hydroxide, containing plumbite, practically no more lead selenide formed from the two diselenides of organic acids. When lead was present, 0.5 g. of PbO was added to the 50 ml. of alkaline solution.

Selenium was determined on the hydrolysate fractions by the distillation method (32). Although the probable error in the determinations average between ±0.2–0.3 %, the values given in Tables I and II are those obtained. The values preceded by < were from nephelometric comparisons.

Preparation of Selenium Compounds

A. *Potassium selenide and potassium diselenide.* These salts were prepared by the methods of Fredga (20) and Backer and van Dam (33), and hydrogen selenide by the method of Green and Bradt (34). Air must be excluded to prevent the deposition of elemental selenium.

In the preparation of the selenides and diselenides, from 0.1 to 0.6 mole quantities were carried through the reaction. The seleninic acids were prepared from smaller quantities, usually 1–2 g. of the diselenide.

B. *Diselenodiacetic acid* ($HO_2CCH_2SeSeCH_2CO_2H$). This compound was prepared by the method of Behaghel and Rollmann (35) and Fredga (20) from acetoselenocyanate. It was crystallized from ether, as this gave a better product than ethyl acetate and benzene (20). The yields were 55–60% of the theoretical, of a compound which melted at 100°.

Anal. Calc'd for $C_4H_6O_4Se_2$: Se, 57.2. Found: Se, 57.0.

C. *β,β'-Diselenodipropionic acid* ($HO_2CCH_2CH_2SeSeCH_2CH_2CO_2H$). This compound was prepared from the potassium salt of β-bromopropionic acid and potassium diselenide by the method of Backer and van Dam (33, 36). Although it was repeatedly crystallized from water and from acetone (20, 36), the melting point was lower than reported. A good crystalline product was never obtained. The yield of a product melting at 134.5–135.5° was about 30%.

Anal. Calc'd for $C_6H_{10}O_4Se_2$: Se, 52.0. Found: Se, 52.2.

D. *Di-n-propyl diselenide* ($C_3H_7SeSeC_3H_7$). The red oil which separated when *n*-propyl bromide was added to potassium diselenide in about 90% alcoholic solution (37) was washed several times with water, filtered through glass wool, and kept under water. Its properties were similar to those reported for di-*n*-propyl diselenide and its identity was proved by conversion to the corresponding seleninic acid.

The purity of this compound as well as that of di-*n*-propyl selenide was never determined.

E. *Dibenzyl diselenide* ($C_6H_5CH_2SeSeCH_2C_6H_5$). To 0.1 mole of potassium diselenide in an aqueous-alcoholic solution, 0.2 mole of benzyl chloride was slowly added, the reaction-mixture heated on the steam-bath for about two hours, and the dibenzyl diselenide allowed to separate out. The dibenzyl diselenide was extracted with ether, which evaporated at room temperature. The residue was dissolved in hot absolute alcohol, and the product, which melted at 92-93°, crystallized as fine yellow needles on cooling.

Anal. Calc'd for $C_{14}H_{14}Se_2$: Se, 46.44. Found: Se, 46.4.

F. *Selenodiacetic acid* ($HO_2CCH_2SeCH_2CO_2H$). Prepared by the method of Fredga (20). The yield was about 70%, melting point 108°.

Anal. Calc'd for $C_4H_6O_4Se$: Se, 40.1. Found: Se, 38.9.

G. *β-Selenodipropionic acid* [$Se(CH_2CH_2CO_2H)_2$]. This compound was prepared from the potassium salt of β-bromopropionic acid and potassium selenide by Fredga's (20) method. Upon acidification of the aqueous solution, it crystallized as white needles. The product melted at 147-148° after it was recrystallized from ethyl acetate.

Anal. Calc'd for $C_6H_{12}O_4Se$: Se, 35.09. Found: Se, 35.1.

H. *Di-*n*-propyl selenide* ($C_3H_7SeC_3H_7$). This was prepared by Tschagaeff's method (38), excepting that potassium selenide was used instead of sodium selenide, and the reaction was carried out in about 80% alcohol instead of absolute alcohol. The selenium ether was washed with sodium hydroxide solution and collected under water.

I. *Dibenzyl selenide* ($C_6H_5CH_2SeCH_2C_6H_5$). Tschagaeff's method (38) for aliphatic selenides was used. Two-tenths mole of benzyl chloride was added to 0.1 mole of potassium selenide. The reaction-flask was placed on the steam-bath for about two hours while the contents were agitated with a small stream of hydrogen. The solution was cooled, acidified with hydrochloric acid and the benzyl selenide extracted with ether. The compound, recrystallized from absolute alcohol, melted at 45°.

Anal. Calc'd for $C_{14}H_{14}Se$: Se, 30.25. Found: Se, 30.1.

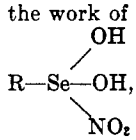
J. *Seleninoacetic acid* ($HO_2CCH_2SeO_2H$). Diselenodiacetic acid was dissolved in ether and 30% hydrogen peroxide was added (20). The seleninic acid, which melted at 101°, immediately crystallized as fine white crystals. Ninety per cent recovery, based on the diselenide, may be expected.

Anal. Calc'd for $C_2H_4O_4Se$: Se, 46.18. Found: Se, 45.2.

K. *β-Seleninopropionic acid* ($HO_2CCH_2CH_2SeO_2H$). Prepared the same as seleninoacetic acid, except in acetone, in about 85% yields. The acid decomposed at the melting point, about 106°.

Anal. Calc'd for $C_3H_6O_4Se$: Se, 42.89. Found: Se, 42.4.

L. n-*Propylseleninic acid* ($C_3H_7SeO_2H + HNO_3$). This compound is formed when *n*-propyl diselenide is oxidized with concd. nitric acid (37). An excess of nitric acid was used to convert the acid to the nitrate. The latter compound, which the work of Shaw and Reid (39) showed to be a selenonium compound of the type



R—Se—OH, was more stable than the free acid. It crystallized from strong nitric acid solution in glistening white plates, melting at 98°.

Anal. Calc'd for $C_3H_9NO_5Se$: Se, 36.22. Found: Se, 36.1.

M. *Benzylseleninic acid* ($C_6H_5CH_2SeO_2H + HNO_3$). The free acid was prepared by oxidation of dibenzyl diselenide with hydrogen peroxide but it was unstable. Several white crystalline products were obtained by oxidation with excess nitric acid, but the selenium contents were low and melting points varied. The compound used in these studies melted at 113° and contained 27.1% selenium (calculated for benzylseleninic acid and one molecule of nitric acid, 29.68% selenium).

SUMMARY

Organic diselenides, selenium ethers, and seleninic acids of acetic, β-propionic, *n*-propyl, and benzyl radicals, were synthesized and their decomposition studied by hydrolyzing in alkaline solutions. Diselenides, like disulfides, decompose in alkaline solutions. Inorganic selenide and selenite formed. Selenium ethers, like sulfur ethers, were stable but the selenide of propionic acid decomposed in alkaline plumbite to give nearly all the selenium as lead selenide. The selenium from seleninic acids of organic acids appeared to be quantitatively cleaved while the seleninic acids of hydrocarbons were partially cleaved. Selenite and lead selenide were formed. It is probable that the mechanism of the decomposition of these compounds is the same as that of the corresponding sulfur compounds.

The relationship of the selenium compounds in plants, and synthesized compounds, in regard to their stability in different solutions and upon storage, was discussed.

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[CONTRIBUTION FROM THE LABORATORY OF ORGANIC CHEMISTRY OF THE STATE UNIVERSITY OF IOWA]

FORMATION OF PYRAZOLINES FROM UNSYMMETRICALLY SUBSTITUTED DIBENZALACETONES

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The purpose of this work was to extend our study of the action of phenylhydrazine on α,β-unsaturated ketones. In previous experiments (1) it was found possible in some instances to isolate the phenylhydrazones assumed by Auwers and co-workers (2) to be the first products in this reaction, but in many cases these compounds rearranged immediately to the isomeric pyrazolines. Straus (3) claimed that the ease of rearrangement will depend on the presence of substituents in the ketone and hydrazine residues. He stated that if one of the latter contains halogen or the nitro radical, closure of the pyrazoline ring will occur readily, while if both are substituted the hydrazone will be stable. It was desired to test these possibilities further.

To decide whether this rearrangement had occurred, in previous work a number of methods have been studied. Auwers and Voss (4) found that the color test for pyrazolines proposed by Knorr (5), in which a drop of solution of ferric chloride, chromic acid, nitrous acid, or similar oxidizing agent is added to a concentrated sulfuric acid solution of the suspected compound, to give a blue-violet color, is not satisfactory. A trace of pyrazoline will give a positive reaction, and the fact that acids are the reagents which most readily bring about the rearrangement of these hydrazones[1] raises the question whether some pyrazoline is formed when the reagent is applied. When the compound in question can be reduced by sodium amalgam (6) to give aniline as one product, it is regarded as a hydrazone.[2] This can usually be rearranged by boiling acetic acid.[3] Products

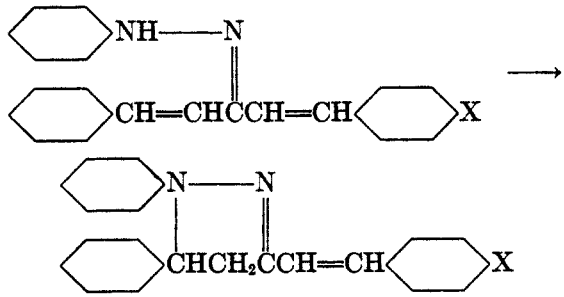
[1] Auwers and co-workers noted that the mother liquors from which the phenylhydrazones have been crystallized often respond to the Knorr test.

[2] This test does not cover all cases, for Auwers and Kreuder [*Ber.*, **58**, 1983 (1925)] could not reduce the compound obtained from benzalacetone and *p*-tolylhydrazine, although this product was reported as a hydrazone because boiling it with acetic acid changed it to an oil that responded to the Knorr test.

[3] Auwers and Voss failed by this method to rearrange the product obtained from cinnamic aldehyde and *p*-nitrophenylhydrazine, although the compound was shown by reduction to be a hydrazone. Bauer and Dieterle [*Ber.*, **44**, 2701 (1911)] had similar experiences.

that cannot be reduced or rearranged are generally regarded as pyrazolines.[4]

Besides the stability of these phenylhydrazones another consideration is of interest here, *viz.*, the direction of ring closure in the rearrangement. If the hydrazone is derived from a ketone containing but one α,β-unsaturation it can rearrange in but one direction to give a pyrazoline. If it is obtained from a symmetrical diunsaturated ketone it must give the same pyrazoline regardless of the radical engaged in closing the ring. When the ketone contains two α,β-unsaturations and is, in addition, unsymmetrical, two products are theoretically possible, depending on the direction in which ring closure takes place, and it is to be expected that this change will depend to some extent on the characters of the substituents in the ketones used.



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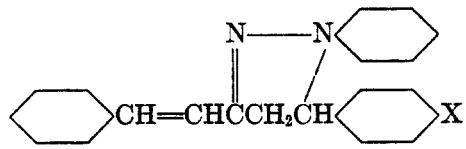


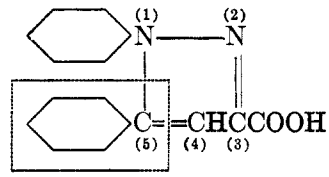
II

To identify the pyrazolines, Straus (3) suggested that if they have been derived from dibenzalacetone or one of its substitution-products they may be oxidized by potassium permanganate solution to give 1,5-diphenylpyrazole-3-carboxylic acid (7) and benzoic acid. He oxidized but two compounds in this way, both of which were derived from symmetrical ketones which contained no substituents. From the first one he obtained benzoic acid and the required pyrazole acid, and from the second benzoic acid only. Bauer and Dieterle (8), also, oxidized two pyrazolines by this

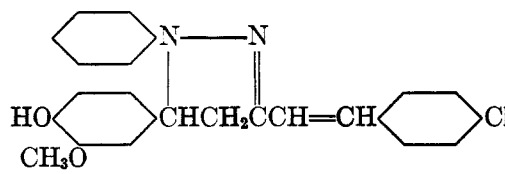
[4] It is of interest here to note that Raiford and Peterson [*J. Org. Chem.*, **1**, 548 (1937)] were able to distinguish between the phenylhydrazones and isomeric pyrazolines obtained from certain chalcones by microscopic examination of their crystals.

method and were able to isolate the required pyrazole acids. Oxidation of the products obtained in the present study should distinguish between structures I and II.

In previous work in this laboratory the oxidation of pyrazolines was done in aqueous mixtures, as suggested by Straus. This involved two difficulties. These compounds are but slightly soluble in water, and under the conditions, heating was required to complete the oxidation. Elevated temperatures favor further reaction which involves degradation of the pyrazole acid. Thus, oxidation of 1,5-diphenyl-3-styrylpyrazoline in this way, by G. V. Gundy formerly of this laboratory, gave but 39% of the required pyrazole acid, and 137% of benzoic acid. Treatment of a purified sample of the pyrazole acid there obtained with permanganate gave benzoic acid, which indicates that the pyrazole ring must be ruptured between atoms 1 and 5 and also between 4 and 5. Degradation was more pronounced when the nitro group was present as a substituent.



In the work now reported an effort was made to avoid oxidative degradation of the pyrazole acid (a) by conducting the reaction in pyridine solution, (b) by working at room temperature or but slightly above, and (c) by choosing for position 5 a residue that would probably resist oxidation. It was thought that the last could be achieved by taking into account the following facts. Our previous studies in this field seemed to show that the closing of the pyrazoline ring takes place in such a way as to involve that radical of the original ketone which contains the less "acidic" substituent (9), which requires the more "acidic" radical to be attached at position 3 in the pyrazoline. The use of vanillal-4-chlorobenzalacetone as the starting ketone would, under such a requirement, bring the vanillyl radical into position 5. The pyrazole acid obtained from such a pyrazoline



might be expected to resist further oxidation under the conditions, for Tiemann (10) found that all attempts to oxidize vanillin to vanillic acid left the material unchanged or degraded it to amorphous products that

could not be identified, according to conditions of the experiment. In a similar way Brady and Dunn (11) failed to oxidize 5-bromovanillin into the corresponding acid by chromic acid and by alkaline permanganate. In simpler cases Bücking (12), and Fittig and Remsen (13) found that 4-hydroxybenzaldehyde and protocatechuic aldehyde, respectively, are not easily oxidized by potassium permanganate solution but require fusion with caustic potash to give the corresponding acids. The resistance to oxidation in these cases appears to be due to the exposed hydroxyl group, for Tiemann (14) found that ethylvanillin can be oxidized smoothly into the corresponding vanillic acid. He did not record the yield of his product, but Perry (15) obtained a 90% yield of acid by oxidation of methylvanillin, and high yields from eleven of its substitution-products.

TABLE I

VANILLAL-4-CHLOROBENZALACETONE AND SUBSTITUTION-PRODUCTS

SUBSTITUENT IN VANILLAL RESIDUE	YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
						Calc'd	Found
Vanillal (unsubs.)...	93	Alcohol (80%)	Yellow prisms	137–138	$C_{18}H_{15}ClO_3$	11.28	11.17
5-Bromo-.....	96	Acetic acid	Yellow needles	191–192	$C_{18}H_{14}BrClO_3$	29.35	29.51
6-Bromo-.....	74	Alcohol	Orange needles	179–180	$C_{18}H_{14}BrClO_3$	29.35	29.12
5-Nitro-.....	67	Alcohol	Orange plates	186–187	$C_{18}H_{14}ClNO_5$	9.87	9.84

EXPERIMENTAL

Preparation of ketones. Vanillalacetone and its substitution-products were prepared as directed by Glaser and Tramer (16) with the exception that a larger proportion of acetone was used. These products were carefully purified before being used in the next condensation. It might be supposed that the desired ketone containing the 4-chlorostyryl radical could be made with equal ease by condensation of the required vanillalacetone with 4-chlorobenzaldehyde or by the interaction of 4-chlorobenzalacetone with vanillin or the required substitution-product. As a matter of experiment, the first method only gave satisfactory results. When the second was attempted, tarry matter was formed and the product was difficult to purify. Similar results were found in closely related cases by Raiford and Cooper (17). Recrystallized vanillalacetone or its substitution-product was mixed with an alcoholic solution of 4-chlorobenzaldehyde, the liquid was made strongly alkaline with sodium hydroxide solution, and the mixture was allowed to stand in the ice chest for several hours. The sodium salt that separated was collected, dissolved in hot water, the ketone was freed by treatment with acetic acid, and was purified by crystallization from a suitable solvent. Analytical data for the new ketones are given in Table I.

TABLE II
PYRAZOLINES

SUBSTITUTED PHENYL GROUPS			YIELD, %	SOLVENT	CRYSTAL FORM	M.P., °C.	FORMULA	ANALYSES, HALOGEN	
Pos. 1	Pos. 3	Pos. 5						Calc'd	Found
4-Chloro-	Phenyl- (unsubs.)	4-Chloro-	55	Acetic acid	Yellow needles	135[a,b] 136	$C_{21}H_{16}Cl_2N_2$	19.34	19.01
4-Chloro-	4-Chloro-	Phenyl- (unsubs.)	78	Alcohol	Yellow needles	135[a,b] 135.5	$C_{21}H_{16}Cl_2N_2$	19.34	18.99
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy-4-hydroxy-	67	Alcohol	Yellow needles	174[b]	$C_{24}H_{21}ClN_2O_2$	8.77	8.84
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy-4-hydroxy-5-bromo-	65	Ethyl acetate	Yellow needles	170[b] 171	$C_{24}H_{20}BrClN_2O_2$	23.88	24.28
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy[c]-4-hydroxy-6-bromo-	94	Alcohol	Pale yellow needles	161[b] 162	$C_{24}H_{20}BrClN_2O_2$	23.88	23.34
Phenyl- (unsubs.)	4-Chlorostyryl-	3-Methoxy[c]-4-hydroxy-5-nitro-	35	Ethyl acetate	Red needles	208–209	$C_{24}H_{20}ClN_3O_4$	7.89	7.72

[a] A mixture of these melted at 114–116°.
[b] Boiling acetic acid caused no change.
[c] The reactants were mixed at about 70° and the liquid was allowed to stand at room temperature.

TABLE III

1,5-Diphenylpyrazole-3-carboxylic Acids

Substituents in phenyl in position 5	Yield, %	Solvent	Crystal form	M.P., °C.	Formula	Analyses			
						Halogen		Nitrogen	
						Calc'd	Found	Calc'd	Found
3-Methoxy-4-hydroxy-	31	Carbon tetrachloride	Yellow powder	165[a]	$C_{17}H_{14}N_2O_4$			9.03	9.23
3-Methoxy-4-hydroxy-5-bromo-	22	Benzene	Pale yellow cubes	161–163[b]	$C_{17}H_{13}BrN_2O_4$	20.56	20.56		
3-Methoxy-4-hydroxy-6-bromo-	25	Alcohol	Yellow powder	175	$C_{17}H_{13}BrN_2O_4$	20.56	20.60		
3-Methoxy-4-hydroxy-5-nitro-	25	Dilute alcohol	Brown powder	90[c] (about)	$C_{17}H_{13}N_3O_6$			11.83	8.23[d]

[a] This product softened a few degress below this temperature. Prolonged heating at 100° caused partial decomposition.

[b] A mixture of this and the pyrazoline, m.p., 166–167°, from which it was obtained melted over a range of 150–155°.

[c] This was not a sharp melting point, but seemed to involve some decomposition.

[d] Though the pyrazoline from which this compound was obtained gave a good analysis for halogen and seemed pure, analyses of the acid for nitrogen were irregular.

Condensation of ketones with phenylhydrazine. One and one-half to two molecular proportions of the required freshly distilled phenylhydrazine was added to a glacial acetic acid solution of the ketone that was about saturated at room temperature, and the mixture was allowed to stand for several days. Usually the product separated spontaneously; when this did not occur it was necessary to cool the mixture or distill off a portion of the solvent under reduced pressure. Attempts to precipitate the products by dilution of the reaction-mixtures with water gave amorphous masses that could not be crystallized. Analytical data and other properties are shown in Table II.

Oxidation of pyrazolines. The calculated amount of finely powdered potassium permanganate was slowly added at room temperature to a pyridine solution of the pyrazoline while the mixture was stirred vigorously. The precipitated manganese dioxide was removed by filtration, suspended in water, the mixture was saturated with sulfur dioxide, and the insoluble material (A) reserved. The pyridine filtrate was distilled, the residue was mixed with (A), and the mixture distilled with steam until 4-chlorobenzoic acid could no longer be detected in the distillate. The distillate was made alkaline with sodium hydroxide, the liquid was evaporated to a small volume, acidified with dilute hydrochloric acid, and extracted with ether. 4-Chlorobenzoic acid was isolated from the extract and identified by mixed melting point determination with a known sample. The average yield was 32%. The non-volatile pyrazole acid remaining after steam distillation was removed by extraction with chloroform, the solution was dried, the solvent was distilled, and the residue was crystallized from a suitable liquid. These acids are listed in Table III.

SUMMARY

Several α,β-diunsaturated unsymmetrical ketones containing the 4-chlorobenzal and the vanillal or substituted vanillal radicals have been condensed with phenylhydrazine. In no case was the phenylhydrazone isolated, but the isomeric pyrazoline was obtained in each instance.

Oxidation of these pyrazolines with potassium permanganate gave, in each case, 4-chlorobenzoic acid and the required pyrazole-3-carboxylic acid, which shows that the direction of rearrangement was away from the chlorobenzal radical.

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[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE UNIVERSITY OF GEORGIA]

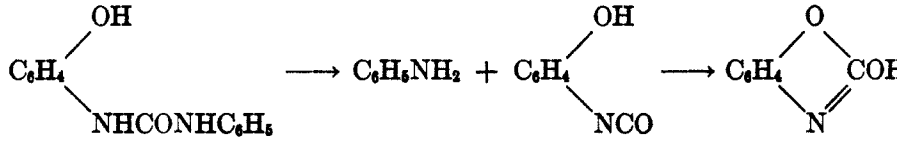
THE BECKMANN REARRANGEMENT OF 2,4-DIHYDROXYBENZHYDROXAMIC ACID DERIVATIVES[1]

ALFRED W. SCOTT AND W. O. KEARSE[2]

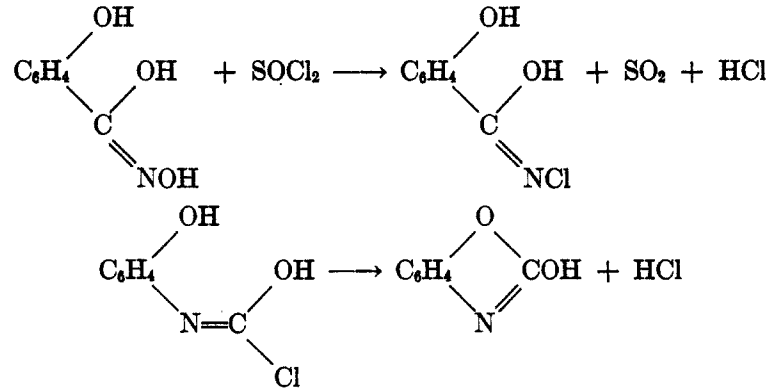
Received June 5, 1940

INTRODUCTION

Several benzene derivatives containing a hydroxyl group and a nitrogenous group in ortho positions to each other can be converted into oxycarbonil by various methods (1). In the formation of oxycarbonil, there is the possibility of the intermediate formation of an isocyanate. A good example of this is brought out in the decomposition of *o*-hydroxydiphenylurea in an alkaline aqueous solution by Leuckart (1h).



In a study of the rearrangment of salicylhydroxamic acid when it was treated with thionyl chloride, Marquis (2) assumed a true Beckmann rearrangement of the Lossen type to take place, and explained the formation of oxycarbonil without the intermediate formation of an isocyanate, as follows:

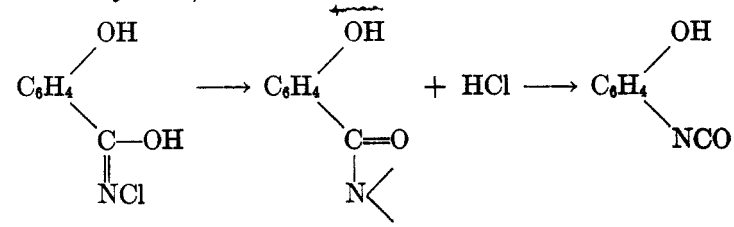


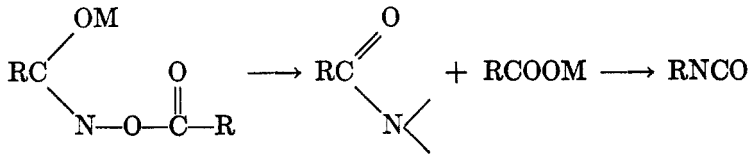
[1] This paper is based upon a thesis presented by W. O. Kearse to the Graduate School of the University of Georgia, in partial fulfillment of the requirements for the degree Master of Science in Chemistry.

[2] Mr. Kearse is now with the Tennessee Eastman Corporation, Kingsport, Tennessee.

Scott and Mote (3) investigated the rearranging properties of the alkali salts of the benzoyl ester of salicylhydroxamic acid and found the rearrangement-product to be oxycarbonil identical with the product obtained by Marquis.

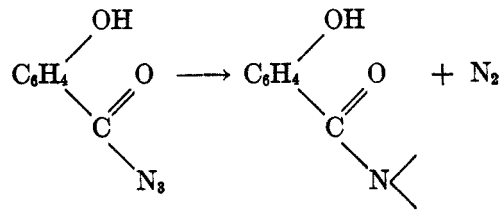
According to the theory advanced by Stieglitz (4) the change of the radical from C to N in I, the rearrangement of salicylhydroxamic acid and II, the rearrangement of the alkali salts of the acid ester, would be caused by the loss of HCl in I and RCOOM in II, with the formation of univalent nitrogen. After the interchange the compounds would assume the structure of an isocyanate, as follows:

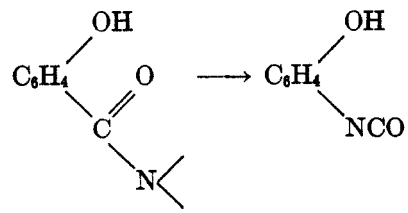
I 

II 

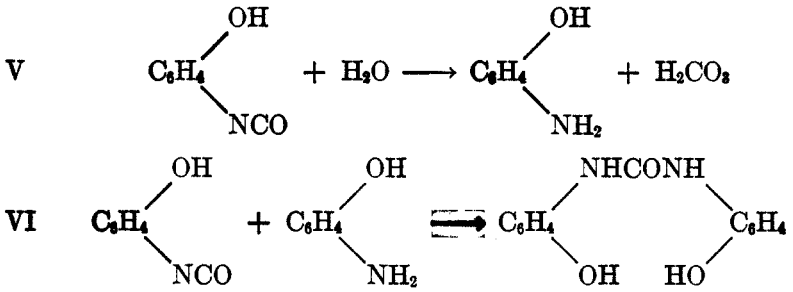
and consequently the formation of the oxycarbonil would take place from the isocyanate.

However, Struve and Radenhausen (5) in a study of the rearrangement of *o*-hydroxybenzazide in boiling water obtained sym.-di-*o*-oxyphenylurea, carbon dioxide, and nitrogen. This is the Beckmann rearrangement of the Curtius type (6) and according to the theory of the mechanism advanced by Stieglitz is assumed to proceed as follows.

III 

IV 

In the presence of water the isocyanate would hydrolyze to give an amine and carbonic acid. The amine would then react with some unchanged isocyanate to give a sym.-di-substituted urea.



In the reactions of Marquis, Leuckart, and Struve and Radenhausen, the same isocyanate would seem to be formed as an intermediate product in the rearrangement. However, in one case a sym.-disubstituted urea resulted and in the other two, oxycarbonil was formed. In the rearrangement of the alkali salts of the esters of salicylhydroxamic acid, in which the theory of Steiglitz predicts the intermediate formation of an isocyanate, Scott and Mote (3) were unable to detect the formation of any isocyanate or *o*-aminophenol. This would indicate that the rearrangement did not proceed according to any of the previously discussed mechanisms.

In view of these results, and in view of the fact that only monosubstituted rings have been used, we decided to study a similar rearrangement using a polysubstituted ring, namely, the alkali salts of the esters of 2,4-dihydroxybenzhydroxamic acid.

DISCUSSION OF RESULTS

Although Herzig and Wenzel (7) claim to have prepared the methyl ester of 2,4-dihydroxybenzoic acid by reaction of methyl iodide on the silver salt of the acid in question, our results do not agree with theirs. They began with 65 g. of 2,4-dihydroxybenzoic acid and obtained 0.35 g. of a product described as white needle-crystals difficultly soluble in hot water and melting from 126–128°. We prepared this ester following the methods employed in preparing the methyl esters of other dihydroxybenzoic acids (8, 9), namely by passing dry hydrogen chloride into a methanol solution of the acid. We obtained a good yield of a product which fits Herzig and Wenzel's description in every detail except one. Our compound, which was identified by two analyses, melts at 76°.

Meyer (10), in a study of the preparation of acid chlorides by means of thionyl chloride, found that 2,4-dihydroxybenzoyl chloride was not formed after prolonged heating of the acid and the chloride together. However,

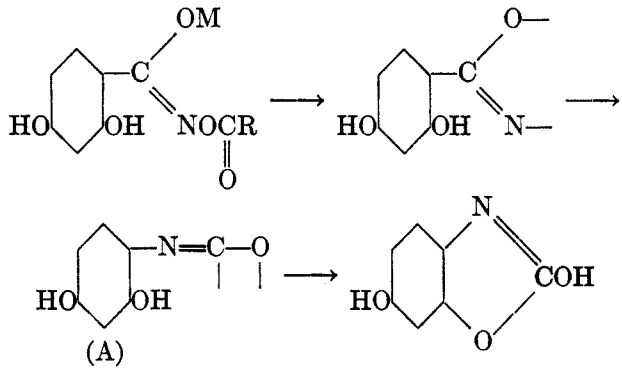
following the method employed by Hurd and Brownstein (11) in the preparation of diphenyl-*p*-tolylacetyl chloride, we were able to prepare 2,4-dihydroxybenzoyl chloride in an almost quantitative yield.

The results of the rearrangement of the potassium salt of the acetyl ester of 2,4-dihydroxybenzhydroxamic acid were in every way in accord with the results obtained by Scott and Mote (3) in their study of similar salicylhydroxamic acid derivatives. We were unable to detect the formation of any isocyanate, and our product was one of the oxycarbonil type. The additional hydroxyl group in the para position apparently had no effect on the course of the Beckmann rearrangement. However, this hydroxyl para to the carboxyl group did seem to have some influence upon the preparation of acid derivatives and especially upon the difficulty of purification of the products formed as previously pointed out by Wilson (12) and one of us.

Since three orthohydroxybenzoic acid derivatives upon undergoing the Beckmann rearrangement give an oxycarbonil, while a fourth gives a sym.-disubstituted urea, we would like to postulate the following probable course of the reactions as an explanation for this difference.

The rearrangements of salicylhydroxamic acid, salicylhydroxamic acid esters, and 2,4-dihydroxysalicylhydroxamic acid esters would proceed similarly, as illustrated by VII,

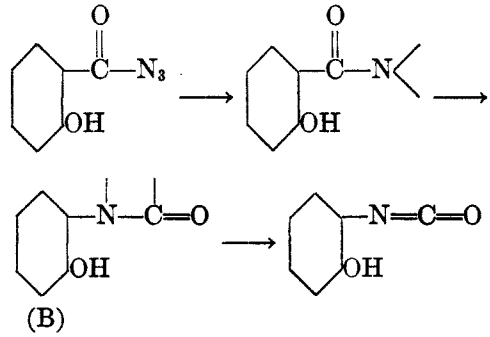
VII



(A)

whereas the rearrangement of *o*-hydroxybenzazide would proceed as follows:

VIII

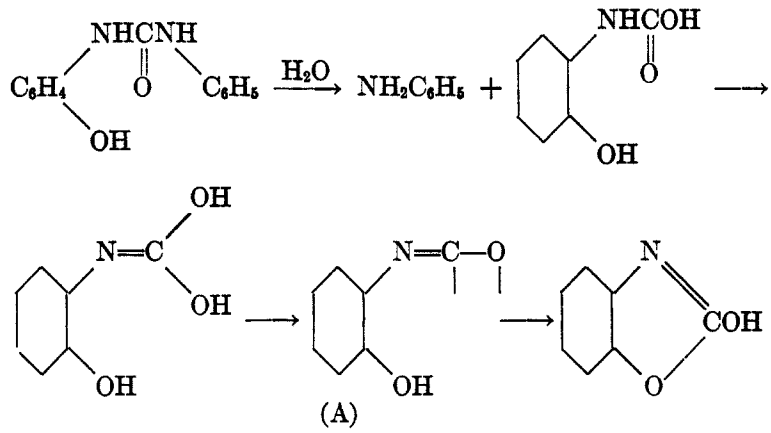


(B)

In VII it would seem that the product (A) formed immediately upon rearrangement would contain no carbonyl oxygen, but would have a double bond between the nitrogen and the carbon of the original carboxyl group (R—N=C—O) and a free valence on the carbon and oxygen.
In the oxycarbonil the double bond between the nitrogen and the carbon is also present. It is proposed that this rearrangement in the presence of the ortho hydroxyl group goes immediately into the oxycarbonil instead of forming the isocyanate.

In the case of the azide, however, the first product of the rearrangement (B) would contain a carbonyl oxygen and a free valence on the carbon and the nitrogen (R—N—C=O), which two valences, even in the presence of the ortho hydroxyl, would unite to give the isocyanate. The isocyanate once formed would follow the customary series of reactions to give the urea.

The formation of the oxycarbonil by the hydrolysis of *o*-hydroxydiphenylurea would be explained by the formation of the same (A) as follows:



(A)

EXPERIMENTAL

A. *Methyl 2,4-dihydroxybenzoate.* This ester was prepared by dissolving 5 g. of 2,4-dihydroxybenzoic acid in 50 cc. of absolute methanol and passing dry hydrogen chloride into the solution for thirty minutes. The solution was then evaporated almost to dryness and neutralized with a saturated solution of sodium carbonate to remove any unchanged acid. The soupy mass obtained was extracted four times with 40-cc. portions of ether. On evaporating the ether, a white solid remained which was recrystallized from hot water, giving needle-shaped crystals. These crystals melted at 76°; yield 65%.

Anal. Calc'd for $C_8H_8O_4$: C, 57.15; H, 4.80.
Found: C, 57.11; H, 4.84.

B. *2,4-Dihydroxybenzoyl chloride.* Three grams of 2,4-dihydroxybenzoic acid and 10 cc. of thionyl chloride were placed in a small flask fitted with a reflux condenser. The flask was then warmed gently for a period of three hours, after which time the evolution of sulfur dioxide and hydrogen chloride had ceased and solution was complete. The contents of the flask were poured onto crushed ice where the excess thionyl chloride was decomposed. The solid acid chloride was filtered, washed with a little cold water, pressed on a porous plate, and dried in a vacuum desiccator. With no further purification, it melted at 142°. The yield was practically quantitative.

Anal. Calc'd for $C_7H_5ClO_3$: Cl, 20.58. Found: Cl, 20.46.

C. *2,4-Dihydroxybenzhydroxamic acid from A.* Following the method employed by Jeanrenaud (13) in the preparation of salicylhydroxamic acid, 6.9 g. of hydroxylamine hydrochloride (2 moles) was added slowly with stirring to 100 cc. of aqueous solution containing 14 g. of potassium hydroxide (5 moles). Then 8.4 g. (1 mole) of methyl 2,4-dihydroxybenzoate was added to this solution in small portions, with vigorous shaking after each addition to ensure complete solution. This mixture was allowed to stand over a period of two days, or until the color of the solution became deep brown, and then just acidified with sulfuric acid. Since no precipitation occurred at this point, the solution was extracted with 25-cc. portions of ether. The ether left a white solid which gave the ferric chloride test for hydroxamic acids. Purification of this compound was found to be extremely difficult and it was never obtained in pure form.

Free hydroxylamine was prepared by the method of Hurd and Brownstein (14).

2,4-Dihydroxybenzhydroxamic acid from B. Three grams of finely divided 2,4-dihydroxybenzoyl chloride was suspended in 30 cc. of low-boiling ligroin in a small flask. To this suspension one gram of free hydroxylamine was added in small portions, with vigorous shaking after each addition. The reaction proceeded somewhat violently and it was necessary to keep the contents of the flask cooled and well mixed for about two hours. The gummy, brownish solid mass obtained was collected upon a filter, dissolved in the least possible quantity of water, and the unchanged acid chloride filtered off. This solution was extracted four times with 25-cc. portions of ether, which on evaporation yielded fairly pure hydroxamic acid. Further purification by precipitation from ethyl acetate with ligroin did not elevate the melting point. The hydroxamic acid was never obtained in a crystalline form, but melted sharply at 162° and decomposed at 171°; yield 40%.

This hydroxamic acid was found to be soluble in methanol, ethyl alcohol, ethyl acetate, acetone, ether, and slightly soluble in cold water. It was insoluble in ligroin, benzene, and toluene. It hydrolyzed in hot water to 2,4-dihydroxybenzoic acid.

Anal. Calc'd for $C_7H_7NO_4$: N, 8.29. Found: N, 8.08.

D. *Benzoyl ester of C.* Attempts were made to prepare this ester, both by fusion with benzoic anhydride and by the Schotten-Baumann reaction with benzoyl chloride. Neither of these methods gave a satifactory product, and consequently the benzoyl ester was abandoned in favor of the acetyl ester which offered no difficulty in preparation.

E. *Acetyl ester of C* was prepared by two methods. (a) By the Schotten-Baumann reaction: One gram of 2,4-dihydroxybenzhydroxamic acid was added to an aqueous solution of 0.25 g. of sodium hydroxide and shaken until solution was complete. Then 0.5 cc. of acetyl chloride was added, and the mixture was cooled and vigorously shaken for a period of one hour. A solid white precipitate was obtained which

turned brown and melted at 188°, after being recrystallized twice from alcohol and water.

(b) By fusion with acetic anhydride: One gram of 2,4-dihydroxybenzhydroxamic acid was mixed with a slight excess of acetic anhydride on a watch glass and warmed over a water-bath. The mixture became soft and then hardened again. This hard mass was pulverized and shaken twice with small quantities of water to remove the excess acetic anhydride and acetic acid. The cream colored product turned brown on being recrystallized twice from alcohol and water and melted at 188°; yield 75%.

Anal. Calc'd for $C_9H_9NO_5$: N, 6.63. Found: N, 6.69.

F. *Potassium salt of E.* The potassium salt of the acetyl ester was prepared by dissolving the ester in the smallest possible quantity of absolute alcohol, placing the solution in a freezing mixture, and adding the calculated amount of potassium ethoxide. A cloudiness was observed at this point, but no actual precipitation took place until anhydrous ether was added. The precipitate was collected and washed with absolute alcohol and anhydrous ether. After drying in a vacuum desiccator over sulfuric acid for one hour, the salt exploded at 84°. This salt was slightly brown in color, and soluble in water.

Rearrangement of F. Two grams of this potassium salt was dissolved in the smallest possible quantity of water and warmed in a water-bath. At 65° a thin film of an oily substance formed on top of the liquid, but no precipitation took place. On raising the temperature to 90°, for a period of two hours, a dark brown precipitate began to form. This precipitate, recrystallized twice from an alcohol and water mixture, gave fine, slightly pink needle-crystals which melted at 288°. Analysis of this rearrangement-product proves it to be an oxycarbonil similar to the rearrangement-product of salicylhydroxamic acid derivatives rather than a symmetrically disubstituted urea.

Anal. Calc'd for $C_{18}H_{12}N_2O_5$ (urea): N, 10.14.
for $C_7H_5NO_3$ (oxycarbonil): N, 9.27. Found: N, 9.35.

SUMMARY

1. Some derivatives of 2,4-dihydroxybenzhydroxamic acid were prepared.

2. The rearranging properties of the potassium salt of the acetyl ester of 2,4-dihydroxybenzhydroxamic acid were investigated and it was found to give an oxycarbonil rather than a sym.-disubstituted urea.

3. A possible course of the rearrangement to form a urea on the one hand and an oxycarbonil on the other was postulated.

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SOME DERIVATIVES OF HOMOANISIC ACID

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In the course of synthetic experiments in the dibenzothiophene series, a number of phenylacetic acid derivatives containing thio and thio ether groups were needed. Their preparation is described in this article.

p-Homoanisic acid (4-methoxyphenylacetic acid) which served as our starting material, may be obtained in several ways (1). We found it advantageous to prepare it by the Arndt and Eistert synthesis (2) from *p*-methoxybenzoyl chloride through *p*-methoxyphenyl diazomethyl ketone and *p*-homoanisamide. The over-all yield of homoanisic acid, based on *p*-methoxybenzoic acid, was 53%.

Nuclear bromination (3) of *p*-homoanisic acid directs the bromine atom into position 3. We found that nitration and chlorosulfonation also direct the incoming substituent into the 3-position. This was proved by reducing nitrohomoanisic acid to aminohomoanisic acid, and converting this product to homoisovanillic acid (4). The reaction between homoanisic acid-3-diazonium chloride and a sodium sulfide solution (5) furnished 3,3′-dithiohomoanisic acid, which was reduced to 3-thiohomoanisic acid. This product was also obtained by reduction of 3-chlorosulfonyl homoanisic acid with zinc dust and acids (6). A further proof of the structure of this series of compounds consisted of the alternate synthesis of 3-nitrohomoanisic acid from 3-nitro-4-methoxybenzyl cyanide, which was prepared from the known 3-nitro-4-methoxybenzyl chloride (7).

Condensation of 3-thiohomoanisic acid with 2-nitro-3-bromobenzoic acid led to 2′-nitro-3′-carboxy-2-methoxydiphenyl sulfide-5-acetic acid which was reduced to the corresponding amino derivative by ferrous hydroxide in ammonium hydroxide suspension.

EXPERIMENTAL

p-*Methoxyphenyl diazomethyl ketone.* One hundred and fifty grams of *p*-methoxybenzoyl chloride was added to an ethereal solution of diazomethane obtained from 380 g. of nitrosomethylurea, and the solution was allowed to stand overnight. The solvent was distilled off, and the crystalline reaction-product was recrystallized from benzene. The diazo ketone appeared as transparent hexagonal prisms, m.p. 90–91°. The yield was 109 g. (70.3%).

Anal. Calc'd for $C_9H_8N_2O_2$: N, 15.82. Found: N, 15.98.

p-*Homoanisic acid.* A solution of 20 g. of the diazo ketone in 100 cc. of dioxane was treated with 150 cc. of concentrated ammonium hydroxide and 30 cc. of 10% silver nitrate solution at 60–70°. The mixture was boiled under reflux for two hours, cooled, and *p*-homoanisamide (8) was precipitated by addition of water. Recrystallization from alcohol yielded 15 g. (81%) of the pure amide, m.p. 188–189°.

A solution of 20 g. of *p*-homoanisamide and 40 g. of potassium hydroxide in 400 cc. of alcohol was boiled on a steam-bath under reflux for five hours. The solution was diluted with 1 liter of hot water, concentrated to 100 cc., and acidified. The homoanisic acid was filtered, washed, and dried. It melted at 86–87°. The yield was 17 g. (85%).

3-Chlorosulfonyl homoanisic acid. Sixteen and six-tenths grams of homoanisic acid was added to 30 cc. of chlorosulfonic acid at −5° at such a rate that the temperature did not rise above 0°. The mixture was kept below 0° for one hour, the temperature was then allowed to rise to 40°, and kept at this point for five minutes. It was then cooled, poured onto ice, the crude sulfonyl chloride was filtered, and recrystallized from benzene. It appeared as colorless prisms, m.p. 164–165°. The yield was 21.3 g. (80.6%).

Anal. Calc'd for $C_9H_9ClO_5S$: Cl, 13.44; CH_3O, 11.76.
Found: Cl, 13.58; CH_3O, 11.61.

3-Thio-p-*homoanisic acid.* Twelve grams of zinc dust was added to a mixture of 72 g. of ice and 24 g. of concentrated sulfuric acid at −5°. Nine grams of 3-chlorosulfonyl homoanisic acid was added with mechanical stirring, and the temperature was raised slowly to 80° in the course of two hours. At the end of this time the mixture was cooled, diluted with water, and the precipitate filtered. The thiohomoanisic acid was dissolved by boiling the precipitate in a 15% sodium hydroxide solution for five minutes, filtered from insoluble material, and reprecipitated by acidifying the filtrate with hydrochloric acid. The crude compound melted at 79–82° and weighed 6.1 g. Recrystallization from benzene-petroleum ether gave colorless prisms, m.p. 83–84°. The yield was 5.6 g. (83%).

Anal. Calc'd for $C_9H_{10}O_3S$: C, 54.49; H, 5.09.
Found: C, 54.62; H, 5.23.

The compound proved to be identical with 3-thiohomoanisic acid prepared from 3-aminohomoanisic acid (see below).

3-Nitro-4-methoxybenzyl cyanide. A solution of 30 g. of 3-nitro-4-methoxybenzyl chloride (7), 10 g. of potassium cyanide, and a few crystals of potassium bromide in 300 cc. of alcohol was boiled under reflux on a steam-bath for six hours, and then evaporated almost to dryness under reduced pressure. Addition of 500 cc. of water furnished yellowish rhombic prisms which, after recrystallization from alcohol, melted at 87–87.5°. The yield was 15.5 g. (54%).

Anal. Calc'd for $C_9H_8N_2O_3$: N, 14.58. Found: N, 14.63.

3-Nitro-p-*homoanisic acid.* (a) A solution of 3 g. of 3-nitro-4-methoxybenzyl cyanide in a mixture of 5 cc. of 50% sulfuric acid and 5 cc. of glacial acetic acid was boiled under reflux for two hours, cooled, and diluted with water. The crude precipitate was filtered, and recrystallized from alcohol. 3-Nitrohomoanisic acid appeared as colorless plates, m.p. 132–133°. The yield was 2.3 g. (70%).

Anal. Calc'd for $C_9H_9NO_5$: N, 6.60. Found: N, 6.81.

(b) A solution of 0.5 g. of homoanisic acid in 5 cc. of glacial acetic acid was cooled and treated with 1 cc. of concentrated nitric acid while the temperature was kept below 0°. After ten minutes, the solution was diluted with water, the precipitate was filtered, and recrystallized from alcohol. The crystals melted at 132–133°,

the yield was 0.3 g. A mixture melting point with 3-nitro-*p*-homoanisic acid prepared by hydrolysis of the nitrile showed no depression.

3-Aminohomoanisic acid. Sixteen grams of 3-nitrohomoanisic acid, dissolved in 200 cc. of alcohol, was hydrogenated in the presence of 0.5 g. of Raney nickel catalyst. The catalyst was filtered, the solvent evaporated, and the solid residue recrystallized from benzene. The amino acid appeared as colorless needles, m.p. 110–111°. The yield was 12.3 g. (90%).

Anal. Calc'd for $C_9H_{11}NO_3$: C, 59.64; H, 6.12.
Found: C, 59.65; H, 6.08.

Homoisovanillic acid (4). Two and seven-tenths grams of 3-aminohomoanisic acid was dissolved in a cold mixture of 5 cc. of water and 3.5 cc. of concentrated sulfuric acid with stirring. Eight grams of ice was added, and a solution of 1 g. of sodium nitrite in 2 cc. of water was dropped in slowly at 0° over a period of five minutes. The solution was allowed to stand for one hour and then dropped into 15 cc. of boiling 40% sulfuric acid. A dark solid precipitated on cooling. Extraction of the precipitate with boiling ethyl acetate, and precipitation with low-boiling petroleum ether furnished light-colored crystals of homoisovanillic acid. Another small amount of this material was obtained by sublimation in a high vacuum of the undissolved residue from the ethyl acetate extraction. Recrystallization from benzene-petroleum ether yielded colorless crystals, m.p. 127–128°.

3-Thiohomoanisic acid from 3-aminohomoanisic acid. A cold solution of 2.7 g. of sodium nitrite in 12 cc. of water was added slowly to a mixture of 7.24 g. of 3-aminohomoanisic acid, 20 cc. of water, and 8 cc. of concentrated hydrochloric acid at −5°. After ten minutes, the diazo solution was added carefully at −5° to an alkaline sodium sulfide solution prepared by dissolving 12.4 g. of sodium sulfide ($Na_2S \cdot 9H_2O$) and 1.3 g. of powdered sulfur in 12 cc. of boiling water, and treating the mixture with a solution of 1.6 g. of sodium hydroxide in 4 cc. of water. Nitrogen was evolved, and the solution was allowed to stand at room temperature for one hour. Acidification with acetic acid caused precipitation of 3,3′-dithiohomoanisic acid. Excess sulfur was removed by dissolving the precipitate in hot sodium carbonate solution, filtering, and reprecipitating the disulfide with hydrochloric acid. The acid solution was decanted, and the semi-solid disulfide was washed with several portions of water. Two grams of zinc dust and 20 cc. of glacial acetic acid were added, and the mixture was boiled under reflux for one hour. The solution was concentrated, and then diluted with 100 cc. of water. The precipitate was filtered, boiled with 20 cc. of 15% sodium hydroxide solution for ten minutes, the solution was filtered, and the thiohomoanisic acid was precipitated from the filtrate by acidification. Sublimation at 0.1 mm. pressure, and recrystallization from benzene-petroleum ether gave colorless crystals, m.p. 83–84°. The yield was 25%. A mixture melting point with 3-thiohomoanisic acid prepared by reduction of 3-chlorosulfonyl homoanisic acid showed no depression.

2-Nitro-3-bromobenzoic acid. The oxidation of 2-nitro-3-bromotoluene was carried out with chromic acid (9) in place of a neutral potassium permanganate solution as described by Elson, Gibson, and Johnson (10).

Sixty-five grams of concentrated sulfuric acid was added with mechanical stirring to a mixture of 26 g. of sodium dichromate, 60 cc. of water, and 14 g. of 2-nitro-3-bromotoluene. The mixture was boiled under reflux for twenty minutes, cooled, and diluted with water. The precipitate was filtered through cloth, washed with water, agitated with 30 cc. of 5% sulfuric acid, and filtered again. It was extracted with boiling 15% sodium hydroxide solution for ten minutes, and the 2-nitro-3-bromobenzoic acid was precipitated from the filtered alkaline solution by acidifica-

tion with dilute sulfuric acid. Recrystallization from dilute alcohol furnished 11 g. (70%) of the pure acid, m.p. 250–251°. A mixture melting point with an authentical sample prepared by the method of Friedländer, Bruckner, and Deutsch (11) showed no depression.

2'-Nitro-3'-carboxy-2-methoxydiphenyl sulfide-5-acetic acid. A mixture of 1.24 g. of 3-thiohomoanisic acid and 2.46 g. of 2-nitro-3-bromobenzoic acid was dissolved in a solution of 1.23 g. of potassium hydroxide in 5.6 cc. of methanol. The solvent was evaporated, the mixture was heated slowly to 190°, and kept at this temperature for two hours. The dark brown solid was dissolved in cold water, the solution was extracted with ether, and acidified. The gray crystalline precipitate was filtered, dried, and boiled out with benzene. The insoluble portion was recrystallized from dilute alcohol. The diphenyl sulfide derivative appeared as small yellowish cubes, m.p. 232–234° (decomp.). The yield was 1.0 g. (46%).

Anal. Calc'd for $C_{16}H_{13}NO_7S$: C, 52.87; H, 3.61.
Found: C, 52.93; H, 3.84.

2'-Amino-3'-carboxy-2-methoxydiphenyl sulfide-5-acetic acid. A solution of 0.35 g. of the nitro derivative in 10 cc. of hot concentrated ammonium hydroxide was added slowly to a suspension of ferrous hydroxide (from 1.52 g. of ferrous sulfate) in 13 cc. of hot dilute ammonium hydroxide. The mixture was stirred on a steam-bath for thirty minutes, and the ferric hydroxide was filtered and washed with several portions of hot dilute ammonium hydroxide. The filtrate was concentrated under reduced pressure to about 50 cc., then acidified with acetic acid, and the yellowish amino acid was filtered. Recrystallization from alcohol furnished 0.22 g. (66%) of colorless diamond-shaped crystals, m.p. 222–224°.

Anal. Calc'd for $C_{16}H_{15}NO_5S$: C, 57.63; H, 4.54; N, 4.20.
Found: C, 57.73; H, 4.71; N, 4.45.

SUMMARY

The synthesis of 3-thiohomoanisic acid and two substituted carboxy diphenyl sulfide acetic acid derivatives is described.

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OZONIZATION OF ORGANIC COMPOUNDS

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I. VAPOR-PHASE OZONIZATION OF DIPENTENE AND *d*-LIMONENE

With the exception of patents granted to Knox (1) and Rogers (2) for vapor-phase ozonization of pinene and cinnamic aldehyde, no reports were found in the literature of methods for preparing ozonides in the vapor phase. Such a procedure is an excellent one, for the necessity of separating the ozonides from solvents is eliminated, and also the reactions may be carried out more rapidly than in solution. The rate of ozonization in solution is dependent upon the solubility of ozone in the solvents, but in vapor-phase ozonization the rate is much greater by virtue of the increased concentration of ozone and the unsaturated substance. Only compounds having an appreciable vapor pressure and those forming stable products were ozonized in the present study. The terpenes, dipentene, *d*-limonene, and $\alpha(d)$-pinene, were successfully ozonized in the vapor phase.

The chief difficulty in the preparation of ozonides in the vapor state is that the ozonide mists are not easily wetted by solvents. This difficulty has been removed by the use of an electrical precipitator. Furthermore, with the greater concentration of ozone and the increased time of contact, oxidation-reactions other than ozonization may occur.

Many different types of ozonizers and reaction-chambers were tried. A description of the most satisfactory apparatus is included in this paper.

APPARATUS

Ozone was generated by means of an ozonizer made according to the specifications of Smith (3). This type of ozonizer gives a higher yield of ozone than others. The dimensions of the ozonizer described by Smith should be closely followed.

A glass reaction-chamber, one meter in length and 20 mm. in diameter, permits increased time for contact of the reactants.

The precipitator was made readily and with very little cost from the outer jacket of a water condenser. The center wire consisted of several strips of galvanized window screen wire. Several of these strips gave many small points for electron discharge to take place rapidly. The lower end of the wire was fastened to a loop on the long end of a T-shaped glass rod. The wire and glass rod were inserted in the lower opening of the condenser jacket and the wire through a cork in the upper opening. The arms of the glass rod were made of suitable length and size to prevent clogging of

the opening and to permit an Erlenmeyer flask to be placed over the bottom to receive the precipitated ozonides. A strip of copper foil was wrapped around the outside of the condenser jacket to serve as the low potential electrode. During operation, 12,000 volts pulsating D. C. was maintained between the wire and the foil. A small window in the foil aided in controlling the precipitator.

Oxygen was supplied from a Linde air cylinder and the pressure kept constant by means of a hydrostat. The oxygen was dried with concentrated sulfuric acid and calcium chloride and then divided into two paths. One led through a calibrated flowmeter and thence through a series of absorption bottles in which the liquid to be ozonized was placed. The other path led through a calibrated flowmeter and thence through the ozonizer. The two paths were then united in the reaction-chamber, where the ozonides appeared as dense white smokes and were swept along to the precipitator by the excess oxygen. The ozonides were collected in the Erlenmeyer

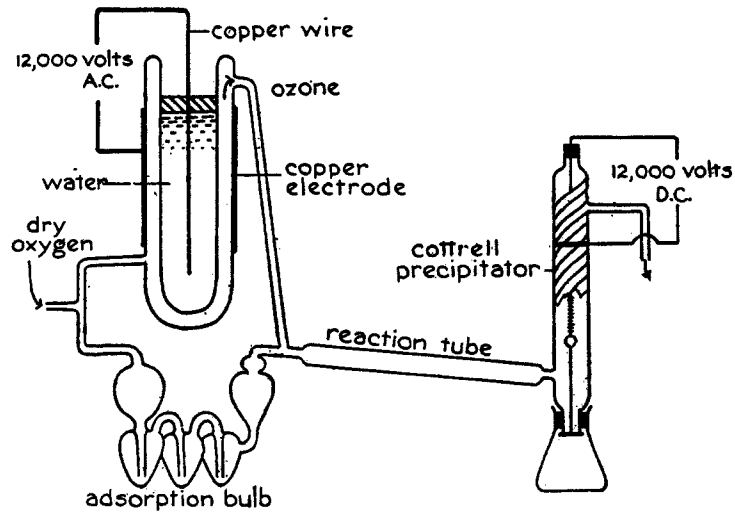
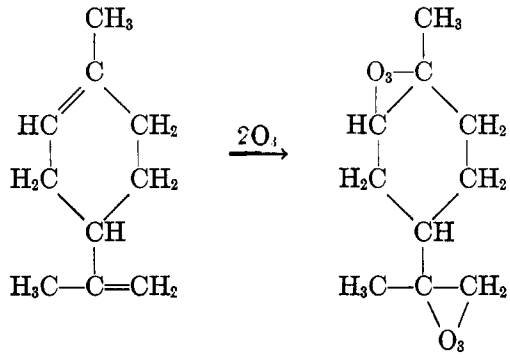


FIGURE 1

receiver, and the excess gases passed out of the exit tube at the top of the precipitator and into a solution of potassium iodide and sodium thiosulfate to destroy any unreacted ozone. To ensure complete ozonization, an excess of ozone was maintained at all times.

COMPARISON OF OZONIZATION OF DIPENTENE IN SOLUTION AND IN THE VAPOR STATE

In the vapor phase the reaction of ozone with dipentene yielded a heavy smoke which was precipitated as a very viscous, yellow liquid. This product was soluble in alcohol (95%) and the solution gave characteristic reactions of ozonides. Combustion data indicated the formation of the diozonide in the gaseous state. The reaction probably proceeds according to the following equation.



Dipentene Dipentene diozonide

An ozonide was formed in the liquid state by dissolving 25 g. of dipentene in 100 g. of heptane. This solution was cooled in an ice-bath as ozone was bubbled through. The ozonide separated as a very viscous, white liquid. The ozone was passed through for ten hours, which was in excess of the time needed for complete ozonization. The excess liquid was decanted, and the ozonide washed with ether and alcohol and then dried under reduced pressure. Combustion data indicated the formation of the monozonide in a heptane solution.

d-Limonene and ozone react in the gaseous state to form a smoke with properties similar to those described above in the case of dipentene. Combustion data indicated that in the gaseous state ozonization took place yielding the diozonide.

Twenty five grams of *d*-limonene was dissolved in heptane and ozonized like dipentene. Again the combustion data indicated the formation of the monozonide in heptane solution.

Citral, pseudoionone, ionone, citronellol, citronellal, terpineol, carvone, geraniol, and isoeugenol were all tried, but these compounds were not volatile enough to produce an appreciable amount of ozonide.

COMBUSTION DATA

Ozonide of dipentene from vapor-phase treatment

Wt. of sample	*Wt. of CO_2*	*Wt. of H_2O*	*%C*	*%H*
0.1339	0.2643	0.0813	53.79	6.8
.1496	.2940	.0915	53.59	6.84
$C_{10}H_{16}O_6$ (theoretical)			51.72	6.90

Ozonide of dipentene in heptane solution

Wt. of sample	*Wt. of CO_2*	*Wt. of H_2O*	*%C*	*%H*
0.1880	0.4306	0.1396	64.95	8.33
.1603	.3518	.1193	59.96*	8.35
$C_{10}H_{16}O_3$ (theoretical)			65.21	8.70

* Rapid decomposition.

Ozonide of d-*limonene from vapor-phase treatment*

Wt. of sample	*Wt. of CO_2*	*Wt. of H_2O*	*%C*	*%H*
0.1429	0.2758	0.0884	53.7	7.01
.1275	.2524	.0799	53.9	7.01
$C_{10}H_{16}O_6$ (theoretical)			51.72	6.90

Ozonide of d-*limonene in heptane solution*

Wt. of sample	*Wt. of CO_2*	*Wt of H_2O*	*%C*	*%H*
0.1483	0.3474	0.1127	63.88	8.50
.2593	.6080	.1982	63.94	8.55
$C_{10}H_{16}O_3$ (theoretical)			65.21	8.70

II. VAPOR-PHASE OZONIZATION OF $\alpha(d)$-PINENE

As previously mentioned, patents have been granted to Knox (1) and Rogers (2) for vapor-phase ozonization of pinene but neither reported any proof of the composition of the product obtained.

In this laboratory ozone was reacted with $\alpha(d)$-pinene vapor. The product formed by this exothermic reaction appeared as a white mist which, since it was not readily absorbed by any solvent, was collected by a modified Cottrell precipitator. A light yellow, viscous oil was obtained, which showed on analysis five oxygen atoms per molecule of pinene. This product was soluble in alcohol and ether, slightly soluble in petroleum ether, and almost insoluble in water. It showed typical ozonide reactions toward heat, potassium permanganate, and potassium iodide.

Hydrolysis of the ozonide proceeded best in alkaline solution, either in alcohol, or more slowly, in water. Hydrolysis in alcohol gave an insoluble white salt which gave with silver nitrate solution and also with hot concentrated sulfuric acid tests indicative of an *alpha* carbonyl group. In the aqueous basic solution, with three per cent hydrogen peroxide added from time to time, degradation to the salt of the next lower acid occurred, and sodium carbonate was produced.

This acid gave a positive iodoform test, and formed a semicarbazone corresponding in nitrogen content and physical properties to pinononic acid semicarbazone.

These results can only be explained by the oxidation of the methylene group alpha to the double bond by the slight excess of ozone present during the reaction, and by the oxygen present in the reaction-mixture. Durland and Adkins (4) have shown that such oxidations can take place even during ozonization in solution, and the ketone produced by this oxidation is known (5) to be one of the major products of the oxidation of pinene by atmospheric oxygen.

The claims based on the original work (6) on the ozonization of pinene in solution, that pinonic acid is the normal product of hydrolysis, is somewhat questionable, since the analysis figures for the product isolated (the

semicarbazone of pinonic acid) agree in nitrogen content for the pinononic acid derivative, while the carbon analysis agrees for pinonic acid semicarbazone. A miscalculation of the theoretical per cent of nitrogen in this article, as well as in the first reported preparation of pinonic acid semicarbazone by Tiemann (7), casts doubt on the validity of the interpretation previously reported.

EXPERIMENTAL

Oxygen, dried by bubbling through sulfuric acid, was directed into two paths. One path led through a calibrated flowmeter and then through a series of absorption bottles filled with pinene to saturate the stream with pinene vapor. The other path led through a Siemen's ozonizer, calibrated against potassium iodide. The two paths joined in a reaction-chamber where the ozonide formed as a white mist which was precipitated electrically.

The product gave the following analyses:

Wt. of sample	*Grams CO_2*	*Grams H_2O*	*%C*	*%H*
0.1678	0.3503	0.1119	56.93	7.46
.1654	.3441	.1095	56.73	7.41
$C_{10}H_{16}O_3$ calculated			65.21	8.70
$C_{10}H_{16}O_4$ calculated			60.00	8.00
$C_{10}H_{14}O_4$ calculated			60.60	7.07
$C_{10}H_{14}O_5$ calculated			56.07	6.54

To 3.2 g. of the ozonide, 42 cc. of 0.4 *N* alcoholic sodium hydroxide was added. A precipitate of 1.5 g. of the sodium salt of the acid was separated and dried. Either the sodium salt, or the free acid obtained from the salt by acidification and extraction, precipitated metallic silver from a silver nitrate solution and gave carbon monoxide when heated with concentrated sulfuric acid.

Hydrolysis of the ozonide with aqueous sodium hydroxide and hydrogen peroxide proceeded readily. To 11.4 g. of the ozonide, 4.8 g. of sodium hydroxide in 200 cc. of water was added. The reaction-mixture gradually darkened, but cleared immediately on the addition from time to time of a few cubic centimeters of hydrogen peroxide (3%).

After evaporation to dryness, 13.09 g. of mixed sodium salts remained. Very small amounts of steam-volatile products were removed during the evaporation. Further purification, which was necessary for easy formation of the semicarbazone, was carried out by adding dilute acid to the sodium salts and skimming off a small amount of resinous material which was floated to the surface by the escaping carbon dioxide. Upon extraction of the acid suspension with chloroform, the free acid could be obtained as an oil. Attempts to crystallize the acid were unsuccessful. The oily acid distilled from 160° to 195° at 12 mm. pressure. The distillate gave the following analyses:

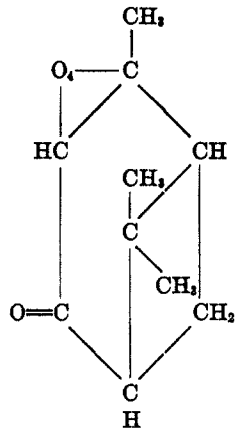
Wt. of sample	*Grams CO_2*	*Grams H_2O*	*%C*	*%H*
0.1783	0.4120	0.1309	63.00	8.20
.2538	.5849	.1828	62.85	8.06
$C_9H_{14}O_3$ (pinononic acid)		calculated	63.53	8.23
$C_{10}H_{16}O_3$ (pinonic acid)		calculated	65.22	8.70

From the oily acid about 45–50% yields of the semicarbazone were obtained using semicarbazide hydrochloride and sodium acetate.

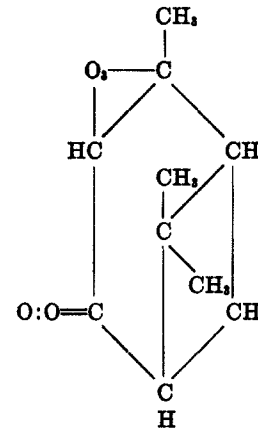
The semicarbazone, after drying in an oven at 135°, and over phosphorus pentoxide for two days gave the following analyses:

Wt. of sample	*Observed volume of N_2*	*%N*
I. 2.842 mg.	0.463 cc. (27°, 758 mm.)	18.16
II. 3.670 mg.	.599 cc. (27°, 758 mm.)	18.28
III. 3.328 mg.	.565 cc. (26°, 741 mm.)	18.59
$C_{10}H_{17}N_3O_3$ (pinononic acid semicarbazone)	calculated	18.50
$C_{11}H_{19}N_3O_3$ (pinonic acid semicarbazone)	calculated	17.42

It was impossible to prepare the pinononic acid in a crystalline form even after hydrolysis of the semicarbazone. This may be due to the fact that various stereoisomers of the structure are possible and would be present together even in the final product. The evidence thus far would indicate the following possible formulas for the product of the reaction between pinene and ozone in the gaseous phase.



Verbenone oxozonide



Verbenone peroxide ozonide

Since both would give the same products on hydrolysis, a decision between them cannot be made by this method.

III. OZONOLYSIS OF 1,3-BUTADIENE

Ozonolysis of unsaturated organic compounds has been employed extensively for proving the location of multiple bonds in a molecule. With the exception of the work of Enklaar (8) on ocimene, ozonolysis of open-chain conjugated systems has not been reported. The object of this work was to study the addition of ozone to butadiene, to determine the type of addition.

1,3-Butadiene gave on complete ozonization in chloroform solution a

1:2,3:4-diozonide, soluble in chloroform, which could not be readily isolated due to its great explosiveness. Oxalic acid crystallized from the chloroform solution of the diozonide on standing. Hydrolysis carried out in the presence of chloroform, using the method of Church, Whitmore, and McGrew (9), gave formaldehyde and glyoxal.

The monozonide of 1,3-butadiene was prepared by bubbling ozone into a solution of butadiene in petroleum ether. The monozonide was only slightly soluble, and collected as a white amorphous solid in the reaction-chamber. Although it is difficult to formulate a mechanism for the hydrolysis of the 1,4-addition-product of ozone to 1,3-butadiene, it would seem that maleic aldehyde would be a likely hydrolytic product. No indication of maleic aldehyde was found as a hydrolytic product of the monozonide in spite of attempts at isolation through the 2,4-dinitrophenylhydrazone, or by oxidation to maleic acid. Hydrolysis carried out as before, gave acrolein and formaldehyde, indicating 1,3-addition. The monozonide is not explosive.

EXPERIMENTAL

Ozone from a Siemens' ozonizer, calibrated against potassium iodide, was precooled by passage through a dry ice condenser and passed into a solution of 1,3-butadiene in chloroform or in petroleum ether. The butadiene solution was cooled by an ice-salt-bath, and a dry ice condenser prevented the loss of butadiene.

Preparation of the diozonide. Ozone was bubbled into a solution of 12 cc. of liquid butadiene in 200 cc. of chloroform for 8 hours until a blue color was apparent in the solution, the blue color being taken as the end-point of complete ozonization.

Hydrolysis of the diozonide. Hydrolysis of the ozonide was carried out by Whitmore's method. Fifty cubic centimeters of the above chloroform solution was added to 200 cc. of water. A few drops of silver nitrate solution and about 4 g. of zinc dust were introduced. Hydrolysis took place immediately, even in the cold. After hydrolysis, the chloroform and water layers were separated. The chloroform layer contained very little of the products. The water layer gave positive color tests for formaldehyde and gave a large amount of methylenedi-β-naphthol, m.p. 189-192° (decomp.). The water solution also gave glyoxal 2,4-dinitrophenylhydrazone m.p. 327° (corr.). The chloroform solution of the ozonide deposited oxalic acid crystals on standing (m.p. 101°, anhydrous 189°).

Preparation of the monozonide. Twenty cubic centimeters of liquid butadiene was dissolved in 200 cc. of petroleum ether, and ozone was bubbled in for 6 hours. The ozonide formed as a white, semi-solid material.

Hydrolysis of the monozonide. The hydrolysis was carried out as before. The petroleum ether was distilled from the solution and from the distillate a 2,4-dinitrophenylhydrazone was obtained (m.p. 156–158°), which gave no lowering of melting point when mixed with known acrolein 2,4-dinitrophenylhydrazone and gave the melting point 130–135° with the known formaldehyde derivative. From the water solution a 2,4-dinitrophenylhydrazone was obtained (m.p. 153–154°). It gave no lowering on mixed melting point with the known formaldehyde derivative and the melting point 132–136° with the known acrolein derivative. No evidence of any other products was found.

SUMMARIES

I

Ozonization in the vapor phase is an excellent method for preparing ozonides of organic compounds having an appreciable vapor pressure and forming stable ozonides. The apparatus used is described. The ozonization of dipentene and *d*-limonene in the gaseous state yields the diozonides.

II

1. The ozonization of pinene in the vapor phase results in the oxidation of the methylene group alpha to the double bond as well as in the addition of ozone to the unsaturated linkage.

2. Errors in the literature in the calculation of the nitrogen content of pinonic acid semicarbazone have been pointed out.

III

1. Ozone adds 1:2,3:4 to 1,3-butadiene to form a diozonide and 1,2 to form a monozonide. The diozonide is very explosive on warming. The monozonide is relatively stable.

2. No evidence of 1,4-addition of ozone could be found in the monozonide.

SYRACUSE, N. Y.

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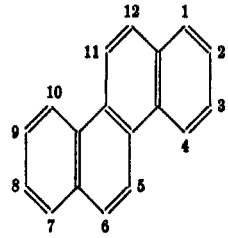
[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF THE OHIO STATE UNIVERSITY]

THE ORIENTATION OF CHRYSENE[1]

MELVIN S. NEWMAN[2] AND JOHN A. CATHCART

Received July 8, 1940

Almost all of the monosubstitution products of chrysene (I) have been made by direct introduction of the substituent into the chrysene nucleus or by simple transformation of a substituent thus introduced. In most of these cases it has been assumed that the entering group occupied the 6 position.[3] However, proof of the positions which these groups occupy has not been furnished to date. It was therefore deemed important to establish conclusively the structure of certain monosubstitution products of chrysene.



I. Chrysene numbering system

The assumption that chrysene is attacked at the 6 position was originally made by Weitzenbock and Lieb (1). These authors had synthesized 5-chrysenecarboxylic acid by the reliable Pschorr method and found it to melt at 222–223°, uncorr., whereas the chrysenecarboxylic acid of Liebermann and Zsuffa (2), prepared by the condensation of oxalyl chloride with chrysene, melted at 303°. Influenced by the knowledge that chrysene on oxidation formed a quinone having carbonyl groups at the 5 and 6 positions, they made the assumption that the higher-melting acid was 6-chrysenecarboxylic acid. Since that time, most workers in the chrysene field have assumed that other substituents directly introduced likewise occupied the 6 position.

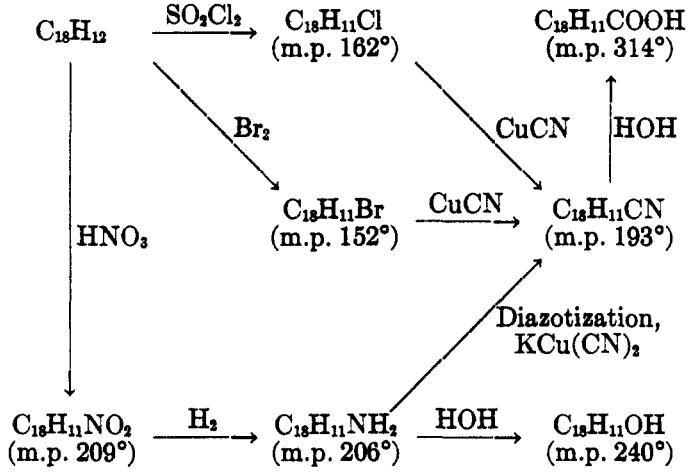
Quite a few chrysene derivatives have been correlated by interconver-

[1] Part of the subject matter herein described was presented to the Organic Division of the American Chemical Society at the meeting in Cincinnati, April, 1940.

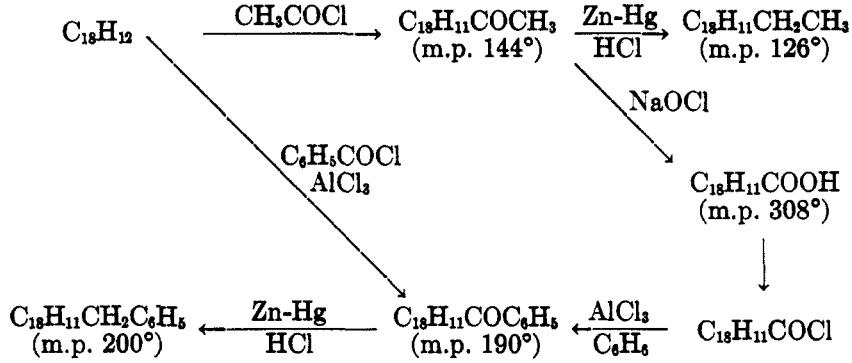
[2] The Elizabeth Clay Howald Scholar at The Ohio State University, 1939–1940.

[3] Chemical Abstracts numbering system.

sions, and it is of some interest to summarize this work, for if the structure of any one of this series is established, then the structures of all are known. In recent patents (3, 4) the following transformations have been demonstrated:



Funke and Müller (5) carried out the reactions indicated below.



In the present work we have shown that only one nitrochrysene (6) is formed on direct nitration. Since reduction to aminochrysene and hydrolysis yielded a chrysenol identical with authentic 6-chrysenol (7), the structure of the above nitration-product is established as 6-nitrochrysene. This finding also provides firm basis for assigning the 6 position to all of the above mentioned substituents. Further evidence is provided by the observation that synthetic 6-ethylchrysene (7) has the same melting point as that recorded for the ethylchrysene of Funke and Müller (5). It is of interest to note that the ethylchrysene, m.p. 236°, of these authors

is not the 5 derivative as tentatively suggested, for 5-ethylchrysene has been synthesized and shown to melt at 92° (8).

In addition, we have sulfonated chrysene (9), isolated pure chrysene-6-sulfonic acid, and characterized it as a *p*-toluidine salt. The position of the entering sulfonic acid group was established by an alkaline fusion which resulted in the formation of 6-chrysenol, identified as its acetate.

EXPERIMENTAL[4]

6-Nitrochrysene. The chrysene used was a commercial product[5], m.p. 253.2–254.2°. It was converted into a finely divided form suitable for reactions by pouring a pyridine solution (10%) into water. The chrysene thus precipitated was thoroughly dried in an oven. Of the many conditions examined the following proved the most satisfactory for nitration. To a mechanically stirred suspension at 40° of 25 g. of chrysene in 700 cc. of glacial acetic acid, was added, all at once, a solution of 20 cc. of nitric acid (sp. gr. 1.42) and 25 cc. of concentrated sulfuric acid in 200 cc. of acetic acid. Within five minutes there was a small rise in temperature, the color became yellow, and flocculation of the suspended solid occurred. After a total of twenty minutes, the solid was collected by filtration, washed with acetic acid and water, and dried in an oven. This product melted at 210.8–212.8°. On one crystallization from 300 cc. of pyridine 21.8 g. (73%) of orange-yellow needles of 6-nitrochrysene, m.p. 213.7–214.2° was obtained. A portion dissolved in pyridine-xylene and purified by means of chromatographic adsorption on activated alumina, formed bright yellow needles, m.p. 214.0–214.6°.

Anal. Calc'd for $C_{18}H_{11}NO_2$: C, 79.10; H, 4.06; N, 5.13.
Found: C, 79.07; H, 4.06; N, 5.10.

Although an extended series of fractional recrystallizations was carried out, no evidence for the presence of a second nitrochrysene was found.

5-Nitrochrysophenazine[3]. The oxidation of 6-nitrochrysene with chromic acid or sodium dichromate in acetic acid resulted in the formation of deep red solids. Although 6-nitrochrysenequinone was undoubtedly present, we were unable to isolate an analytically pure sample. However, treatment with *o*-phenylenediamine yielded the phenazine derivative, which crystallized from pyridine-alcohol as fine yellow needles, m.p. 277.6–279.6°.

Anal. Calc'd for $C_{24}H_{13}N_3O_2$: C, 76.80; H, 3.49.
Found: C, 76.69; H, 3.71.

6,12-Dinitrochrysene. To a stirred suspension at 45–50° of 1 g. of chrysene in 35 cc. of acetic acid containing 1 cc. of concentrated sulfuric acid was added 10.5 cc. of fuming nitric acid over a period of six hours. After standing overnight, the mixture was heated for four hours on the steam-bath and then cooled and poured into water. The solid was crystallized from pyridine to yield 0.90 g. of fine bright yellow needles, m.p. 380.5–382.5° (10).

Anal. Calc'd for $C_{18}H_{10}N_2O_4$: C, 67.92; H, 3.17; N, 8.80.
Found: C, 68.10; H, 3.15; N, 8.79.

6-Aminochrysene. A mixture of 20 g. of 6-nitrochrysene, 5 g. of red phosphorus, 50 cc. of hydriodic acid (sp. g. 1.5), and 250 cc. of acetic acid was refluxed in an all-

[4] All melting points corrected. The analyses were performed by Mr. J. H. Walker whose assistance was made possible by the Ohio State W.P.A. project 65-1-42-89.

[5] Frankel and Landau, Berlin.

glass apparatus until the color was gray (two to three hours). The solid was collected, washed well with acetic acid and water, dried, and extracted with 350 cc. of hot alcohol. This filtered extract was made slightly alkaline with alcoholic potassium hydroxide (color change to orange-red with a blue fluorescence) and cooled quickly. The pale tan leaflets of 6-aminochrysene weighed 15.3 g. (86%) and melted at 210.0–211.0° (11). A product having a lighter color was obtained by shaking a benzene solution of the crude product with sodium bisulfite solution.

Anal. Calc'd for $C_{18}H_{13}N$: C, 88.86; H, 5.38; N, 5.76.
Found: C, 89.08; H, 5.66; N, 5.83.

6-Acetylaminochrysene. A solution of 0.28 g. of 6-aminochrysene in 20 cc. of ethyl acetate was concentrated until solid began to appear, whereupon 15 cc. of hot acetic acid was added to bring the amine into solution. Then 0.1 g. of fused sodium acetate and 2 cc. of acetic anhydride were added. After heating for a few minutes, crystals appeared; cooling to room temperature and filtering gave 0.27 g. (82%) of pale tan needles, m.p. 296.5–299.0°. A sample recrystallized from acetic acid for analysis melted at 299.5–301.0° (12).

Anal. Calc'd for $C_{20}H_{15}NO$: C, 84.18; H, 5.30; N, 4.91.
Found: C, 83.88; H, 5.20; N, 4.86.

6-Diacetylaminochrysene. A solution of 0.14 g. of 6-aminochrysene in 20 cc. of acetic anhydride was refluxed for two hours, cooled somewhat, and diluted to cloudiness with water. There separated 0.15 g. (80%) of glistening tan needles, m.p. 215.8–217.8°. A sample for analysis, recrystallized twice from benzene-petroleum ether, using decolorizing carbon, formed large colorless prisms, m.p. 221.8–223.0° after sintering at 218° (12).

Anal. Calc'd for $C_{22}H_{17}NO_2$: C, 80.71; H, 5.24; N, 4.28.
Found: C, 80.95; H, 4.95; N, 4.24.

6-Chrysenol. In a typical experiment, 2.44 g. of 6-aminochrysene and 15 cc. of 10% sulfuric acid were heated at 220–225° in a sealed tube for six hours. After cooling, the solid was collected and extracted with methyl alcoholic potassium hydroxide. On acidification of this filtered extract, 1.86 g. (76%) of tan solid was obtained. This was recrystallized from acetone-benzene to yield pale tan needles of 6-chrysenol, m.p. and mixed m.p. 248–250° (7). Portions of this product were converted into the acetate, m.p. 158.6–159.2° (7) and the methoxy derivative, m.p. 127.2–127.8° (7). Neither of these derivatives showed a depression of melting point when mixed with authentic specimens (7).

6-Chrysenesulfonic acid. To a well-stirred suspension at 0–5° of 11.4 g. of finely divided chrysene in 100 cc. of *s*-tetrachloroethane was added dropwise over a period of one hour 3.5 cc. of chlorosulfonic acid (9). As the drops came in contact with the suspension a local purple color was produced. The color of the reaction-mixture became gray and darkened as the reaction proceeded. An additional 50 cc. of solvent was used during this time to wash down the sides of the flask. The stirring was continued for five hours at 0–5° and for fifteen hours at room temperature. Ice was then added and the solvent was removed by steaming. To the hot solution (about 1 l.) was added about 30 g. of sodium bicarbonate and then about 400 g. of salt. The precipitate which formed was collected after cooling, and was crystallized from a minimal amount of water, filtering from substances insoluble in water. On cooling, 13.8 g. (83%) of pale tan sodium 6-chrysenesulfonate was obtained. A sample for analysis was further recrystallized from water.

Anal. (13). Calc'd for $C_{18}H_{11}NaO_3S$: Na, 6.96; Found: Na, 6.55.

6-Chrysenesulfonic acid was obtained in 65% yield by strongly acidifying a solution of the sodium salt with hydrochloric acid. The acid was thoroughly dried *in*

vacuo over solid sodium hydroxide and then recrystallized from ethyl acetate-ligroin, separating as stout transparent pale yellow hydrated prisms. Some decomposition took place on recrystallization. On drying *in vacuo* at 110° the solvent was removed and the crystals, now almost colorless, opaque and powdery, melted at 193–194° when heated at the rate of 4° per minute.

Anal. Calc'd for $C_{18}H_{12}O_3S$: C, 70.11; H, 3.92.
Found: C, 69.62; H, 4.19.

This acid was further characterized by the formation of its *p*-toluidine salt (14), m.p. 273–274.5° with decomposition, when heated at the rate of 5° per minute.

Anal. Calc'd for $C_{25}H_{21}NO_3S$: C, 72.27; H, 5.10; N, 3.37.
Found: C, 72.40; H, 5.19; N, 3.27.

6-Chrysenyl acetate from 6-chrysenesulfonic acid. Into a melt of 7 g. of potassium hydroxide at 220° was stirred 0.5 g. of sodium 6-chrysenesulfonate. The temperature was raised slowly to 250° with constant stirring by which time the salt had changed to a viscous dark oil. After the temperature was raised to 270° during three minutes, the melt was cooled somewhat and poured into water. The alkaline solution was acidified, and the precipitate when dry amounted to 0.24 g. This crude product was acetylated to yield 0.22 g. of a crude acetate which upon sublimation and recrystallization from dioxane-water melted at 158.0–158.6°. The melting point was not depressed when the substance was mixed with an authentic sample of 6-chrysenyl acetate (7).

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[CONTRIBUTION FROM THE CONVERSE MEMORIAL LABORATORY OF HARVARD UNIVERSITY]

A QUANTITATIVE STUDY OF THE SO-CALLED "POSITIVE HALOGEN" IN KETONES AND ESTERS

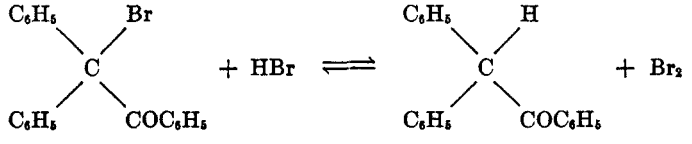
ROLF ALTSCHUL AND PAUL D. BARTLETT

Received July 10, 1940

Many cases are known in which halogen, especially when in the alpha-position to one or more carbonyl groups, undergoes replacement by hydrogen in the presence of ammonia (1), amines (2), hydrazine (3), alcoholic alkalies (4), organometallic compounds (5), or halogen acids (6). In each such case the product possesses more or less active hydrogen in the place of the halogen. Such halogen has accordingly been designated as "positive" (7), this term being used by different authors with varying degrees of literalness. Most of the criteria for "positive" halogen have been qualitative in nature and have suggested a sharp distinction between halogen which was "positive" and halogen which was not. It seems more likely that the replacement of halogen by hydrogen is a mode of reaction which is available in all halogen compounds, but comes to the fore only when the equilibrium, or rate of reaction, or both, is more favorable to it than to other competing reactions.

Our present purpose is to discover the importance of equilibria, rates, and mechanisms in determining the degree of apparent "positivity" of halogen in a series of compounds. The results show that when a reversible reaction is chosen as the basis of comparison of a series of compounds, both the equilibrium and the rate of the reaction are greatly dependent upon structure; that there are at least two mechanisms for establishing the equilibrium, and the relative importance of these two mechanisms also varies with structure. In no case does the mode of reaction characteristic of "positive halogen" disappear, but it may become very slow and the equilibrium may become unfavorable to its occurrence.

The reaction chosen for comparison is that between a bromo compound and hydrogen bromide to give bromine and the debrominated compound, illustrated by the debromination of bromodiphenylacetophenone:



This is a general reaction for α-bromo ketones. The more active the the hydrogen in the parent ketone, broadly speaking, the more rapidly this reaction occurs. It is, moreover, an entirely typical "positive halogen" reaction, in which the bromine of the original organic compound pairs up with the negative part of the attacking reagent. It is free from the usual competing reaction, since an interchange of the bromide ion with the bromine of the ketone would lead to products identical with the starting materials.

Despite the apparent simplicity of this reaction, there were many difficulties in the way of accurate velocity and equilibrium determinations. The results in some individual cases are much more reproducible than in others. Divergences of 50% between determinations of the same quantity by different methods often occur. Nevertheless, the differences between compounds being compared are so large that these rough measurements are capable of yielding useful information, and are accordingly presented.

This debromination reaction is the reverse of the bromination of a ketone, a reaction which has been much studied kinetically in polar solvents (8). Such studies have usually been carried out on ketones and under conditions such that the bromination is practically irreversible Under these conditions the rate of bromination is found to be governed by the rate of formation of the enol and independent of the bromine concentration. For our studies it has been convenient to make the reaction irreversible in the direction of debromination by including a compound which would react with the bromine as fast as it was liberated. Under these conditions the rate is bimolecular, depending upon the concentrations of the bromo ketone and of the hydrogen bromide and independent of the bromine-acceptor. Now, despite the generally recognized fact that at equilibrium a reaction must be proceeding both forward and backward by the same mechanism and with the same rate-determining step, we have here an illustration of the fact that if a forward and reverse reaction are studied separately and under irreversible conditions, they may not have the same rate-determining step and the quotient of the constants determined will not be equal to the equilibrium constant. We have accordingly studied the bromination of diphenylacetophenone in glacial acetic acid containing fourteen equivalents of sodium acetate to prevent its reversal, and the debromination of the resulting bromo ketone in glacial acetic acid containing cyclohexene to consume the bromine. The irreversible bromination is promoted by light, but in the dark proceeds very slowly and at a rate independent of the bromine concentration and not inhibited by antioxidants. This indicates that enolization, an acid-base catalyzed reaction, is the rate-determining step. The irreversible debromination is unaffected by light and by substantial concentrations of

peroxides or antioxidants. It proceeds at a reproducible rate which is proportional to both the hydrogen bromide and bromo ketone concentrations. In the chart of Figure I the equilibrium constant K for the debromination reaction can be seen to be equal to k_2k_4/k_1k_3, whereas under the irreversible conditions of the kinetic measurements only k_1 and k_4 have been determined.

A run conducted without added sodium acetate began very slowly but showed autocatalysis and, after starting, went rapidly to equilibrium. The equilibrium constant for debromination was 0.0015 as determined from this run. This was in rough agreement with values (0.003) determined by approaching the equilibrium from the direction of bromodiphenylacetophenone and hydrogen bromide. It is not certain that the alpha carbon atom is brominated exclusively in this case, but this is rendered highly probable by the fact that in the runs carried out under reversible conditions

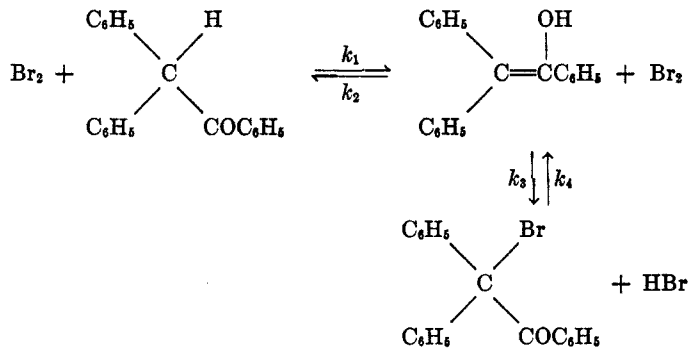


FIGURE I

a constant equilibrium point was reached. Any bromination of the benzene rings would occur irreversibly and result in constantly diminishing bromine concentration rather than an equilibrium. If there is an atomic-chain mechanism for the bromination there must be one also for the debromination. The failure of this to appear under the conditions of our work is doubtless due to the method which we used to ensure irreversibility. The excess cyclohexene which is present in the debrominations must be a very active acceptor for bromine atoms, and must thus serve as an effective inhibitor for the peroxide-catalyzed debromination. When a cyclohexene molecule picks up such a bromine atom in the presence of much hydrogen bromide, it may be expected to start a chain addition of hydrogen bromide to cyclohexene according to the mechanism of Kharasch, Engelmann, and Mayo (9). If these chains are short they will lower the concentrations of cyclohexene and hydrogen bromide by negligible amounts in the process

of inhibiting the chain debromination. Since light requires molecular bromine, and peroxides require hydrogen bromide, in order to produce bromine atoms, the absence of a light effect on the irreversible debrominations and of a peroxide effect on the brominations in the presence of base, is to be expected.

The existence of reproducible rates in each direction in the absence of peroxides shows that there is also a polar mechanism of bromination and debromination, probably identical with that which has been discussed previously for the bromination of enols in polar solvents (10).

Like bromodiphenylacetophenone, the related diketones—methyl-, phenyl-, and benzhydryl- bromodibenzoylmethanes—and bromodi- and bromotri- benzoylmethanes in their irreversible reactions with hydrogen bromide showed no detectable peroxide effect.

Triphenylmethane has weakly active hydrogen, but offers no possibility of an enolic polar mechanism for the establishment of equilibrium in its bromination. It is not surprising to find that triphenylbromomethane shows no reaction with hydrogen bromide in glacial acetic acid in the absence of peroxide, but that added peroxide brings about a liberation of bromine (titer, 1.47 cc. of thiosulfate) in excess of that due to oxidation of the hydrogen bromide by the peroxide (titer, 0.74 cc. of thiosulfate). The reaction is slow at best and the catalyst is used up before equilibrium has been reached. However, by approaching this equilibrium from both directions we were able to find that the equilibrium constant for the debromination of bromotriphenylmethane by hydrogen bromide must lie between the limits 0.015 and 0.043. It is probably very near the latter value, which was the constant limit approached in the bromination of triphenylmethane.

The conversion of alpha- into gamma- bromoacetoacetic ester in the presence of hydrogen bromide is most simply regarded as a reversal of the original bromination to an equilibrium, followed by a slower and less reversible bromination in the new position. Kharasch, Sternfeld, and Mayo (11) have observed that this conversion is dependent upon the presence of peroxide for its occurrence. From our results we should predict that the debromination ought to be capable of occurring by a polar mechanism, since the bromine involved is in the alpha position to two carbonyl groups. The peroxide mechanism would, on the other hand, be expected to be rather important in the rebromination stage at a position at which enolization is probably uncommonly slow.

Table I summarizes the equilibrium and rate constants for the debromination of eight bromo compounds by hydrogen bromide in glacial acetic acid. With the exception of bromobenzhydryldibenzoylmethane and bromotriphenylmethane, all the equilibrium constants have been checked

by approaching the equilibrium from both sides, and a common value obtained. Rate constants have been obtained under antioxidant conditions for the debromination reaction of all but bromotriphenylmethane and triethyl bromomethanetricarboxylate. The progressive replacement of benzoyl groups of bromotribenzoylmethane by phenyl leads to a lowering of both the equilibrium and rate constants for the debromination reaction. The replacement of one benzoyl by methyl has about the same effect as the replacement of two benzoyls by phenyl. Dibenzoylbromomethane has an enormously high rate constant but a rather low equilibrium constant. The latter is intelligible in terms of a high degree of enolization of this bromo ketone, which has very active hydrogen, but this is only an explanation if it is the keto form of the bromo ketone which undergoes debromination, and this renders the high reactivity of the compound the more puz-

TABLE I

EQUILIBRIUM CONSTANTS K AND FORWARD RATE CONSTANTS k_2 (UNDER ANTIOXIDANT CONDITIONS) FOR THE DEBROMINATION OF BROMO COMPOUNDS WITH HYDROGEN BROMIDE IN GLACIAL ACETIC ACID SOLUTION AT 25°

COMPOUND	K	k_2
Bromotribenzoylmethane	2.4	26.
Phenylbromodibenzoylmethane	0.17	11.
Bromodiphenylacetophenone	.003	1.2
Bromotriphenylmethane	.04	.....
Benzhydrylbromodibenzoylmethane	.30	0.65
Methylbromodibenzoylmethane	.0006	0.24
Bromodibenzoylmethane	.01	550.
Triethyl bromomethanetricarboxylate	.075	.....

$$K = \frac{[RH]\,[Br_2]}{[RBr]\,[HBr]}.$$

zling. This bromo ketone cannot, of course, proceed to equilibrium with its debromination product without at the same time establishing equilibrium with dibromodibenzoylmethane. This may influence the apparently displaced equilibrium, in which each atom of organically combined bromine is assumed to be in a molecule of the monobromo compound.

EXPERIMENTAL

Materials

Cyclohexene was fractionally distilled in a slow stream of nitrogen. The fraction used, boiling at 83.2°, was stored under nitrogen, as were the stock solutions in glacial acetic acid made up from it. All these were tested for peroxide with potassium iodide.

The ketones and bromo ketones were prepared and purified by standard methods

in the literature. Table II shows their properties. Bromotribenzoylmethane was prepared as described by Bartlett and Cohen (10) and not by the method of Werner (12), which gives cleavage of the triketone.

The *glacial acetic acid* was purified as follows. The technical product of the Niacet Co. was fractionally distilled through a nine-foot column packed with glass helices at a reflux ratio of 10 to 1. A yield of 63% was obtained of fractions melting sharply at 16.6°. This solvent was used for the equilibrium determinations. Two more batches were prepared with preliminary treatment with chromic anhydride (13), and these samples were used in all the runs in which the control of peroxide content was important.

TABLE II

PURIFICATION OF COMPOUNDS USED FOR MEASUREMENTS

COMPOUND	SOLVENT FOR RECRYSTALLIZATION	M.P., °C.
Dibenzoylmethane	Methanol	75.8–76.8
Bromodibenzoylmethane	Chloroform-ligroin	90.8–91.2
Triphenylmethane	Benzene	92.5–93
Bromotriphenylmethane	Carbon disulfide	151–152
Diphenylacetophenone	Acetic acid	136
Bromodiphenylacetophenone	Pet. ether-chloroform	97.0
Phenyldibenzoylmethane	Ether-pet. ether	147–148
Phenylbromodibenzoylmethane	Methanol	87.5–88.5
Tribenzoylmethane	Acetone	206–210
Bromotribenzoylmethane	Methanol	118–119
Benzhydryldibenzoylmethane	Methanol-acetone	220.5–222
Bromobenzhydryldibenzoylmethane	Methanol-acetone	115.5–116.5
[a]Methyldibenzoylmethane	Ether	82–83
[a]Methylbromodibenzoylmethane	Ethanol-water	64–64.8
Triethyl methanetricarboxylate		(b.p. 150.1–150.2/25 mm.)
Triethyl bromomethanetricarboxylate		(b.p. 154–155 at 13 mm.)

[a] These preparations were made by A. Bavley.

Measurements

In the reactions being studied it is possible either to titrate the bromine by a method which will not affect the bromo ketone or to destroy the bromine quickly, then liberate and titrate the bromine from the bromo ketone. Which method is advantageous depends upon the speed with which the "positive" halogen reacts with hydrogen bromide or hydrogen iodide. We have used altogether four variations of procedure, to which we shall hereafter refer by number.

Method 1. An aliquot portion of the solution was added by pipette to excess cyclohexene in glacial acetic acid under nitrogen, which quickly removed the bromine. To this solution was added solid potassium iodide and the flask was swirled for a time determined to be adequate in the individual case. An aqueous solution of sodium acetate was then added and the iodine was titrated with standard thiosulfate solution in the presence of the precipitated organic material.

Method 2. This is like Method 1 except that the potassium iodide was added in aqueous solution instead of in solid form to the bromine compound in acetic acid. This method was applicable only to the most reactive bromo compounds, but for these it saved a step in the analysis.

Method 3 consisted in the direct determination of bromine by adding the solution to aqueous potassium iodide and partially neutralizing the acetic acid with sodium hydroxide, or adding sodium acetate, then titrating with thiosulfate immediately. This and the following method were applied only to bromo compounds whose reaction with hydrogen iodide was slow.

Method 4. This was used only for rate determinations. A known amount of cyclohexene was used in the run. In each aliquot sample the excess of cyclohexene was determined by reaction with excess bromine and iodimetric back-titration.

Methods 1 and 2 suffered from the disadvantage that a considerable excess of cyclohexene was necessary to make the consumption of the free bromine rapid. Such an excess of cyclohexene, when it contained peroxide, seemed to react to some extent with the iodine liberated in the later step. Method 3 obviously could not be used in the rate runs conducted in the presence of cyclohexene.

Rate of bromination of diphenylacetophenone. The brominations in the presence of sodium acetate were so slow that it was not convenient to carry them to more than a small fraction of completion. Method 3 was used. A typical run in the dark required 432 hours for the bromination of 25% of the ketone. Therefore in all the dark runs the first- and second-order equations fitted equally well, and to determine the order of the reaction it was necessary to compare the values of the unimolecular and bimolecular velocity constants k' and k'' obtained with different concentrations of bromine. For all completely dark runs for which constants are reported the plots of log [ketone] and log $\frac{[\text{ketone}]}{[\text{Br}_2]}$ against time are linear beyond the initial jump. In the runs conducted in the light such plots are not linear, but the time required for attainment of a given fraction of the reaction is so much less than in the dark as to indicate a strong effect of diffuse light. Table III summarizes the runs. Runs 1, 2, 3, and 4 were carried out without the complete exclusion of daylight. The blackened flask of Run 4 was moved into the dark room after 96 hours. Runs 5 to 12 were conducted in the dark room, the solutions being added and samples taken by dim artificial light. The unimolecular constants for the six runs containing sodium acetate vary only from 4.9 to 6.9 $\times 10^{-4}$, whereas the bimolecular constants vary from 1.1 to 3.1 $\times 10^{-2}$ as the initial bromine concentration is changed from 0.0535 to 0.0261. Among these runs giving concordant values of the unimolecular constant are five with access of air and one with an antioxidant. In addition there were two runs without sodium acetate in which the reaction, slow to start, approached equilibrium rapidly when once started. In Run 10 the reaction appeared not to have started after five hours, but at six hours it had reached equilibrium. We might interpret this as meaning either that hydrogen bromide is a powerful catalyst for enolization or that its presence, with undetected peroxide, starts a rapid atomic chain leading to bromination. The latter alternative is less probable, since there was an antioxidant present in Run 10 which should have suppressed the chain reaction.

There was always an initial jump in the unimolecular or bimolecular plot corresponding to the rapid consumption of about 4% of the diphenylacetophenone. From Runs 7 and 8 this rapid consumption appeared to require about two hours, although in most of the runs the first titration was not taken until about five hours had elapsed,

and this and all subsequent points lay on the straight line. This may indicate an enol content of about 4% in a solution of diphenylacetophenone in acetic acid at equilibrium. The magnitude of the jump was independent of the time the solution stood before the bromine was added. If this interpretation of the effect is correct, it is strange that the subsequent enolization rate of the ketone should be so small, either in the presence or absence of sodium acetate. Four per cent of reducing impurity in the ketone is perhaps not out of the question.

Rates of debromination. These runs as well as all others in this paper were conducted in a thermostat at 25°. A freshly prepared solution of weighed bromo compound was brought to temperature in the thermostat. Where Method 1 was to be used for analysis, the solution was evacuated and the air replaced by nitrogen, followed by the introduction of a known amount of standard cyclohexene solution.

TABLE III

SUMMARY OF UNIMOLECULAR (k') AND BIMOLECULAR (k'') CONSTANTS FOR THE BROMINATION OF DIPHENYLACETOPHENONE IN GLACIAL ACETIC ACID AT 25°

RUN	CONDITIONS	[KETONE]	[Br_2]	$k' \times 10^4$ (Time in hours)	$k'' \times 10^2$ (Time in hours)	% COMPLETION
1	Daylight	0.0214	0.02384	....	....	33 (46 hrs.)
2	Daylight	.0205	.0496	....	....	65 (120 hrs.)
3	Blackened flask in daylight	.0210	.0503	27.	5.7	23 (103 hrs.)
4	Blackened flask	.0204	.0556	12.5	2.4	40 (331 hrs.)
5	Dark	.0220	.0250	4.9	2.3	28 (572 hrs.)
6	Dark	.0228	.0292	6.2	2.4	21 (287 hrs.)
7	Dark	.0210	.0238	5.7	2.8	25 (432 hrs.)
8	Dark	.0182	.0216	5.3	2.6	10 (68 hrs.)
9	No NaOAc, Dark—Reversible, autocatalytic					
10	No NaOAc, Dark 0.01 mole tetrabromohydroquinone	.0155	.02445	Reversible, autocatalytic		
11	Satd. hexabromodiphenylamine dark	.0173	.0261	6.9	3.1	31 (19 days)
12	Dark	.0216	.0535	5.6	1.1	35 (28 days)

The reaction was started by adding a standard solution of hydrogen bromide in acetic acid from a pipette. The peroxides used were ascaridole and, more often, cyclohexene peroxide. The concentrations of these peroxides were determined before addition of the bromo compound to the solution, by iodometric titration. When cyclohexene peroxide was used it was obtained by using a cyclohexene solution which had been exposed to the air. In all peroxide-free runs the absence of peroxides was confirmed by blank titrations. Tetrabromohydroquinone was used as an antioxidant.

Diphenylbromoacetophenone. Table IV summarizes the runs which were performed with this ketone without peroxide.

In the titration by Method 1 the iodine liberated is the sum of that due to the

bromo ketone and that due to any peroxide present. The latter quantity was determined on blank samples, and with ascaridole good checks were obtained between the observed and calculated amounts of iodine liberated. On a test solution of ascaridole the calculated thiosulfate titer was 3.66 cc. and that found, after 45 minutes with hydrogen bromide and potassium iodide in acetic acid under nitrogen, was 3.70. The entire amount of added ascaridole still appeared to be present after the bromo ketone had completely reacted in the debromination runs.

Run 2, in which a considerably oxidized solution of cyclohexene was used, showed an apparently arrested reaction for which we are unable to account. The solution turned quite dark and the end-points were poor. The same was true of Run 4, carried out with somewhat less of the same cyclohexene-peroxide solution, and which gave a rate constant distinctly lower than the rest.

TABLE IV

RATE OF DEBROMINATION OF DIPHENYLBROMOACETOPHENONE AT 25° IN GLACIAL ACETIC ACID BY HYDROGEN BROMIDE

RUN	$[Br\text{-}KETONE]_0$	$[HBr]_0$	PEROXIDE OR ANTIOXIDANT	MOLE-EQUIV.	k (TIME MIN.)	% COMPLETION
1	0.0113	0.0625	$C_6Br_4(OH)_2$	0.046	1.1	90
2	.0119	.0626	$C_6H_{10}O_2$	.041	No reaction	....
3	.0114	.0616	None		1.2	85
4	.0120	.0656	$C_6H_{10}O_2$	.025	0.9	75
5	.0122	.0656	Ascaridole	.052	1.2	95
6	.0167	.0656	"	.037	1.1	90
7	.0124	.0616	$C_6Br_4(OH)_2$ (in dark)	.042	1.2	95

TABLE V

RATE OF DEBROMINATION OF BROMODIBENZOYLMETHANE BY HYDROGEN BROMIDE IN ACETIC ACID SOLUTION AT 25°

RUN	$[Br\text{-}KETONE]_0$	$[HBr]_0$	CONDITIONS	k'
5	0.0171	0.0212	0.009 m.e. $C_6Br_4(OH)_2$	550
6	.0089	.0089	.027 m.e. "	580
7	.0047	.0058	.033 m.e. cyclohexene peroxide	550

Bromodibenzoylmethane. When the results of Runs 1–4 were plotted as bimolecular reactions, curves of decreasing slope were obtained. This was found to be due to the inability of a low concentration of cyclohexene to remove the bromine fast enough to prevent some reversal of the reaction. This was overcome in the later runs by the use of an excess of cyclohexene, tenfold for Runs 5 and 6. Table V summarizes the results.

In this table "m.e." means mole-equivalents, moles of the inhibitor or peroxide per mole of bromo ketone. The time in the rate constants is expressed in minutes. The data for Runs 1–4 are omitted since no constants could be calculated from them and they were hence uninformative.

Phenylbromodibenzoylmethane. Method 1 was used. The only difficulty encountered in the runs with this bromo ketone was its slow reaction with potassium

iodide. Run 1, in which only thirty minutes was allowed for the decomposition of the samples, gave a curve of decreasing slope when plotted as a bimolecular reaction. By extending the time of decomposition to 4½ hours we obtained straight lines and concordant values of the rate constant from runs having from a threefold (Run 3) to a sevenfold (Run 2) excess of cyclohexene. In the three runs of Table VI the points covered 70, 99, and 90% of the total reaction, respectively, and the bimolecular plots were quite linear.

Benzhydrylbromodibenzoylmethane. Methods 1 and 4 were used in the titration. In both cases an excess of cyclohexene containing a small amount of peroxide introduced an error during the titration which prevented the plots from being linear. This was the case with Runs 1 and 5. The minimum time of standing with the potassium iodide was found to be three hours for complete decomposition of the bromo ketone by Method 1.

TABLE VI

RATE OF DEBROMINATION OF PHENYLBROMODIBENZOYLMETHANE BY HYDROGEN BROMIDE IN ACETIC ACID AT 25°

RUN	[Br-KETONE]$_0$	[HBr]$_0$	CONDITIONS	k' (TIME IN MINUTES)
2	0.0108	0.0192	0.04 m.e. $C_6Br_4(OH)_2$	10.6
3	.0069	.0181	.06 m.e. "	11.1
4[a]	.0086	.0282	No antioxidant	13.7

[a] Run 4 was performed by A. J. Wells, Jr.

TABLE VII

RATE OF DEBROMINATION OF BENZHYDRYLBROMODIBENZOYLMETHANE BY HYDROGEN BROMIDE IN ACETIC ACID AT 25°

RUN	[Br-KETONE]$_0$	[HBr]$_0$	$C_6Br_4(OH)_2$ MOLE-EQUIV.	METHOD	k'
2	0.00812	0.0262	0.052	1	0.5
3	.00366	.1653	None	1	.65
4	.01068	.0973	None	1	.71
6	.00693	.0362	0.06	4	.65

In a single experiment on the bromination of benzhydryldibenzoylmethane there was no rapid immediate consumption of bromine, indicating the absence of any appreciable amount of enol at equilibrium.

Table VII summarizes the results of the runs on the debromination of benzhydrylbromodibenzoylmethane.

Methylbromodibenzoylmethane. Method 4 was used. It was determined in blank tests that the reduced ketone had no disturbing effect on the bromometric titration of cyclohexene, which made it probable that there was no disturbing enol content at equilibrium. Table VIII summarizes the results.

Bromotribenzoylmethane. Method 2 was used, the time for decomposition of a sample being 6–15 minutes. Blank tests showed that the peroxides and antioxidants used did not interfere with the determination of bromo ketone. Table IX sum-

marizes the results of the kinetic runs. These runs usually covered about 90% of the total reaction and within this limit gave satisfactory straight lines when plotted as bimolecular reactions. Although from a solution containing bromotribenzoylmethane and hydrogen bromide the cleavage products, benzoyl bromide and bromodibenzoylmethane, are readily obtained, it has been shown that under the present conditions, in the presence of cyclohexene, this cleavage is avoided and we are in fact measuring the debromination of the bromo ketone (14).

TABLE VIII

RATE OF DEBROMINATION OF METHYLBROMODIBENZOYLMETHANE BY HYDROGEN BROMIDE IN ACETIC ACID AT 25°

RUN	[Br-KETONE]$_0$	MOLE EQUIVALENTS		k'
		Peroxide	$C_6Br_4(OH)_2$	
1	0.00965	0.025	0.038	0.26
2	.00992		.037	.25
3	.01102		None	.22
4	.00826		0.046	.27
5	.00923		None	.24
6	.00985		None	.24

The bimolecular plots were all linear.

TABLE IX

RATE OF DEBROMINATION OF BROMOTRIBENZOYLMETHANE BY HYDROGEN BROMIDE IN ACETIC ACID AT 25°

RUN	[Br-KETONE]$_0$	[HBr]$_0$	MOLE-EQUIVALENTS PEROXIDE OR ANTIOXIDANT		k'
1	0.00675	0.01340	None		26.7
2	.00760	.01202	None		26.1
3	.00780	.0160	$C_6H_5NH_3Cl$	0.34	25.6
4	.00817	.0160	Cyc. peroxide	.043	24.
5	.00779	.0160	$C_6Br_4(OH)_2$	.073	26.5
6	.00905	.02525	None		21.
7	.00621	.0206	$C_6Br_4(OH)_2$	.016	28.2
8	.00659	.0252	Cyc. peroxide	.043	25.
9	.00631	.0062	None		38.
10	.00777	.0253	None		25.

Run 9, which deviates most from the others in the value of the rate constant determined, was carried out with approximately equal concentrations of the reactants. Accordingly, instead of plotting $\log\frac{[HBr]}{[Br\text{-}Ketone]}$ against time, the quantity plotted was the reciprocal of the common concentration of these reactants. This made the rate constant somewhat more sensitive to small errors in the concentrations.

Run 1 was carried out in the dark and the others in the light.

Measurement of equilibrium constants

The experience gained in making the rate determinations served as a guide in the choice of conditions and methods for the equilibrium measurements. In each case a knowledge of the rates involved told us how long to allow for the attainment of equilibrium and what titration method to employ for its measurement. In each case the equilibrium was approached from both sides and measurements were made over a wide enough time interval to confirm the attainment of equilibrium. When Method 1 was used, the amount of added cyclohexene was kept down to the minimum consistent with accurate titration.

No attempt will be made to report all the experiments which were made on equilibrium constants. In many cases samples from the same run were analyzed by slightly different methods in the course of discovering the procedure best adapted to the case at hand. In each case samples were taken at times different enough to ensure

TABLE X

EQUILIBRIUM OF DEBROMINATION OF PHENYLBROMODIBENZOYLMETHANE BY HYDROGEN BROMIDE IN GLACIAL ACETIC ACID AT 25°

TIME, HRS.	$[Br_2] \times 10^3$	[KETONE] $\times 10^3$	$[HBr] \times 10^3$	[Br-KETONE] $\times 10^3$	K
			Run 1		
20.4	0.029	0.156	0.186	0.186	0.13
22.6	.027	.154	.188	.188	.12
23.6	.027	.154	.188	.188	.12
			Run 2		
22.0	.014	.274	.114	.114	.29
24.9	.009	.269	.119	.119	.17
43.4	.011	.271	.117	.117	.22
			Run 3		
17.7	.145	.131	.445	.247	.17
18.2	.142	.128	.448	.250	.16
41.6	.145	.131	.445	.247	.17

the attainment of equilibrium. As illustrative data we report in Table X three runs on phenyldibenzoylmethane. Runs 1 and 2 began with the ketone and bromine, and Run 3 began with bromo ketone and hydrogen bromide. Method 1 was used on all samples, 12–18 minutes being allowed for decomposition of the samples by potassium iodide.

Table XI compares the values of the equilibrium constant obtained from different runs and from the two directions for each bromo ketone. K is, as before, the equilibrium constant for the debromination.

As is obvious from the table, the equilibrium values are not nearly so concordant as the rate values. This would be expected since the determination in most cases depends upon hydrogen iodide reacting much more rapidly than hydrogen bromide with the bromo ketone. In a velocity determination the errors are all in the same direction and tend to compensate for one another.

With benzhydryldibenzoylmethane, an attempt was made to determine the equi-

librium point starting with the ketone and bromine, but the cleavage reaction (14) proved more disturbing in this case than when starting with the bromo ketone and hydrogen bromide.

TABLE XI

EQUILIBRIUM CONSTANTS FOR DEBROMINATION OF BROMO KETONES BY HYDROGEN BROMIDE IN GLACIAL ACETIC ACID AT 25°

KETONE	RUN	EQUILIBRIUM CONSTANT FROM	
		Ketone + Br_2	Br-Ketone + HBr
Phenyldibenzoylmethane	1	0.13	.....
	2	.22	.....
	3		0.17
Diphenylacetophenone	1	.002	.....
	2	.002	.....
	3	.....	.004
	4	.....	.003
Dibenzoylmethane	1	.....	.002
	2	.....	.01
	3	.....	.004
	4	.....	.02
	5	.....	.01
	6	.01	.....
Tribenzoylmethane	1	.....	1.7
	2	.....	2.9
	3	2.5	.....
Benzhydryldibenzoylmethane	1	.....	0.27
	2	.....	.20
	3	.....	.31
Methyldibenzoylmethane	1	0.0007	.....
	2	.....	.0006
Triethyl methanetricarboxylate	1	.....	.070
	2	.080	.....
Triphenylmethane	1	.....	.015
	2	.043	.....

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SUMMARY

Measurements of rate and equilibrium have been made on the debromination of some bromo ketones by hydrogen bromide in glacial acetic acid

solution. This is regarded as a typical reaction of the so-called "positive halogen." The measurements are summarized in Table I.

The establishment of equilibrium in the bromination of diphenylacetophenone is strongly promoted by light. By implication there must be a peroxide-catalyzed mechanism for the reverse reaction, but the special conditions of our measurements prevented its detection. Peroxides are necessary to the reaction between hydrogen bromide and bromotriphenylmethane. However, the compounds having bromine in the α-position to a carbonyl group react with hydrogen bromide at a rate which is independent of the concentration of peroxides or antioxidants (in the presence of cyclohexene) and which is attributable to a polar mechanism, presumably the exact reversal of the bromination of a ketone through its enol in a polar solvent. These peroxide-independent rates are compared in Table I.

Both the equilibrium and rate of the debromination are greatly dependent upon structure, but do not show any general parallelism with each other. The results emphasize that there can be no sharp distinction between "positive" halogen and other halogen. In no case does the mode of reaction characteristic of "positive" halogen disappear, but it may become very slow and the equilibrium may become unfavorable to its occurrence.

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[CONTRIBUTION FROM THE DEPARTMENT OF BIOCHEMISTRY, COLLEGE OF AGRICULTURE, UNIVERSITY OF WISCONSIN]

THE PREPARATION OF 2-(ALDO-POLYHYDROXYALKYL)-BENZIMIDAZOLES[1]

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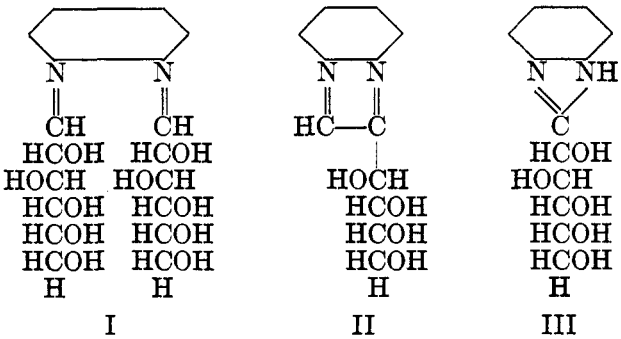
Griess and Harrow (1) in 1887 studied the condensation of carbohydrates with *o*-phenylenediamine and were able to isolate three types of reaction-products. When an aqueous solution of *o*-phenylenediamine and two equivalents of aldose was evaporated to dryness, simultaneous oxidations and condensations occurred with the formation of a Schiff base (I), oxidation on carbon two to give a quinoxaline (II), and oxidation on carbon one to produce a 2-(aldo-polyhydroxyalkyl)benzimidazole (III).[3]



The preparation of compounds of the quinoxaline type from osones is a general reaction, and the structure of the hydroxyquinoxalines from osonic acids has recently been studied by Ohle (3, 4). But the derivatives

[1] Published with the approval of the Director of the Wisconsin Agricultural Experiment Station.

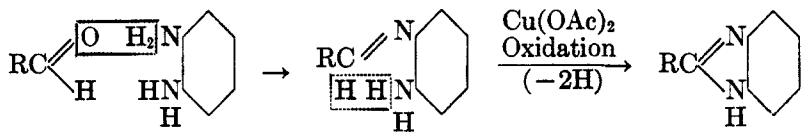
[2] Based on a thesis submitted by Stanford Moore to the Graduate Faculty of the University of Wisconsin in partial fulfillment of the requirements for the degree of Doctor of Philosophy, June 1938. S.M. is indebted to the Wisconsin Alumni Research Foundation for a fellowship in 1935–36 and to the Graduate Research Fund for assistantships for 1936–39. We also wish to thank Dr. R. J. Dimler for the valuable assistance that he has given to this study.

[3] The imidazole structure was assigned by Hinsberg and Funcke (2) and confirmed by Ohle (3) in 1934. In the same year Kuhn and Bar (5) prepared *d*-galacto-benzimidazole to test its reaction to sunlight irradiation as in the lumichrome and lumiflavin cleavages. Karrer and coworkers (6) encountered *l*-arabo-benzimidazole as a side product in the synthesis of flavins.

with the benzimidazole heterocyclic nucleus have received less attention and methods for their preparation in satisfactory yields have been lacking. The benzimidazole derivatives show chemical and physical properties which are superior from a characterization standpoint to those of the hydrazine derivatives of aldo-monosaccharides. The objective in the following investigation has been the development of a satisfactory method of preparation for aldo-benzimidazoles in order to utilize the favorable properties inherent in this type of carbohydrate derivative. An extension of the present study has been its application in a procedure for the identification of a series of naturally occurring aldoses (7).

The direct oxidative condensation of aldehyde and *o*-phenylenediamine, as used in the experiments of Griess and Harrow, gives very low benzimidazole yields. A more promising method of preparation, and the one which has proved satisfactory, would appear to be offered by the preliminary oxidation of aldose to aldonic acid and formation of the benzimidazole by the carboxylic acid-*o*-phenylenediamine condensation (7, 8, 9).

The first and earlier method, however, is not to be discarded in favor of the second path without consideration, because of the advantage it possesses of general applicability to disaccharides as well as to monosaccharides. Therefore the possibility of increasing the yields in this direct aldose condensation has been investigated. In general, with simple aldehydes (acetaldehyde or benzaldehyde), in which there is only one path for oxidation, the condensation with *o*-phenylenediamine gives fair yields of benzimidazoles (Landenburg-Hinsberg synthesis). The yields in this reaction were increased by Weidenhagen (10) in 1936 by introducing cupric acetate into the solution to serve as an immediately available oxidizing agent.

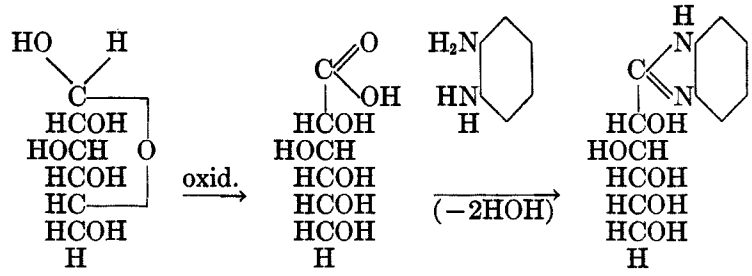


Weidenhagen, however, reported no experiments on the preparation of aldo-benzimidazoles. Under the cupric acetate conditions, which give a sixty per cent yield of 2-phenylbenzimidazole from benzaldehyde, we have been able to obtain only a trace of the desired heterocyclic derivative from glucose. This same procedure, when applied to galactose, gave a forty per cent yield of galacto-benzimidazole.

This fair result with galactose, which is known to be less sensitive to keto-oxidation than the stereoisomeric structure of glucose, suggested that minor changes in Weidenhagen's experimental conditions might also bring the glucose reaction into a satisfactory range. Gradual addition

of the oxidizing agent, decrease in the temperature of the reaction, and increase in the acidity of the reaction-mixture were tried. The yield of gluco-benzimidazole was increased to twenty-five per cent by carrying out the reaction in dilute acetic acid for twelve hours at 50°. But this yield is still low and side reactions are prominent. Therefore, the direct oxidative condensation must be considered impractical for aldo-monosaccharides, at least for the present, in view of the seventy to eighty per cent yields which are obtained by the following procedure involving the aldonic acid condensation.

In the aldonic acid reaction, as an application of the condensation of a carboxylic acid with *o*-phenylenediamine, the oxidative step in the preparation can be made essentially free from side reactions. The several available methods for the oxidation of aldoses to aldonic acids may be used (7).



Glucose Gluconic acid Gluco-benzimidazole

The general procedures for the condensation of carboxylic acids with *o*-phenylenediamine cannot be satisfactorily transferred to the carbohydrate group without modification. With aliphatic and aromatic acids the procedure most frequently used for the *o*-phenylenediamine condensation has been the heating of a mixture of the acid with the base at 100°, 150°, or 180°. More recently the refluxing of an excess of the carboxylic acid with *o*-phenylenediamine in 4 *N* hydrochloric acid has been used by Phillips (11) in the aliphatic series. It is first to be noted that with the stereoisomeric hexonic or pentonic acids, the fusion method, in the absence of acid catalysts, fails to work in certain cases. We have found that xylonic acid, for example, cannot be converted to its corresponding benzimidazole by this method. Haskins and Hudson (9), in the preparation of a series of aldo-benzimidazole bases for use in the resolution of racemic acids, have encountered similar difficulty in the condensation of idonic and *D*-manno-*D*-galaheptonic acids. The addition of hydrochloric acid to the reaction-mixtures gave them thirty and fifty-eight per cent yields of benzimidazoles from the two aldonic acids.

Another factor which arises in the carbohydrate series, and is not present

in the fusion method on optically inactive aliphatic acids, is the consideration of racemization or epimerization. It is well known that when carbohydrate acids are heated to 100° (or above) with organic bases, epimerization may take place at an appreciable rate. In the *o*-phenylenediamine condensation (in the absence of hydrochloric acid) the amount of epimerization appears to be negligible at 100°. However, if an attempt is made to induce condensation of unreactive lactones by increasing the temperature to 135–150°, which is the range in which the majority of aliphatic acids react most satisfactorily, we have found that epimerization may occur. From the fusion of xylonic acid and *o*-phenylenediamine at 150°, in the absence of mineral acids, we have isolated the epimeric lyxo derivative. Addition of acid catalysts prevents this change. In any condensation method to be applied to the carbohydrate series, the question of epimerization must be under complete control. Therefore, from the standpoints both of facility of reaction and elimination of epimerization, the use of acid catalysts in a general procedure for the aldonic acid condensation is to be preferred.

In use of the acid catalyzed condensation, it has been found that the procedure of refluxing the reactants with 4 *N* hydrochloric acid gives less satisfactory yields with carbohydrate acids than with the fatty acid series. For example, the yield from galactonic acid was 24%. If the reaction-mixture was allowed to concentrate to a syrup during the boiling, the yield of the same aldo-benzimidazole was 70%. The use of phosphoric acid (in addition to hydrochloric) has been found to provide a reaction medium which gives more uniformly complete condensation with most aldonic acids. Concentration of the solution of aldonic acid and a slight excess of *o*-phenylenediamine to a syrup at 135° in the presence of hydrochloric and phosphoric acids gives 60–80% yields of aldo-benzimidazoles from arabonic, galactonic, gluconic, lyxonic, mannonic, and rhamnonic acids.

Xylonic acid, however, is an exception to the generality of this 135° procedure. The difference in ease of benzimidazole formation shown by stereoisomeric acids is remarkably great for this aldonic acid and its epimer, lyxonic. Under the above conditions no xylo-benzimidazole is formed, but one equivalent of *o*-phenylenediamine has reacted with xylonic acid and is non-extractable from the reaction-mixture with ether after neutralization with ammonia. Isolation and analysis of the intermediate proves the preliminary reaction to involve condensation with the elimination of *one* molecule of water. Removal of the second molecule of water to give the heterocyclic benzimidazole structure can be accomplished in this case at a higher temperature. An acid reaction medium at 180° gives xylo-benzimidazole in good yields. The catalyst which has proved most satisfactory for the 180° condensation is a mixture of zinc chloride and

hydrochloric acid. However, the phosphoric and hydrochloric acid catalyst can be used.

Together with these differences in the reactivity of aldonic acids with *o*-phenylenediamine, differences are observed in the stability of the benzimidazoles which result from the reaction. Xylo-benzimidazole forms at 180° and is relatively stable at that temperature in the presence of hydrochloric acid and zinc chloride. Gluco-benzimidazole, on the other hand, which forms at 100–135° undergoes appreciable decomposition at 180°. In general, the six aldo-benzimidazoles which can be prepared at the lower temperature are relatively stable up to about 165° in the two hour condensation period.

An indication of the stability of the gluco derivative can be observed in Table I. From 100° to 165° the values for $[\alpha]_D$ are satisfactorily near to the figure of +9.4° which would be obtained if benzimidazole formation were quantitative. However, when a sample of gluco-benzimidazole is heated for two hours with hydrochloric acid and zinc chloride at 180° the calculated rotation rises to +43.4°.

TABLE I

TEMPERATURE-ACID STABILITY OF *d*-GLUCO-BENZIMIDAZOLE

STARTING MATERIAL	CATALYST	TEMPERATURE °C	$[\alpha]_D$ CALCULATED FROM ROTATION OF REACTION-MIXTURE*
d-Gluco-benzimidazole			+9.4
d-Glucono-lactone and *o*-phenylenediamine	$HCl—H_3PO_4$	100	+9.8
" "	$HCl—H_3PO_4$	135	+10.0
" "	$HCl—H_3PO_4$	165	+10.2
" "	$HCl—ZnCl_2$	165	+10.0
d-Gluco-benzimidazole	$HCl—ZnCl_2$	180	+43.4

* The specific rotations of the reaction-mixtures (decolorized and made to volume) have been calculated in terms of the benzimidazole equivalents of the weighed samples of glucono-lactone or benzimidazole used as starting material.

The general chemical properties of this class of derivatives can be briefly summarized. The 2-(aldo-polyhydroxyalkyl)benzimidazoles obtained from aldoses or aldonic acids are amphoteric compounds. As bases (tertiary amines) they dissolve in aqueous acids but may be precipitated by the addition of a stronger base (ammonium hydroxide). Crystalline salts of strong acids (*e.g.*, benzimidazolium chloride) may be readily prepared. The hydrogen on the secondary nitrogen is weakly acidic and aldo-benzimidazoles dissolve in an excess of a strong base (sodium hydroxide)

but not in ammonium hydroxide. They may be precipitated from solution in sodium hydroxide by the addition of carbon dioxide. Ammoniacal silver, zinc, and copper solutions cause the formation of insoluble complex salts. In the absence of excess ammonium hydroxide the precipitation of aldo-benzimidazoles as copper salts is quantitative as shown by an $[\alpha]_D$ of 0.00° on the filtrate. The secondary nitrogen can be alkylated. Gluco-benzimidazole reacts with benzyl bromide in aqueous alcohol to give 1 - benzyl - 2 - (*d* - gluco - pentahydroxyamyl)benzimidazole. The physical properties of individual derivatives (m.p., $[\alpha]_D$, m.p. of picrate and hydrochloride) are tabulated by Moore and Link (7) and by Haskins and Hudson (9) and are therefore not included here.

EXPERIMENTAL

Cupric acetate procedure on glucose. The conditions for the direct oxidative condensation of glucose with *o*-phenylenediamine which have given the best yields in our experiments are as follows. One gram of *o*-phenylenediamine, 4 g. of $Cu(OAc)_2 \cdot H_2O$, and 3 cc. of glacial acetic acid were dissolved in 80 cc. of water in a 100 cc. centrifuge tube. To the solution 2 g. of glucose was added and the stoppered tube was placed in a 53° oven for 14 hours. A small amount of grey precipitate was formed, along with a thin red film on the wall of the tube.

Concentrated ammonium hydroxide was added dropwise to the tube from a dropping-funnel until addition failed to cause further precipitation. Adjustment to complete precipitation was made by testing the supernatant liquid with a drop of ammonia or with dilute acetic acid if an excess of ammonia had been added.

The voluminous precipitate of copper hydroxide and copper salt of the benzimidazole was finally centrifuged, the supernatant solution decanted, and the precipitate washed twice with 40 cc. of water by suspending and centrifuging. Twenty-five cubic centimeters of water and 2 cc. of glacial acetic acid were added and the suspension was decomposed with hydrogen sulfide. After addition of carbon and removal of copper sulfide and hydrogen sulfide, the filtrate was reheated on the steam-bath and made alkaline with ammonia. From the concentrated filtrate *d*-gluco-benzimidazole crystallized to give a yield of 0.6 g. (24%), m.p. 215°. Similarly, galactose gave 40–50% yield of *d*-galacto-benzimidazole (m.p. 245°).

Aldonic acid condensation. Representative is the preparation from gluconic acid (or lactone). To 1.6 g. (9 mM) of gluconolactone (γ or δ) were added 1.1 g. (10 mM) of *o*-phenylenediamine, 4 cc. of water, 1 cc. of ethanol, 0.9 cc. of conc'd hydrochloric acid, and 0.9 cc. of syrupy phosphoric acid. The mixture (with boiling-chip) was warmed in a test tube until in solution, and heated for two hours on an oil-bath kept at 135° ± 5°. During the condensation, water boils off to leave a thick syrup, which was dissolved while still warm in about 10 cc. of water, and filtered with carbon through asbestos. The filtrate (about 30 cc.) was made basic with ammonia. The yield of gluco-benzimidazole (washed with water, acetone, ether) was 1.9 g. (80%).

Calcium, barium, or potassium salts of gluconic, arabonic, galactonic, lyxonic, mannonic, and rhamnonic acids serve equally well as starting products (7).

Reaction of xylonic acid. Under the above conditions at 135° xylonic acid gave no benzimidazole. All products of the reaction remained water-soluble after addition of ammonia. Extraction of unreacted *o*-phenylenediamine with ether gave a recovery of less than 0.1 g. The addition of ammoniacal copper solution (7), how-

ever, gave a heavy precipitate of a copper salt which was centrifuged and decomposed with hydrogen sulfide to give an aqueous solution of the reaction-product free from inorganic salts. After concentration of the solution to a thin syrup, the addition of 25 cc. of acetone caused the formation of an insoluble oil from which the supernatant solution was decanted and the oil heated with a second portion (15 cc.) of acetone to remove water further. The oil was dissolved in a few cc. of hot butanol, acetone added until a permanent cloudiness resulted, and the solution filtered through carbon. After the acetone was removed by evaporation, the butanol solution was slowly concentrated in a vacuum desiccator, and allowed to crystallize for 48 hours. The crystals (needles) were triturated with cold butanol, filtered, and washed with butanol, acetone, and ether; m.p. 140–141°. Recrystallized from butanol (m.p. 140–141°, picrate, m.p. 187–189°) $C_{11}H_{16}N_2O_5$, calc'd N, 10.94; found N, 10.9.

A sample of these crystals heated with hydrochloric acid-zinc chloride for one hour at 180° gave xylo-benzimidazole, m.p. 224°. Xylo-benzimidazole is also obtained by direct condensation from xylonic acid at 180° (7).

*N-Benzyl-*d*-gluco-benzimidazole.* One gram of *d*-gluco-benzimidazole was dissolved in 25 cc. of hot water, and 1.8 cc. of benzyl bromide was added together with sufficient ethanol to keep the alkyl halide in solution. To the warm solution on a steam-bath, 8 cc. of 10% sodium carbonate was added dropwise over a period of about 15 minutes. The alcohol was allowed to boil off during the next hour and the benzyl alcohol which separated as an oil was shaken out with ether. The benzyl derivative crystallized during the ether extraction or upon evaporation of the aqueous solution; yield 0.4 g. (30% of theory, plates, m.p. 188°, $[\alpha]_D^{25}$ +37.0°). $C_{19}H_{22}N_2O_5$ calc'd N, 7.82; found N, 7.74. The benzyl derivative is non-acidic (insoluble in sodium hydroxide). The second crop of crystals from the aqueous solution was completely soluble in sodium hydroxide, m.p. 215° (unreacted gluco-benzimidazole).

SUMMARY

1. Study has been made of the preparation of 2-(aldo-polyhydroxyalkyl)-benzimidazoles by two methods. The earlier yields in the direct oxidative condensation of aldo-monosaccharides with *o*-phenylenediamine have been raised to twenty-five per cent and forty per cent for the gluco and galacto derivatives. For the preparation from the aldonic acid, instead of the aldose, conditions have been developed which give seventy to eighty per cent benzimidazole yields with a series of carbohydrate acids.

2. Observation has been made of the variation in the condensation of stereoisomeric aldonic acids with *o*-phenylenediamine and of the differences in stability of the resulting benzimidazoles.

3. The methods of preparation and the chemical properties of the benzimidazole nucleus have been studied in reference to the use of these derivatives in carbohydrate characterization.

MADISON, WIS.

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[CONTRIBUTION FROM THE RESEARCH LABORATORY OF ARMOUR AND COMPANY]

ORIENTATION IN THE ACYLATION OF PHENOL AND IN THE REARRANGEMENT OF PHENOLIC ESTERS

A. W. RALSTON, M. R. McCORKLE, AND S. T. BAUER

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It has long been known that both the Friedel-Crafts acylation of phenol and the Fries rearrangement of phenolic esters yields a mixture of ortho and para hydroxy ketones, but a systematic study of the factors which influence the relative amounts of isomers obtained has not been reported. It is the purpose of this work to study the influence of conditions upon orientation in these two reactions, and it is hoped that this study may throw some light upon the reaction-mechanisms.

Earlier work upon the acylation of phenol has been directed more to ascertaining the optimum conditions for the preparation of specific compounds than to a study of the reaction itself. We have confined this study to the acylation of phenol with straight chain saturated acid chlorides and to the rearrangement of phenyl esters of the saturated fatty acids in the presence of aluminum chloride. It was undertaken with the purpose of determining the effect of reaction conditions upon orientation. It is believed that the major factors which affect orientation under these conditions are: the molecular proportions of the reactants, the order of addition, temperature, time, the chain-length of the acylating group, and the solvent.

It is known that phenol and acid chlorides can form complexes with the aluminum chloride, and that the formation of one or both of these complexes precedes the formation of a ketone complex. Sandulesco and Girard (1) have shown the formation of $C_6H_5OAlCl_2$ when phenol and aluminum chloride react in equal molecular proportions, and that this compound can react with acid chlorides to form ketones. Where these authors used equal molecular proportions of phenoxyaluminum dichloride and acid chlorides at 125° in the absence of a solvent, both ortho and para ketones were obtained. When caprylyl chloride was used as the acylating agent, the amount of para and ortho hydroxy ketones was 38% and 45%, respectively, and when nonoyl chloride was used, 35% para and 55% ortho hydroxy ketones were obtained. The ratio (p/o) is, therefore, 0.85 in the former case and 0.64 in the latter. It is sig-

nificant to note that the conditions employed by these authors gave a value for p/o which is less than unity.

Perrier (2) first showed that acid chlorides are capable of forming complexes with aluminum chloride and this was confirmed by several authors, among whom may be mentioned Böeseken (3) and Kohler (4). These workers also stated that ketones form a complex with aluminum chloride and Olivier (5) has shown that this complex, $RCOR \cdot AlCl_3$, is not capable of liberating aluminum chloride to promote further acylation. This is in accord with the observations made by Olivier (5) and Groggins (6), that in acylations with acid chlorides at least a molecular equivalent of condensing agent is required.

Since in the acylation of phenol both of the reactants and also the product can form complexes with the aluminum chloride, it follows that the molecular proportion of aluminum chloride employed should play an important role, not only in determining the products obtained, but in the reaction-mechanism itself. It appears logical that the aluminum complexes present have a directing influence upon orientation and since the complexes which can be present are dependent upon the molecular proportion of aluminum chloride used, the amount employed is an important factor. In order to study this factor we have run a series of experiments in which only the complex, $C_6H_5OAlCl_2$, is present and a series in which both the acid chloride complex and phenol complex are present. Caprylyl chloride was chosen as the acylating agent because the para hydroxy ketone is a solid and the ortho a liquid, and thus lend themselves easily to separation. The solvent employed was tetrachlorethane and the reaction time six hours, unless otherwise indicated. The isomers were separated by the preferential solubility of the para hydroxy ketones in sodium hydroxide solution. Table I shows the isomeric hydroxycaprylophenones obtained using various molecular proportions of aluminum chloride.

An examination of Table I shows that the use of equal molecular proportions of aluminum chloride and phenol favors ortho hydroxy ketone and that more aluminum chloride favors the formation of the para isomer. It, therefore, appears that when both complexes are present there is a preferential para orientation. It also appears that when excess aluminum chloride is used the ratio (p/o) is independent of the order of addition of the reactants. In order to test this conclusion, two runs were made in which the complexes were formed separately and then allowed to react in the presence of tetrachlorethane. The results obtained are shown in Table II.

It is evident that where both complexes are previously formed the acyl group shows a decided preference for the para position. If the

acid chloride complex is allowed to react with phenoxyaluminum dichloride the ratio (p/o) is greater than unity. The previous formation of the complexes excludes the possibility of the reaction,

$$RCOCl \cdot AlCl_3 + C_6H_5OH \rightarrow RCOCl + C_6H_5O \cdot AlCl_2 + HCl \rightarrow HOC_6H_4COR \cdot AlCl_3,$$

taking place, and it is significant to note that when this possibility is excluded the yield of the para isomer is materially increased. That this

TABLE I

EFFECT OF THE MOLECULAR PROPORTION OF ALUMINUM CHLORIDE ON THE ACYLATION OF PHENOL WITH CAPRYLYL CHLORIDE. SOLVENT: TETRACHLORETHANE

RUN NO.	TEMP., °C.	MOLECULAR RATIOS	ORDER OF ADDITION	% PARA	% ORTHO	% ESTER	RATIO p/o
1	70	Phenol 2 $AlCl_3$ 2 RCOCl 1	Phenol $AlCl_3$ RCOCl	35.4	47.0	11.6	0.75
2	70	Phenol 1 $AlCl_3$ 2 RCOCl 1	RCOCl $AlCl_3$ Phenol	68.2	23.4	1.1	2.91
3	70	Phenol 1 $AlCl_3$ 2 RCOCl 1	Phenol $AlCl_3$ RCOCl	67.4	24.8	0.0	2.72

TABLE II

REACTION OF $C_7H_{15}COCl \cdot AlCl_3$ WITH $C_6H_5O \cdot AlCl_2$ SOLVENT: TETRACHLORETHANE

RUN NO.	TEMP., °C.	MOLECULAR RATIOS	ORDER OF ADDITION	% PARA	% ORTHO	% ESTER	RATIO p/o
4	50	Phenol 1 $AlCl_3$ 2 RCOCl 1	$RCOCl \cdot AlCl_3$ $C_6H_5O \cdot AlCl_2$	70.0	16.4	2.1	4.27
5	50	Phenol 1 $AlCl_3$ 2 RCOCl 1	$C_6H_5O \cdot AlCl_2$ $RCOCl \cdot AlCl_3$	72.5	18.5	1.1	3.93

reaction may occur is borne out by the observation that the p/o ratio is essentially independent of the order of addition (Table I).

Table III shows the effect of temperature upon the relative yields of isomeric ketones when the complex $C_6H_5O \cdot AlCl_2$ is present, but not the complex $RCOCl \cdot AlCl_3$. All of these runs were conducted in tetrachlorethane and were heated for six hours.

Table IV shows the effect of temperature upon the relative yield of

isomers when the phenol is added to the previously formed acid chloride-aluminum chloride complex.

An examination of the data reported in Table III shows that the relative yield of isomers is independent of the temperature over the range 50° to 100°, but that the run at 30° abnormally favors ortho orientation. The very low ratio obtained at 30° shows that the low temperature has exerted a directing influence. Table IV shows that the runs made at 50° and 100° are comparable as regards the p/o ratio and are not sig-

TABLE III

EFFECT OF TEMPERATURE UPON THE ACYLATION OF PHENOL WITH CAPRYLYL CHLORIDE IN THE PRESENCE OF ALUMINUM CHLORIDE. SOLVENT: TETRACHLORETHANE

RUN NO.	TEMP., °C.	MOLECULAR RATIOS	ORDER OF ADDITION	% PARA	% ORTHO	% ESTER	RATIO p/o
6	30	Phenol 2	Phenol				
		$AlCl_3$ 2	$AlCl_3$	4.1	11.4	72.3	0.36
		RCOCl 1	RCOCl				
7	50	"	"	24.5	31.0	34.0	.79
1	70	"	"	35.4	47.0	11.6	.75
8	80	"	"	31.0	42.7	10.9	.72
9	100	"	"	39.5	50.0	1.0	.78

TABLE IV

EFFECT OF TEMPERATURE UPON THE ACYLATION OF PHENOL WITH CAPRYLYL CHLORIDE IN THE PRESENCE OF ALUMINUM CHLORIDE. SOLVENT: TETRACHLORETHANE

RUN NO.	TEMP., °C.	MOLECULAR RATIOS	ORDER OF ADDITION	% PARA	% ORTHO	% ESTER	RATIO p/o
10	30	RCOCl 1	RCOCl				
		$AlCl_3$ 1	$AlCl_3$	16.8	11.2	61.1	1.50
		Phenol 1	Phenol				
11	50	"	"	15.5	17.4	49.0	0.89
12	100	"	"	23.5	25.0	....	.95

nificantly different from those reported in Table III over the same temperature range. It is of interest to note that the run at 30° also gives a p/o ratio decidedly different from the runs made at the higher temperatures. These observations necessitate some modification of the statement previously made that the p/o ratio is independent of the order of addition of the reactants. It was stated previously that it is our belief that conditions in which the complex $C_6H_5O \cdot AlCl_2$ is present have an ortho directing influence and the presence of $RCOCl \cdot AlCl_3$ has a para

directing influence. It will be noted that at 30°, when the complex $C_6H_5O \cdot AlCl_2$ is formed, the ortho orientation is decidedly favored, but when the phenol is added to the previously formed $RCOCl \cdot AlCl_3$ complex at this temperature, a para orientation is preferred. Low temperatures, therefore, favor the presence of the complex initially formed, and the fact that higher temperatures mask this effect suggests a possibility of an exchange of the aluminum chloride from the acid chloride to the phenol prior to the actual acylation. This exchange is evidently not a controlling reaction at the lower temperatures and explains why the ratio (p/o) is dependent on the order of addition of the reactants at low temperatures but independent at the higher temperatures. The ratio (p/o) is, therefore, dependent upon the temperature only to the extent that temperature determines the complexes which actually enter into ketone formation.

Ester formation is the predominant reaction at the lower temperatures, but decreases with an increase in the amount of aluminum chloride or temperature. It is evident that any study of the influence of reaction conditions upon orientation must take this ester formation into consideration. We are not, however, justified in assuming the presence of the ester as such during the reaction, since it may be formed by the hydrolysis of an aluminum chloride-ester complex. This opinion is based upon our work on the Fries rearrangement of the same phenyl ester, which shows that if we rearrange phenyl caprylate in the presence of aluminum chloride the ratio of isomers differs decidedly from that obtained using a Friedel-Crafts procedure. The following reactions are offered as an explanation of ester formation:

(A) $$C_6H_5O \cdot AlCl_2 + RC\begin{matrix}O\\ \diagup\\ \diagdown\\ Cl\end{matrix} \rightleftarrows C_6H_5OCOR \cdot AlCl_3$$

(B) $$C_6H_5OCOR \cdot AlCl_3 \rightarrow HOC_6H_4COR \cdot AlCl_3$$

The ester complex apparently does not form by reaction of aluminum chloride with the ester itself as in the Fries rearrangement, but results from a sharing of the aluminum chloride by the phenol and the acid chloride. Ester-complex formation proceeds very rapidly as compared with ketone-complex formation and if the reaction is hydrolyzed at any intermediate point, the product will consist of a mixture of ortho and para hydroxy ketones and ester, the respective amounts being dependent upon the amounts of the various complexes present at the time of hydrolysis.

Ever since the work reported by Fries and Finck (7), that phenyl esters will rearrange in the presence of aluminum chloride to give hydroxy

ketones, there has been a question whether the products resulted from an intra- or inter- molecular reaction. During the past few years there has been an imposing amount of evidence presented to show that the Fries rearrangement is an intermolecular reaction, the mechanism of which is a scission of the ester followed by an acylation. Rosenmund and Schnurr (8) isolated mixed products when a mixture of 2-chloro-4-methyl acetyl phenol and 4-methyl benzoyl phenol reacted in the presence of aluminum chloride. Cox (9) has shown that when a phenyl ester rearranged in the presence of diphenyl ether and aluminum chloride the product contained both the acyl phenol and the acyl diphenyl ether, and stated that it is difficult to account for the formation of such products except by assuming an intermolecular reaction-mechanism. It is, however, significant that many workers have observed that the products obtained are often dependent upon whether one uses Fries or Friedel-Crafts conditions. Witt and Braun (10), von Auwers and Mauss (11), and Mosettig and Burger (12) have commented upon this distinction. Hey and Jackson (13) concluded, after a study of former work coupled with their own observations, that these two reactions do not necessarily follow the same course.

It has been shown in the first portion of this paper that the products obtained in the Friedel-Crafts reaction between phenol and caprylyl chloride are quite dependent upon the amount of catalyst employed and to a limited extent upon the temperature and order of addition of the reactants. It is possible that these factors may also influence the Fries rearrangement and that a study of them may show a correlation between the Fries and Friedel-Crafts reactions and throw some light upon the mechanism of the Fries rearrangement. The work of Cox (9) on the rearrangement of phenyl esters in diphenyl ether was repeated using phenyl caprylate with excess aluminum chloride in excess diphenyl ether. The product consisted of 85% *p*-phenoxycaprylophenone, 3.9% *p*-hydroxycaprylophenone, and a trace of *o*-hydroxycaprylophenone. It appears that the most logical explanation of the high yield of *p*-phenoxycaprylophenone is to assume an intermolecular reaction. Another possible explanation of these results would be a reaction of *p*-hydroxycaprylophenone with the diphenyl ether. Although this possibility is remote, it should be confirmed or excluded and we, therefore, attempted to acylate diphenyl ether with *p*-hydroxycaprylophenone in the presence of aluminum chloride. Using a ratio of one mole of ketone to two moles of aluminum chloride in excess diphenyl ether at 70° for six hours we recovered 96% of the original *p*-hydroxycaprylophenone and found no evidence of the formation of *p*-phenoxycaprylophenone, which shows that the *p*-phenoxycaprylophenone isolated in the former case must have

been formed directly and not by a shift of the acyl group from the hydroxy ketone to the diphenyl ether.

Table V shows the products obtained in the Fries rearrangement of phenyl caprylate in the presence of aluminum chloride using tetrachlorethane as the solvent.

It will be noted that the Fries rearrangement of phenyl caprylate gives a p/o ratio greater than unity. When we compare the Friedel-Crafts reaction of phenol with caprylyl chloride in the presence of aluminum chloride using equal molecular proportions of the three reactants (Run 12) with the Fries rearrangement of phenyl caprylate using equal molecular proportions of ester and aluminum chloride (Run 15), we see that the latter condition favors para orientation to a greater extent than the former. An increase of temperature from 70° to 100° decreases the amount of ester but does not have a significant effect upon the ratio of isomers. When the amount of aluminum chloride is increased to two moles, the

TABLE V

FRIES REARRANGEMENT OF PHENYL CAPRYLATE

RUN NO.	TEMP., °C.	MOLECULAR RATIOS	% PARA	% ORTHO	% ESTER	RATIO p/o
13	70	Ester 1 $AlCl_3$ 1	45.0	33.5	15.0	1.35
14	70	"	42.1	31.4	4.6	1.34
15	100	"	55.5	38.1	0.4	1.43
16	70	Ester 1 $AlCl_3$ 2	63.0	30.0	.4	2.10

p/o ratio is markedly increased, which effect was likewise observed in the Friedel-Crafts acylation.

It was stated previously that the weight of evidence favors the intermolecular reaction-mechanism as an explanation of the Fries rearrangement but that many observations have been reported which show that the products differ from those obtained in Friedel-Crafts reactions. This suggests some fundamental difference between the two reactions. The work presented by Rosenmund and Schnurr (8) and that contained in this paper shows that under certain conditions the ester is a major product of the Friedel-Crafts reaction. This has led to the belief that the Friedel-Crafts acylation of phenol is initiated by an esterification, and has been used to support the statement that the two reactions have a common mechanism. Knowledge that the amounts of products differ, dependent upon whether Fries or Friedel-Crafts conditions are employed, is quite disturbing if we are dealing essentially with the same reaction in both cases. There are two considerations which may serve to explain this

apparent discrepancy: first, the ester resulting from the Friedel-Crafts acylation of phenol may not be present as an ester during the acylation; second, since ketone formation removes the aluminum chloride as a complex, the initial conditions in the rearrangement differ from the conditions in the latter stages of the reaction in the molecular ratio of aluminum chloride present.

As regards the first of these considerations, the runs summarized in Table VI show that in spite of the initial high yields of ester at 30° (Run 6), a typical Friedel-Crafts p/o ratio, for equal molecular proportions of the three reactants, is obtained if the temperature is raised after ester formation to a point where the Friedel-Crafts reaction is complete, or if the reaction is allowed to proceed for an extended period of time.

The ratios obtained in runs 17 and 18 are in substantial agreement with the value of 0.74 for the ratio obtained with the same molecular

TABLE VI

EFFECT OF INCREASED TEMPERATURE AND TIME UPON ACYLATION PRODUCTS OF PHENOL AND CAPRYLYL CHLORIDE AT 30°. SOLVENT: TETRACHLORETHANE

RUN NO.	TIME AND TEMP.	MOLECULAR RATIOS	% PARA	% ORTHO	% ESTER	RATIO p/o
17	30° for 6 hrs. and then 100° for 6 hrs.	Phenol 2 $AlCl_3$ 2 RCOCl 1	39.5	53.6	1.4	0.74
18	30° for 72 hrs.	"	19.5	28.6	40.5	.68

proportions of reactants at 100° (Run 9) and differ decidedly from the value 1.43 for the Fries rearrangement (Run 15).

Regarding the second of these considerations, it will be noted that the p/o ratio for the Fries rearrangement of phenyl caprylate is intermediate between the values obtained in the Friedel-Crafts acylation of phenol with caprylyl chloride using one mole of aluminum chloride and that obtained when two moles are employed.

The Fries rearrangement of phenyl caprylate can be represented as follows:

$$C_6H_5OCOC_7H_{15} \xrightarrow{2AlCl_3} C_6H_5O\cdot AlCl_2 + RCOCl\cdot AlCl_3 + HCl \longrightarrow Cl_2AlOC_6H_4COC_7H_{15}.$$

Most of the work heretofore reported upon this rearrangement has employed equal molecular proportions of ester and aluminum chloride. When these ratios are employed the initial conditions decidedly favor the formation of the para isomer because of the great excess of aluminum

chloride present, but as the reaction proceeds the later stages are under conditions favoring the formation of the ortho isomer.

The effect of chain-length upon orientation in the Friedel-Crafts acylation of phenol has recently been determined by Ralston and Bauer (14). The work reported in the present article shows that any conclusion as to the effect of a variable applies only to the specific conditions employed and must be coordinated with the possible influence of other variations. A repetition of our work on the effect of chain-length upon orientation has substantiated our findings; however, it was found that in the case of the 50% yield of *o*-hydroxycaprylophenone reported, the product contained 64.5% of phenyl caprylate. The other *o*-hydroxyphenones reported were found to be free of ester.

The effect of chain-length in the Fries rearrangement of phenyl esters using equal molecular proportions of esters and aluminum chloride at 70° is shown in Table VII. In view of the data presented in Table VII,

TABLE VII

EFFECT OF CHAIN-LENGTH IN FRIES REARRANGEMENT AT 70° (EQUAL MOL. RATIOS OF ESTER AND ALUMINUM CHLORIDE). SOLVENT: TETRACHLORETHANE

RUN NO.	ESTER	% PARA	% ORTHO	% ESTER	RATIO p/o
13	Phenyl caprylate	45.0	33.5	15.0	1.35
14	Phenyl laurate	46.1	28.0	....	1.64
15	Phenyl myristate	43.3	34.5	22.8	1.26
16	Phenyl palmitate	19.7	14.9	....	1.32
17	Phenyl stearate	21.2	18.3	....	1.16

it appears that chain-length does not have a consistent influence upon orientation in the Fries rearrangement for the series of esters studied. No generalization can be drawn from the work of others as to the effect of chain-length upon orientation during the rearrangement of the lower molecular weight phenyl esters. Coulthard, Marshall, and Pyman (15) report a preferential ortho orientation for phenyl butyrate, hexoate and heptoate; however, Hartung, Munch, Miller, and Crossley (16) and Edkins and Linnell (17) state that the para position is favored in the rearrangement of phenyl propionate and phenyl acetate, respectively. The proportions of reactants and the conditions employed by these various authors differ, so that no comparison can be rigidly drawn.

Considerable work has previously been reported indicating that solvents markedly influence orientation, but most of these findings were subordinate to other considerations and the work is difficult to coordinate because of the variety of reaction conditions imposed. Riddell and Noller (18) state that solvents influence the catalytic activity of aluminum chloride-

ferric chloride mixtures; however, Fieser and Bradsher (19) found that the ratio of homo- and hetero-nuclear substitution-products in the acylation of *p*-methoxydiphenyl with acetyl chloride was essentially independent of the solvent employed. In view of the fact that the data presented in this paper are all based upon the use of tetrachlorethane, it was decided to ascertain if the conclusions would hold if other solvents were employed. The influence of four solvents—nitrobenzene, carbon disulfide, a hydrocarbon (Skellysolve "B"), and tetrachlorethane—upon orientation in the acylation of phenol with caprylyl chloride in the presence of aluminum

TABLE VIII

INFLUENCE OF SOLVENTS IN THE ACYLATION OF PHENOL WITH CAPRYLYL CHLORIDE

RUN NO.	TEMP., °C.	SOLVENT	MOLECULAR RATIOS	% PARA	% ORTHO	% ESTER	RATIO p/o
18	70	Nitrobenzene	Phenol 2 $AlCl_3$ 2 RCOCl 1	60.0	22.7	....	2.64
1	70	Tetrachlorethane	"	35.4	47.0	11.6	0.75
19	46	Carbon disulfide	"	3.2	21.8	68.1	0.15
20	65	Skellysolve "B"	"	45.5	43.8	1.6	1.05

TABLE IX

INFLUENCE OF SOLVENTS IN THE ACYLATION OF PHENOL WITH CAPRYLYL CHLORIDE (EXCESS ALUMINUM CHLORIDE)

RUN NO.	TEMP., °C.	SOLVENT	MOLECULAR RATIOS	% PARA	% ORTHO	% ESTER	RATIO p/o
21	70	Nitrobenzene	Phenol 1 $AlCl_3$ 2 RCOCl 0.66	71.4	19.1	...	3.74
22	70	Tetrachlorethane	"	68.0	25.1	...	2.71
23	46	Carbon disulfide	"	53.2	32.7	2.7	1.62
24	65	Skellysolve "B"	"	57.0	34.8	0.7	1.64

chloride was determined. Two series were run, one containing an insufficient amount of aluminum chloride to form both complexes and the other employing an excess. Previous work using tetrachlorethane has shown the former condition to favor ortho and the latter para orientation. The products resulting from the reaction of the phenol-aluminum chloride complex and caprylyl chloride in various solvents are shown in Table VIII, and Table IX shows the effect of solvent on the acylation when an excess of aluminum chloride is employed.

The results reported in Tables VIII and IX show that solvents have a profound influence upon the p/o ratio. Where only the phenol-alumi-

num chloride complex is present the solvents can be arranged in the following order of decreasing ortho directing influence: carbon disulfide, tetrachlorethane, Skellysolve "B," and nitrobenzene. When excess aluminum chloride is employed, this order is: carbon disulfide, Skellysolve "B," tetrachlorethane, and nitrobenzene. The extreme para directing influence of nitrobenzene is noteworthy. Stockhausen and Gattermann (20) have stated that nitrobenzene and aluminum chloride form a complex compound and it is possible that the presence of this complex accounts for the directing influence of this solvent. In all cases the use of an increased amount of aluminum chloride increased the para to ortho ratio and also this ratio was greater than unity when an excess of aluminum chloride was employed.

Since nitrobenzene has been shown to have a para directing influence in the Friedel-Crafts reaction, a comparison of nitrobenzene with tetrachlorethane as a solvent for the Fries rearrangement was indicated. Table X shows a comparison of these solvents for the rearrangement of

TABLE X

FRIES REARRANGEMENT OF PHENYL CAPRYLATE

RUN NO.	TEMP., °C.	SOLVENT	MOLECULAR RATIOS	% PARA	% ORTHO	% ESTER	RATIO p/o
16	70	Tetrachlorethane	Ester 1 $AlCl_3$ 2	63.0	30.2	0.4	2.10
25	70	Nitrobenzene	"	71.4	20.1	...	3.67

phenyl caprylate using two moles of aluminum chloride per mole of ester. It will be noted that the p/o ratio is decidedly higher for nitrobenzene than for the tetrachlorethane.

In arriving at the conclusions presented in this paper, it was realized that one possible explanation for the data would be to assume that the ketones themselves changed from the ortho to para isomers or *vice versa* under the experimental conditions imposed. In order to eliminate this as a possible explanation, *o*-hydroxycaprylophenone was heated for six hours at 100° in tetrachlorethane in the presence of three molecular proportions of aluminum chloride. Considerable decomposition was encountered and only 35.0% of the original ketone was recovered. The amount of aluminum chloride was then reduced to two molecular proportions and 89% of *o*-hydroxycaprylophenone was recovered with no evidence of the presence of its para isomer. A repetition of this experiment using *p*-hydroxycaprylophenone resulted in a recovery of 96.5% of the original ketone with no evidence of the ortho isomer. This shows rather conclusively that the ketones themselves do not rearrange.

It was also considered possible that the high ratio of para to ortho isomers obtained when nitrobenzene was employed as the solvent may be due to a rearrangement of the ortho ketone to para ketone under the influence of aluminum chloride in this solvent. When *o*-hydroxycaprylophenone was heated for six hours at 70° in nitrobenzene with two molecular proportions of aluminum chloride, the recovery of the *o*-hydroxycaprylophenone was 93%, and since no *p*-hydroxycaprylophenone was found in the product, it was concluded that the directing influence of nitrobenzene must exert itself prior to ketone formation.

EXPERIMENTAL

The following procedures are typical examples of the runs reported in preceding tables.

Reaction of caprylyl chloride with phenol-aluminum chloride complex. Phenol (20 g., 0.2 mole) and 50 cc. of tetrachlorethane were placed in a three-necked flask equipped with a mercury-sealed stirrer and a thermometer. Aluminum chloride (26 g., 0.2 mole) was added slowly with stirring. There was a vigorous evolution of hydrogen chloride during the addition. The mixture was heated to 70° and after the evolution of gas had subsided, caprylyl chloride (16.2 g., 0.1 mole) dissolved in 20 cc. of tetrachlorethane was added dropwise. The reaction temperature was maintained at 70° for six hours, after which the mixture was hydrolyzed by pouring into water. Tetrachlorethane was then removed by steam distillation, and the residue cooled and extracted three times with 50-cc. portions of ether. The ether solution was extracted with 3% aqueous sodium hydroxide solution, and the extraction was repeated with fresh portions of sodium hydroxide solution until the aqueous layer was colorless.

The ether solution was then washed with water and this washing added to the alkaline extraction, after which the ether solution was dried with anhydrous sodium sulfate. After removal of the ether the residue was distilled under 1 mm. pressure, the fraction boiling between 120–130° collected and weighed.

The alkaline extract was acidified with hydrochloric acid and heated to boiling in order to remove the ether. *p*-Hydroxycaprylophenone solidified upon cooling and was filtered, dried, and weighed. After one crystallization from a mixture of petroleum ether (b.p. 60–68°) and carbon tetrachloride it melted at 62.0–62.5° (mixed melting point 62.5°).

The following procedure was used for the determination of ester in the ortho-ester fraction: a one-gram sample was weighed into a 50 cc. Erlenmeyer flask and 10 cc. of approximately 0.5 *N* sodium hydroxide solution together with 15 cc. of 95% ethyl alcohol added. The mixture was refluxed until solution was completed (usually one hour), the condenser then washed down with water, and the alcohol removed by boiling. The excess sodium hydroxide was titrated with standard hydrochloric acid using phenolphthalein as the indicator. A blank determination was made for each analysis. The results were calculated to give the per cent of phenyl caprylate in the original mixture. In order to check this procedure a sample of pure phenyl caprylate was analyzed and the per cent of ester found to be 99.4%.

Reaction of phenol with caprylyl chloride-aluminum chloride complex. Caprylyl chloride (16.2 g., 0.1 mole) was mixed with 50 cc. of tetrachlorethane and placed in a three-necked flask equipped with stirrer and thermometer. Aluminum chloride

(14 g., 0.11 mole) was added slowly with stirring, after which the mixture was heated to 100°. Phenol (10 g., 0.11 mole) dissolved in 30 cc. of tetrachlorethane was then added dropwise. The reaction was heated for six hours at 100°, after which the reaction-product was hydrolyzed and the solvent removed by steam distillation. The isomers were then separated and weighed as described in the preceding example. All of the runs reported in which phenol was added to a caprylyl chloride-aluminum chloride complex were made in a similar manner.

Addition of phenol-aluminum chloride complex to caprylyl chloride-aluminum chloride complex. Caprylyl chloride (16.2 g., 0.1 mole) was dissolved in 30 cc. of tetrachlorethane in a three-necked flask. Aluminum chloride (14 g., 0.105 mole) was then added with mechanical stirring and the temperature raised to 50°. Phenol (10 g., 0.11 mole) was then weighed into a separate flask and aluminum chloride 14.5 g., 0.11 mole) was added slowly. The mixture was heated to 50° and maintained at this temperature until the evolution of hydrogen chloride had subsided. The solution of the complex in tetrachlorethane was added dropwise to the caprylyl chloride-aluminum chloride complex and the mixture heated at 50° for six hours. The mixture was hydrolyzed, the solvent removed, and the isomers separated as previously described.

Preparation of phenyl caprylate. Phenol (37.6 g., 0.4 mole) was mixed with caprylyl chloride (48.6 g., 0.3 mole). Hydrogen chloride was immediately evolved and the mixture was heated for two hours at 100°. It was distilled from a Claisen flask at a pressure of 9 mm. The forerun of phenol was discarded and the fraction boiling between 140–143° retained (62.5 g., yield 95%).

Fries rearrangement of phenyl caprylate. Phenyl caprylate (15.4 g., 0.07 mole) was dissolved in 50 cc. of tetrachlorethane and the mixture placed in a three-necked flask equipped with a mechanical stirrer and thermometer. Aluminum chloride (10 g., 0.75 mole) was added, and the mixture heated for six hours at 100°, after which it was hydrolyzed, steam distilled, and the isomers separated as previously described. All of the rearrangements of phenyl caprylate reported were made by this procedure.

Fries rearrangement of phenyl caprylate in diphenyl ether. Phenyl caprylate (15.4 g., 0.07 mole) was dissolved in diphenyl ether (85 cc., 0.5 mole) in a three-necked flask equipped as previously described. Aluminum chloride (26.6 g., 0.2 mole) was added and the mixture heated for six hours at 100°, after which it was hydrolyzed and extracted with 100 cc. of carbon tetrachloride, and the carbon tetrachloride solution washed once with dilute hydrochloric acid. The carbon tetrachloride was removed by distillation and the residue distilled under reduced pressure. The following fractions were obtained: I, b.p. 60–65° (2.7 g.) which was identified as phenol; II, b.p. 105–110° (69 cc.) identified as diphenyl ether. The residue was dissolved in ether and the ether solution extracted twice with 20-cc. portions of 5% aqueous sodium hydroxide solution. The sodium hydroxide solution was acidified with hydrochloric acid and boiled to remove the ether. The oil present crystallized on cooling and was removed by filtration and dried; 0.6 g., 3.9%.

The ether solution was dried with anhydrous sodium sulfate and the ether removed by distillation. The residue was distilled under reduced pressure and two fractions were obtained: I, 1.6 g., b.p. 85–150° at 1 mm. and II, 17.6 g. (85%), b.p. 150–205° at 1 mm. The latter fraction was redistilled and 17 g. boiling at 203–205° at 1 mm. obtained. This fraction was crystallized from dilute ethanol and gave white crystals, m.p. 31–32°.

Anal. Calc'd for $C_{20}H_{24}O_2$: C, 80.8; H, 8.5.
Found: C, 81.0; H, 8.3.

Attempted acylation of diphenyl ether with p-*hydroxycaprylophenone.* *p*-Hydroxycaprylophenone (22 g., 0.1 mole) was dissolved in 70 cc. of diphenyl ether and the mixture placed in a three-necked flask. Aluminum chloride (26.6 g., 0.2 mole) was added, and the mixture heated for six hours at 70°. After hydrolysis, the mixture was extracted with carbon tetrachloride and washed with water. The carbon tetrachloride was removed by distillation, and the diphenyl ether removed under reduced pressure. The recovery of diphenyl ether was 60 cc., b.p. 67–93° at 1 mm. The residue was dissolved in ether and extracted with an excess of 5% aqueous sodium hydroxide. The alkaline extract was acidified with hydrochloric acid and boiled to remove ether. The oily layer crystallized on cooling and was filtered and dried (21.1 g., recovery 90%). The produce was identified as *p*-hydroxycaprylophenone by mixed melting point.

Attempted rearrangement of o-*hydroxycaprylophenone to* p-*hydroxycaprylophenone in tetrachlorethane.* *o*-Hydroxycaprylophenone (22 g., 0.1 mole) was dissolved in 60 cc. of tetrachlorethane and the mixture placed in a three-necked flask. Aluminum chloride (26.6 g., 0.1 mole) was added and the mixture heated at 70° for six hours. The product was hydrolyzed, steam distilled, and the isomers separated as previously described. The recovery was 19.5 g. (89%) of *o*-hydroxycaprylophenone. The alkaline extract contained only a trace of an oily product which would not solidify on cooling. The attempted rearrangement of *p*-hydroxycaprylophenone to *o*-hydroxycaprylophenone under similar conditions gave a recovery of 96.5% of the original ketone.

Attempted rearrangement of o-*hydroxycaprylophenone to* p-*hydroxycaprylophenone in nitrobenzene.* *o*-Hydroxycaprylophenone (22 g., 0.1 mole) was dissolved in 70 cc. of nitrobenzene and the mixture placed in a three-necked flask. Aluminum chloride (26.6 g., 0.2 mole) was added, and the mixture heated at 70° for six hours, after which it was hydrolyzed and extracted with carbon tetrachloride. The carbon tetrachloride was removed by distillation and the residue vacuum distilled. Nitrobenzene (60 cc., b.p. 80–85° at 1 mm.) was recovered and 20.5 g. (93%) of *o*-hydroxycaprylophenone (b.p. 115–120° at 1 mm.).

Fries rearrangement of phenyl stearate. Phenyl stearate, m.p. 51.5–53.0° (9 g., 0.025 mole) was dissolved in 25 cc. of tetrachlorethane and the solution placed in a three-necked flask. Aluminum chloride (4 g., 0.03 mole) was added and the mixture heated at 70° for ten hours. The product was hydrolyzed by pouring into water, the solvent removed by steam distillation and the solid residue which weighed 8.0 g. was extracted with 100 cc. of 25% aqueous alcohol which contained 2 g. of sodium hydroxide. The insoluble solid was removed from the aqueous solution by filtration and boiled with dilute hydrochloric acid. The solid was crystallized from alcohol and dried. The product (m.p. 60–64°) was identified as *o*-hydroxystearophenone by mixed melting point (yield 1.58 g., 18.3%).

The aqueous alcohol portion was acidified with hydrochloric acid and the solid filtered. One crystallization from Skellysolve "B" followed by a recrystallization from alcohol gave light tan crystals (m.p. 84–87°; mixed m.p. 84–87°) (yield 1.82 g., 21.2%).

Phenyl laurate, myristate, and palmitate were rearranged in a similar manner. The constants of the esters used were as follows: phenyl laurate, b.p. 159–161° at 1 mm.; phenyl myristate, m.p. 35.5–37°, and phenyl palmitate, m.p. 44.5–46.0°.

SUMMARY

1. The effect of the molecular proportions of aluminum chloride used, the temperature, and the solvent employed in the acylation of phenol

have been studied. It has been shown that the ratio of isomers obtained is influenced by the molecular complexes present, by the temperature within the limits where it influences the reacting complexes, and by the solvent used.

2. The influence of temperature, molecular ratios of reactants, solvents, and chain-length in the rearrangement of phenyl esters in the presence of aluminum chloride has been investigated.

3. High molecular ratios of aluminum chloride favor the formation of para hydroxy ketones under both Friedel-Crafts and Fries conditions.

4. The effect of temperature is significant within those limits where it is a factor in determining the complexes which enter into the reaction.

5. The chain-length of the acid group is not a significant influence in the rearrangement of phenyl esters.

6. Some solvents exert a marked effect upon orientation, and the solvents studied can be arranged in the following order of increasing ortho directing influence: nitrobenzene, Skellysolve "B," tetrachlorethane, and carbon disulfide.

7. It has been shown that *p*-hydroxy ketones and *o*-hydroxy ketones do not rearrange under the experimental conditions imposed.

8. Some suggestions as to the mechanism of both the Friedel-Crafts acylation of phenol and the rearrangement of phenyl esters have been proposed and a possible correlation between the two reactions has been offered.

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[CONTRIBUTION FROM THE GEORGE S. COX MEDICAL RESEARCH INSTITUTE, UNIVERSITY OF PENNSYLVANIA]

INVESTIGATIONS ON STEROIDS. IV. NEW DEGRADATION PRODUCTS OF CHOLIC ACID AND STUDIES ON THE SYNTHESIS OF 7,12-DIHYDROXYPROGESTERONE[1]

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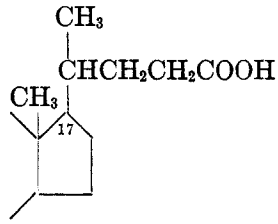
In a previous paper (1) it was pointed out that it appears desirable to obtain for physiological examination compounds which are derived from progesterone or desoxycorticosterone by the attachment of hydroxyl groups to various carbon atoms of the sterol nucleus.

Four such *hydroxylated progesterones* are known at the present time. A 12-hydroxyprogesterone was synthesized from desoxycholic acid (2), a 17-hydroxyprogesterone was isolated from beef adrenal glands (3), and recently an 11-hydroxyprogesterone was prepared from corticosterone by Reichstein (4). These three compounds possess no noticeable progestational activity; definite data are not available concerning the adrenal cortical activity. Ehrenstein and Stevens (1) prepared from pregnenolone the acetate of 6(α)-hydroxyprogesterone, which manifests a distinct progestational effect, and possibly also slight adrenal cortical activity. All known *hydroxylated desoxycorticosterones* have been found in the adrenal cortex. In all of these, hydroxyl groups are attached to carbon atoms 11 or 17 of the sterol nucleus, or to both. These compounds counteract the manifestations of adrenal insufficiency; some of them are known to possess also slight progestational activity.

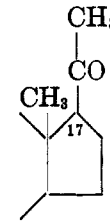
Certain bile acids appear to afford a suitable starting material for the preparation of compounds of the above mentioned types. They carry hydroxyl groups at carbon atoms of the sterol nucleus where they cannot be easily introduced by the available chemical procedures. By systematic degradation of bile acids according to the method of Wieland (5) one can obtain a 17-methyl ketone and a 17-carboxylic acid (etio acid). Such a 17-methyl ketone can serve as starting material for the preparation of a compound belonging to the progesterone series, whereas the 17-carboxylic acid (etio acid) may be transformed into a substance derived from desoxycorticosterone.

[1] Aided by a grant from the Smith, Kline, and French Laboratories in Philadelphia.

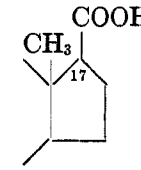
Reported on October 28, 1940 at the Autumn Meeting of the National Academy of Sciences at the University of Pennsylvania.



Bile acid type



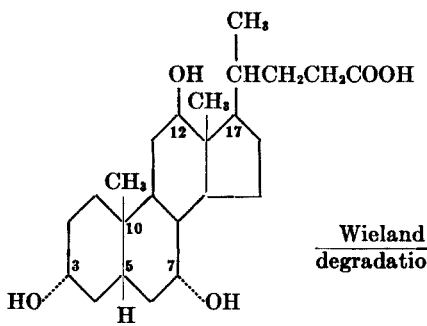
17-Methyl ketone



17-Carboxylic acid (etio acid)

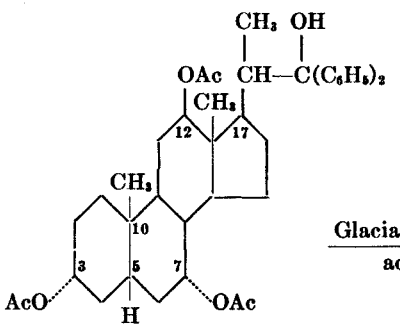
Dalmer (6) and his associates found that the Wieland degradation (5) is applicable not only to cholanic acid, but also to hydroxylated cholanic acids, provided that the hydroxyl groups are protected by acetylation. A number of bile acids were subsequently subjected to such a degradation. Sawlewicz and Reichstein (7) degraded lithocholic acid [3(α)-hydroxycholanic acid] to etiolithocholic acid [3(α)-hydroxyetiocholanic acid] which in turn was transformed into desoxycorticosterone (8). Recently Hoehn and Mason (9) repeated this degradation and isolated etiolithocholic acid along with 3(α)-hydroxypregnane-20-one. Desoxycholic acid [3(α),12-dihydroxycholanic acid] was degraded by Hoehn and Mason (10) as well as Reichstein and von Arx (11) to etiodesoxycholic acid [3(α),12-dihydroxyetiocholanic acid] and 3(α),12-dihydroxypregnane-20-one. The latter substance was transformed into 12-hydroxyprogesterone (2). Chenodesoxycholic acid [3(α),7-dihydroxycholanic acid] was subjected to a Wieland degradation by Ishihara (12); thus etiochenodesoxycholic acid [3(α),7-dihydroxyetiocholanic acid] and 3(α),7-dihydroxypregnane-20-one were obtained. Kimura and Sugiyama (13) subjected hyodesoxycholic acid [3(α),6-dihydroxycholanic acid] to a similar series of reactions, the end-product of which was 3(α),6-dihydroxypregnane-20-one; the corresponding etio acid was not described. The most readily available bile acid is cholic acid [3(α),7,12-trihydroxycholanic acid] (I). Morsman, Steiger, and Reichstein (14) subjected it to a Wieland degradation. The end-product was 3(α),7,12-trihydroxypregnane-20-one (V); the corresponding etio acid (VIII) was not described.

We decided to repeat the degradation of cholic acid as worked out by Reichstein and his associates (14). It was our intention to transform the 3(α),7,12-triacetoxypregnane-20-one (IV) into 7,12-dihydroxyprogesterone or its diacetate (XV). Another object of our investigation was the preparation of the still unknown etiocholic acid [3(α),7,12-trihydroxyetiocholanic acid] (VIII), which we intend later to transform into 7,12-dihydroxy-11-desoxycorticosterone (7,12,21-trihydroxy-4-pregnene-3,20-dione). We found the procedure described by Reichstein (14) easily reproducible. Diphenyl-[3(α),7,12-triacetoxy-ter-norcholyl]



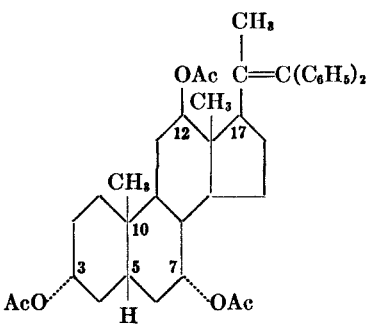
I. Cholic acid.

Wieland degradation.



II. Diphenyl-[3(α),7,12-triacetoxy-ter-norcholyl] carbinol.

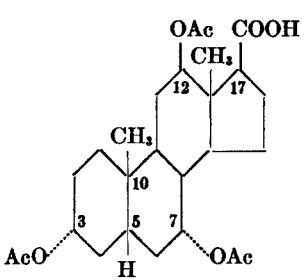
Glacial acetic acid.



III. 1,1-Diphenylmethyl-[3(α),7,12-triacetoxyetiocholyl]ethylene.

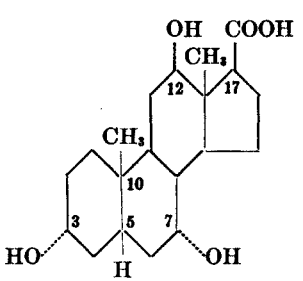
CrO_3

Ozone.

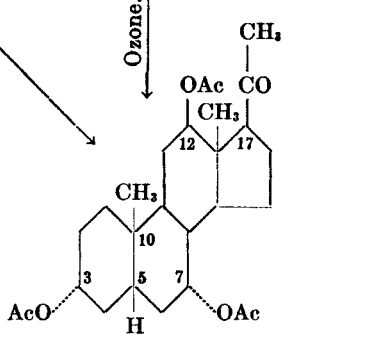


VII. 3(α),7,12-Triacetoxyetiocholanic acid.

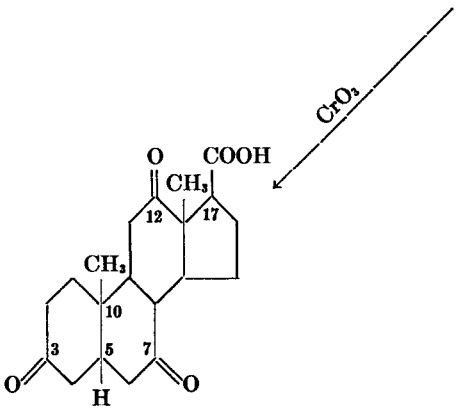
sapon.



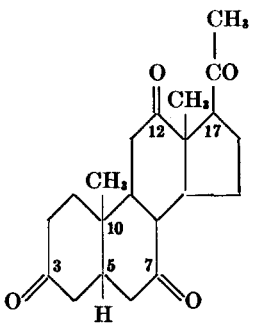
VIII. Etiocholic acid.



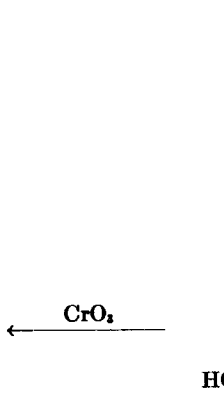
IV. 3(α),7,12-Triacetoxypregnane-20-one.

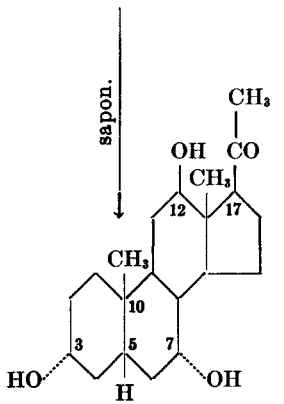


IX. Dehydroetiocholic acid.

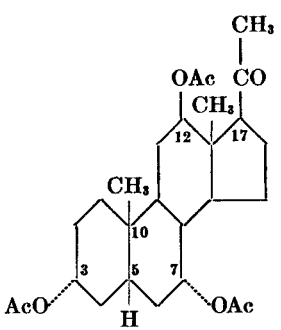


VI. Pregnane-3,7,12,20-tetraone.

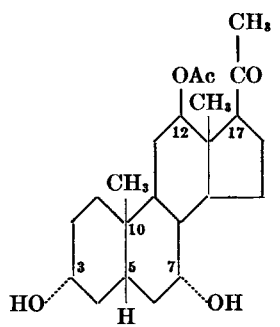




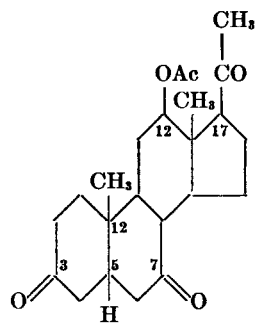
V. 3(α),7,12-Trihydroxypregnane-20-one.



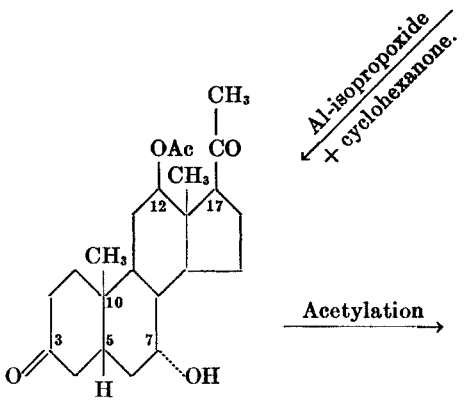
IV. 3(α),7,12-Triacetoxypregnane-20-one.



X. 12-Acetoxypregnane-3(α),7-diol-20-one.

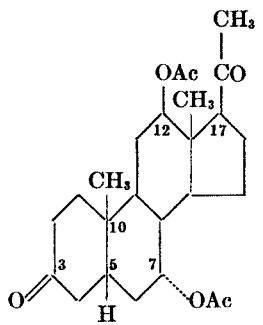


XI. 12-Acetoxypregnane-3,7,20-trione.

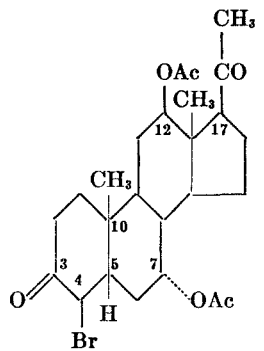


Al-isopropoxide + cyclohexanone.

Acetylation



1 mole Br_2

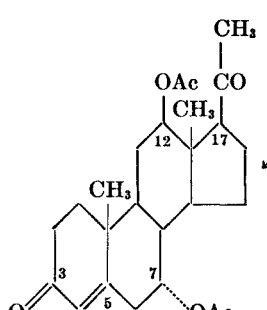


XII. 12-Acetoxypregnane-7-ol-3,20-dione.

XIII. 7,12-Diacetoxypregnane-3,20-dione.

XIV. 4-Bromo-7,12-diacetoxypregnane-3,20-dione.

Collidine.



XV. 7,12-Diacetoxy-4-pregnene-3,20-dione. [7,12-Diacetoxyprogesterone; 7,12-dihydroxyprogesterone diacetate]

carbinol (II) was subjected to oxidation with chromic acid. Attempts to isolate from the acid fraction of this oxidation the 3(α),7,12-triacetoxyetiocholanic acid (VII) in a crystalline form failed. After saponification of the acid fraction the crystalline etiocholic acid (VIII) was obtained. Attempts to secure the crystalline 3(α),7,12-triacetoxyetiocholanic acid (VII) by re-acetylating the pure etiocholic acid (VIII) were of no avail. From the neutral fraction of the oxidation with chromic acid we were able to isolate a small amount of 3(α),7,12-triacetoxypregnane-20-one (IV). We had already finished this part of our investigation when Hoehn and Mason (10) described a new procedure for the preparation of etio acids (17-carboxylic acids) by way of the 17-methyl ketones. The latter method was slightly modified by Reichstein and von Arx (11) and generally utilized by Marker and Wittle (15). It is possible that the new procedure applied to 3(α),7,12-trihydroxypregnane-20-one (V) will furnish better yields of the etiocholic acid (VIII) than the above described method. When etiocholic acid (VIII) was oxidized with chromic acid, a compound was obtained which we consider to be dehydroetiocholic acid (3,7,12-triketoetiocholanic acid) (IX), although the analytical figures are in better agreement with a monohydroxydiketoetiocholanic acid.

The 3(α),7,12-trihydroxypregnane-20-one (V) was secured according to the procedure given by Reichstein and his associates (14). Oxidation of this compound with chromic acid yielded the hitherto unknown pregnane-3,7,12,20-tetraone (VI). We attempted the partial hydrolysis of 3(α),7,12-triacetoxypregnane-20-one (IV) with the original intention of hydrolyzing the acetyl group at carbon atom 3 only. The observations of Wieland and Kapitel (16) as well as Miyazi and Isaka (17) on acylated bile acids indicate that distinct differences exist between the rates of hydrolysis at carbon atoms 3, 7, and 12 respectively. Treatment of 3(α),7,12-triacetoxypregnane-20-one (IV) with potassium carbonate did not yield the monohydroxy compound desired, but crystalline material whose analysis indicated that the hydrolysis had resulted in a mixture which consisted predominantly of a dihydroxy compound. We therefore tried to saponify IV with exactly one mole of potassium hydroxide. Also under these experimental conditions the dihydroxy rather than the monohydroxy compound was the main product of the reaction; purification by chromatographic adsorption yielded almost the theoretical amount of 12-acetoxypregnane-3(α),7-diol-20-one (X). Hence the conclusion may be drawn that in this case the rates of hydrolysis at carbon atoms 3 and 7 are of about the same order. Therefore it was decided to subject IV to a saponification with two moles of potassium hydroxide in the expectation that this would furnish a satisfactory

yield of 12-acetoxypregnane-3(α),7-diol-20-one (X). In this case a mixture was obtained, which on repeated chromatographic treatments and recrystallizations gave about 78% of the theoretical yield of the dihydroxy compound (X). When X was oxidized with chromic acid, 12-acetoxypregnane-3,7,20-trione (XI) was obtained.

Recently Gallagher (18) reported briefly that Oppenauer's method (19) for the dehydrogenation of secondary alcohols can be utilized in the bile acid series for the selective dehydrogenation of a hydroxyl group at carbon atom 3. When we treated 12-acetoxypregnane-3(α),7-diol-20-one (X) according to Oppenauer's method with aluminum isopropoxide and cyclohexanone we observed also a selective dehydrogenation of the hydroxyl group at carbon atom 3. The reaction-product (12-acetoxypregnane-7-ol-3,20-dione, XII) was not isolated in a pure form but immediately acetylated to 7,12-diacetoxypregnane-3,20-dione (XIII). We consider it probable that the same substance (XIII) can also be obtained by treatment of 3(α),7,12-trihydroxypregnane-20-one (V) with aluminum isopropoxide and cyclohexanone and subsequent acetylation.

Butenandt and his associates (20) found that in such steroids of the allo series (H at carbon atom 5 trans to CH_3 at carbon atom 10) in which carbon atom 3 forms a keto group, bromination takes place at carbon atom 2. The corresponding compounds of the coprostane series (H at carbon atom 5 cis to CH_3 at carbon atom 10) brominate at carbon atom 4. Treatment of 7,12-diacetoxypregnane-3,20-dione (XIII) with one mole of bromine furnished a crystalline monobromide which could not be obtained in a completely pure form. Since cholic acid and hence also compound XIII possess the coprostane configuration the monobromo compound must be assigned the structure of 4-bromo-7,12-diacetoxypregnane-3,20-dione (XIV).

When 4-bromo compounds of this type are refluxed with pyridine they suffer a splitting of hydrogen bromide from the molecule to form α,β-unsaturated ketones (4:5). Compound XIV was subjected to a debromination by refluxing it with collidine (2,4,6-trimethylpyridine). This was recently introduced as a debrominating agent by Butenandt and his associates (21); its action was plausibly interpreted by Inhoffen and his co-workers (22). We obtained a bromine-free compound to which must be assigned the structure of 7,12-diacetoxy-4-pregnene-3,20-dione (7,12-diacetoxyprogesterone; 7,12-dihydroxyprogesterone diacetate, XV). It was obviously not pure. The ultraviolet absorption spectrum of a sample of this substance (Figure I) was determined in the Department of Physics of the Massachusetts Institute of Technology (Professor George R. Harrison). The maximum is at the expected wave-length (about

240 mμ). The unusual shape of the absorption curve is probably due to the impurity.

EXPERIMENTAL

All melting points were determined with the Fisher-Johns melting point apparatus of the Fisher Scientific Company (Pittsburgh, Pa.). The readings are sufficiently near the true melting points so that no corrections have been made. All microanalyses, unless otherwise stated, were carried out by Mr. William Saschek, Columbia University, New York. Valuable assistance was rendered by Mrs. Marguerite Twaddell Decker in the preparation of the starting material for this investigation.

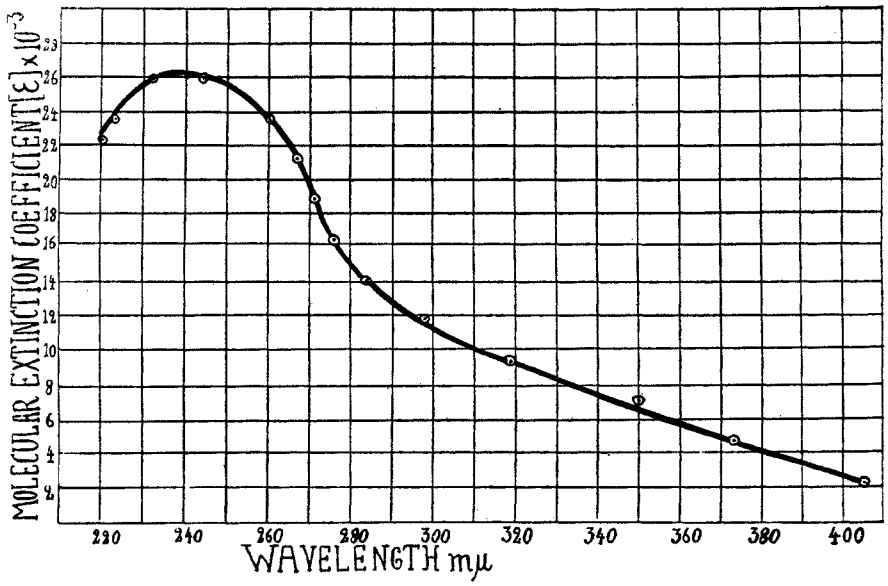


FIG. I. ABSORPTION CURVE OF A SAMPLE OF 7, 12-DIACETOXYPROGESTERONE (1.1 MG. IN 60 CC. OF ABSOLUTE ALCOHOL)

Etiocholic acid [3(α),7,12-trihydroxyetiocholanic acid] (VIII) by oxidation of diphenyl-[3(α),7,12-triacetoxy-ter-norcholyl] carbinol (II) with chromic acid. To a solution of 2.6 g. of carbinol (II) in 115 cc. of glacial acetic acid was added on a water-bath over a period of 25 minutes 2.3 g. of chromium trioxide dissolved in a mixture of 2.3 cc. of water and 60 cc. of glacial acetic acid. The heating was continued for 5½ hours; stirring was applied during the whole procedure. The major part of the acetic acid was removed *in vacuo* (55–60°). Water was added to the sticky residue and the whole was extracted three times with ether. After the washing of the combined ether phases with dilute sulfuric acid and with water, the acid products of the oxidation were removed by treatment with dilute sodium carbonate. The ether phase, containing the neutral products of the oxidation, was dried with sodium sulfate and brought to dryness; weight of the almost colorless viscous residue 1.23 g. (neutral). The sodium carbonate solution was acidified (Congo red) by the

addition of hydrochloric acid, which caused a precipitate to appear. The acid products of the oxidation were obtained by extracting the acidified phase three times with ether, drying with sodium sulfate, and evaporating to dryness; weight of the almost colorless brittle residue: 1.04 g. (acid).

Etiocholic acid [3(α),7,12-trihydroxyetiocholanic acid] (VIII) About 910 mg. of the acid residue was distilled in a high vacuum. The main part distilled between 230° and 240° at a pressure of approximately 5×10^{-5} mm.; slightly yellow glass, weight 657 mg. The forerun and the afterrun were not investigated. When the main fraction was treated with several solvents and combinations of solvents it did not show any tendency to crystallize.

Saponification: To a solution of 0.38 g. of the above described main fraction in 2.0 cc. of methanol was added a solution of 0.30 g. of potassium hydroxide (calc'd 0.18 g.) in 0.6 cc. of water. This mixture was refluxed on a water-bath for two hours. Water was added and the methanol removed *in vacuo*. The aqueous solution was acidified to Congo red and extracted several times with ethyl acetate. After short drying (about 1 hour) with sodium sulfate, the ethyl acetate extracts were concentrated to a low volume *in vacuo*, which caused crystals to separate; wt. 0.090 g., m.p. 232–237°. From the mother liquor (solid content 0.033 g.) another 0.014 g. of crystals was obtained. Repeated crystallization from acetone yielded 0.074 g. of beautiful white needles of constant m.p. 254–258°; $[\alpha]_D^{27.5}$ +65.2° (50 mg. in 2.0 cc. of absol. alcohol).

Anal. Calc'd for $C_{20}H_{32}O_5$: C, 68.13; H, 9.16.
Found: C, 67.85; H, 8.98.

3(α),7,12-triacetoxypregnane-20-one (IV) The neutral fraction of the oxidation (1.23 g.) was subjected to treatment with Girard's reagent T (23) which furnished 0.15 g. of ketonic (almost colorless resin) and 1.02 g. of non-ketonic material. Crystals were obtained from the ketonic fraction by dissolving it in ether and gradually adding petroleum ether; clusters of prisms grew slowly; wt. 0.036 g., m.p. 149–151°. More prisms were obtained from the mother liquor.

Anal. Calc'd for $C_{27}H_{40}O_7$: C, 68.02; H, 8.46.
Found: C, 68.13, 68.24; H, 8.26, 8.36.

Dehydroetiocholic acid (3,7,12-triketoetiocholanic acid) (IX) Twenty-nine milligrams of etiocholic acid (VIII) of m.p. 254–256° was dissolved in 1.0 cc. of glacial acetic acid and 17.3 mg. of chromium trioxide (= 3.15 atoms O) in 1.0 cc. of 90% acetic acid was added. The mixture was allowed to stand at room temperature for 17 hours, and after the addition of ten drops of methanol, the solution was brought almost to dryness *in vacuo*. Some water was added to the residue; after a few minutes standing the separation of beautiful crystals began. These were filtered the next day, washed with water, and dried; wt. 16.7 mg., m.p. 240.5–243.5°. After recrystallizing from a mixture of acetone and ether the melting point was raised to 245–246°.

Anal. Calc'd for $C_{20}H_{26}O_5$: C, 69.32; H, 7.57.
(for $C_{20}H_{28}O_5$: C, 68.92; H, 8.10.)
Found: C, 68.85; H, 7.92.

3(α),7,12-trihydroxypregnane-20-one (V) 3(α),7,12-triacetoxypregnane-20-one (IV) was prepared according to Reichstein's procedure (14) by ozonizing 1,1-diphenylmethyl-[3(α),7,12-triacetoxyetiocholyl]ethylene (III). The average yield was 61.8%; the yield obtained by Reichstein was 57.3%. The melting point of the substance was 150–152°; Reichstein recorded 134–135°. The difference of the melting points may be due to the existence of two polymorphic forms.

To a solution of 1.3 g. of IV in 5.2 cc. of methanol was added a solution of 0.68 g.

of potassium hydroxide in 1.6 cc. of water. The mixture was refluxed on a water-bath for two hours. After the addition of some water the methanol was removed *in vacuo*. The whole was extracted three times with ether and three times with ethyl acetate. The extracts were washed with water and dried with sodium sulfate. From the ether extract was secured 0.3 g. of crystalline material melting slightly above 120°. The ethyl acetate extract furnished several crops of crystalline material totalling 0.41 g. and melting between 120° and 125°. The saponification was carried out several times; the average yield was 72.4%, the yield computed from Reichstein's figures is 34.0%.

Pregnane-3,7,12,20-tetraone (VI) To a solution of 160 mg. of 3(α),7,12-trihydroxypregnane-20-one (V) in 40 cc. of glacial acetic acid was added 130 mg. of chromium trioxide (calc'd for 3 atoms O: 91.4 mg. of CrO_3) dissolved in 10 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature for one hour. After the addition of about 10 drops of methanol the solution was concentrated to a very low volume *in vacuo*. Water was added, which caused a white precipitate to appear. Because this was rather difficultly soluble in ether, the suspension was extracted 5 times with ample quantities of ether and thereafter 3 times with ethyl acetate. The ether and ethyl acetate extracts were washed with *N* hydrochloric acid, *N* sodium carbonate, and water. After drying over sodium sulfate, the ether was brought to a small volume, which caused the separation of 102 mg. of long, irregularly-shaped plates; m.p. 238–241°. The ethyl acetate was brought completely to dryness and the residue treated with some ether. By this means about 12 mg. of crystals melting at 239–241° was secured. The total yield of almost pure crystalline material was 114 mg. The optical rotation and analysis refer to a sample of m.p. 238–242°; $[\alpha]_D^{26}$ +76.3° (20 mg. in 2.0 cc. of acetone).

Anal.[2] Calc'd for $C_{21}H_{28}O_4$: C, 73.21; H, 8.20.
Found: C, 73.30, 73.51; H, 8.15, 8.08.

12-Acetoxypregnane-3(α),7-diol-20-one (X) To a solution of 0.486 g. of 3(α),7,12-triacetoxypregnane-20-one (IV) in 35 cc. of absol. alcohol was added over a period of 48 hours in 0.75-cc. quantities, 19.5 cc. of a solution of 0.1 *N* potassium hydroxide in absol. alcohol (about 2 moles of KOH). After standing at room temperature for two more days the solution was made neutral to litmus by the addition of 50% acetic acid. It was then concentrated to a low volume *in vacuo*. After the addition of some water, a white crystalline precipitate (designated A; dry wt. 0.170 g.) appeared, which was filtered and washed with water. Further concentration furnished 0.110 g. of additional crystalline material (designated B). A third concentration *in vacuo* furnished a sticky precipitate which was taken up in chloroform. The aqueous phase was re-extracted three times with chloroform. All chloroform extracts were combined, washed with water, dried with sodium sulfate, and evaporated. The dry residue (designated C; wt. 0.120 g.) was a yellow resin. The crystalline precipitates A and B were separately and repeatedly recrystallized from a mixture of acetone and ether. A total of 0.260 g. of material was secured, which melted between 220° and 230°. To these combined fractions was added 0.015 g. of similar material from a previous experiment. The whole (0.275 g.) was subjected to a further purification by means of chromatographic adsorption. It was dissolved in a mixture of 25 cc. of chloroform and 30 cc. of benzene to which 100 cc. of petroleum ether was added. This solution was allowed to run slowly through a properly prepared column of 13.75 g. of aluminum oxide (aluminum oxide anhydrous; standardized for chromato-

[2] Microanalysis by Dr. Ing. A. Schoeller, Berlin-Schmargendorf.

graphic adsorption acc. to Brockmann, E. Merck, Darmstadt). Long needles separated from this solution before the filtration through the column was finished; they were poured with the solution onto the aluminum oxide. The adsorbed material was eluted first with 100 cc. of chloroform, thereafter with a mixture of 25 cc. of chloroform and 25 cc. of methanol, and eventually with 50 cc. of methanol. The original filtrate and the last eluate contained only a little material and were hence discarded. The residue of the first eluate (*a*) weighed 0.115 g.; m.p. 225–232°. The weight of the residue of the second eluate (*b*) was 0.145 g.; m.p. 222–230°.

By recrystallization of residue (*a*) from mixtures of chloroform, benzene, and petroleum ether, as well as acetone and ether, a total of 0.106 g. melting at 228–232° was obtained. No satisfactory purification could be achieved when residue (*b*) was subjected to recrystallization. It was therefore decided to combine residue (*b*) with the filtrates from the recrystallization of residue (*a*) and to subject the total to chromatographic adsorption. For this purpose the material was dissolved in a mixture of benzene and chloroform to which petroleum ether was added. The eluting was performed with chloroform and thereafter with four mixtures of chloroform and methanol (methanol content gradually increasing). After working up the several fractions, a total of 0.130 g. melting at 228–232° was secured.

The resinous residue C (0.120 g.) was combined with low-melting fractions obtained during the purification procedures described above; also low-melting material from previous experiments was added. The total (0.207 g.) was subjected to chromatographic adsorption. The material was dissolved in a mixture of 40 cc. of benzene and 16 cc. of petroleum ether. This solution was allowed to drip through a column of 10 g. of aluminum oxide. The eluting was begun with a mixture of 20 cc. of benzene and 5 cc. of petroleum ether, and continued with 25 cc. of benzene, a mixture of 12.5 cc. of benzene and 12.5 cc. of ether, a mixture of 12.5 cc. of ether and 12.5 cc. of chloroform, and finally with several mixtures of chloroform and methanol (methanol content gradually increasing). A crystalline residue (85.6 mg.) was obtained only from the first chloroform-methanol eluate (24.5 cc. of chloroform + 0.5 cc. of methanol). Recrystallization of this material furnished 64 mg. of m.p. 228–232°.

The analyzed sample had the melting point 230–233°; $[\alpha]_D^{27}$ +81.6° (20 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{36}O_5$: C, 70.36; H, 9.25.
Found: C, 70.40; H, 9.23.

12-Acetoxypregnane-3,7,20-trione (*XI*) To a solution of 49 mg. of 12-acetoxypregnane-3(α),7-diol-20-one (X) in 11 cc. of glacial acetic acid was added 1.8 cc. (the equivalent of about 2.2 atoms of O) of a solution of 1 g. of chromium trioxide in 100 cc. of 90% acetic acid. The mixture was allowed to stand at room temperature for about 16 hours. After the addition of 20 drops of methanol it was brought to dryness *in vacuo*. Water was added to the residue and it was extracted three times with redistilled ether. The combined ether phases were washed with *N* hydrochloric acid, *N* sodium carbonate, and water, and were finally dried with sodium sulfate. On concentrating this ether solution to a small volume, stout needles separated slowly, wt. 33.4 mg., m.p. 158–161°. The constant melting point was 160.5–163.5°; $[\alpha]_D^{26}$ +125.9° (14 mg. in 2.0 cc. of acetone).

Anal. Calc'd for $C_{23}H_{32}O_5$: C, 71.09; H, 8.31.
Found: C, 71.04; H, 8.24.

7,12-Diacetoxypregnane-3,20-dione (*XIII*) To 88 mg. of 12-acetoxypregnane-3(α),7-diol-20-one (X) was added 15 cc. of toluene (dried over calcium chloride),

3 cc. of cyclohexanone, and 300 mg. of aluminum isopropoxide (Eastman Kodak). This mixture was refluxed for two hours and then brought to dryness *in vacuo* at a temperature of about 70°. After the addition of water and *N* sulfuric acid the whole was extracted four times with redistilled ether. The combined ether extracts were washed with water, with a solution of sodium carbonate, and again with water. After drying over sodium sulfate, the ethereal solution was brought to a small volume. While standing overnight crystals separated out, which were filtered and dried; wt. 41.0 mg., m.p. 210–226°. No appreciable quantity of crystals could be secured from the filtrate or its acetylation product.

The crystalline material was dissolved in a mixture of 1 cc. of pyridine and 1 cc. of acetic anhydride. This solution was heated on the water-bath for about 4 hours and then brought to dryness *in vacuo*. The addition of some water caused an apparently crystalline residue to appear; wt. about 32 mg. A little more crystalline material could be secured by extracting the filtrate with chloroform. Because the crystals were fairly insoluble in acetone they were recrystallized by dissolving in chloroform and adding acetone. Repeated recrystallizations yielded 22.8 mg. of m.p. 256–262°; $[\alpha]_D^{24}$ +113.7° (20 mg. in 2.0 cc. of chloroform).

Anal. Calc'd for $C_{25}H_{36}O_6$: C, 69.40; H, 8.39.
Found: C, 69.17; H, 8.26.

4-Bromo-7,12-diacetoxypregnane-3,20-dione (*XIV*) To a solution of 76.1 mg. of 7,12-diacetoxypregnane-3,20-dione (XIII) in 5.25 cc. of glacial acetic acid was added one drop of 40% hydrogen bromide and thereafter over a period of 20 minutes 28.7 mg. of bromine (1 mole Br_2 = 28.1 mg.) dissolved in 0.95 cc. of glacial acetic acid. After standing for 20 minutes, water was added to the decolorized solution, which caused very fine, short white crystals to appear. The crystallization was completed by allowing the solution to stand in a refrigerator overnight. Weight of the first crop 77.8 mg.; m.p. 202–216°. A second crop was secured by concentrating the filtrate to a very low volume *in vacuo*; wt. 6.0 mg.; m.p. 202–215°. It was decided to purify the first fraction (77.8 mg.) by chromatographic adsorption, for which purpose it was dissolved in a mixture of 24 cc. of benzene and 15 cc. of petroleum ether. This solution was allowed to run through a suitably prepared column of 3.5 g. of aluminum oxide (acc. to Brockmann). The adsorbed material was successively eluted with a mixture of 24 cc. of benzene and 6 cc. of petroleum ether, with 30 cc. of benzene, with a mixture of 24 cc. of benzene and 6 cc. of chloroform, with a mixture of 15 cc. of benzene and 15 cc. of chloroform, and finally with 30 cc. of chloroform. Thereafter the aluminum oxide was thoroughly extracted with methanol. The total recovered material weighed 74.6 mg.; the crystalline fractions totalled only 43 mg. It appears possible that the chromatographic treatment caused destruction of part of the crystalline material. The crystalline fractions were repeatedly recrystallized from mixtures of chloroform and 95% alcohol. The melting point was finally 210–218° (decomp.). Analyses were performed with the last substance, as well as with material of m.p. 211–217° obtained from a preliminary experiment (no chromatographic treatment). The melting points and the analytical figures indicate that the substances were not quite pure.

Anal. Calc'd for $C_{25}H_{35}BrO_6$: C, 58.69; H, 6.90.
Found: C, 59.69, 59.80; H, 7.33, 7.24.

7,12-Diacetoxy-4-pregnene-3,20-dione (*7,12-diacetoxyprogesterone*) (*XV*) A solution of 36.5 mg. of 4-bromo-7,12-diacetoxypregnane-3,20-dione (XIV) in 1.0 cc. of collidine was refluxed (metal-bath, temperature about 190°) for four hours, causing it to turn dark brown. The collidine (Eastman-Kodak) had been freshly distilled

(b.p. 165°) and dried overnight with potassium hydroxide. After the addition of *N* hydrochloric acid the solution was extracted four times with ether. The combined ether extracts were washed with *N* hydrochloric acid, *N* sodium carbonate, and water. The ether solution was dried over sodium sulfate and concentrated to a small volume, which caused the separation of crystals (5.6 mg.; m.p. 215–232°). The filtrate of these crystals was brought to dryness; weight of the residue 20.2 mg. It was decided to combine the crystals and the residue again and to subject this material (25.8 mg.) to chromatographic adsorption. For this purpose it was dissolved in a mixture of 15 cc. of benzene and 15 cc. of petroleum ether and was allowed to drip through a column of 1.8 g. of aluminum oxide (acc. to Brockmann). The elution was carried out with 50-cc. quantities of the following solvents: benzene-petroleum ether 3:2; benzene-petroleum ether 4:1; benzene only; benzene-ether 1:1; ether only; ether-chloroform 1:1; chloroform only; and finally with three mixtures of chloroform and increasing amounts of methanol. Only the second and third eluate yielded crystalline residues (8.3 + 4.1 mg.; clusters of long white needles). These (total: 12.4 mg.) were washed with ether and repeatedly recrystallized from mixtures of chloroform and ether. Eventually material (4.9 mg.) melting between 240° and 249° was secured; it was combined with a fraction (0.8 mg.) of similar melting point obtained in a preliminary experiment. Renewed recrystallization yielded 5.1 mg. of m.p. 249.5–252° (without decomp.).

Anal. Calc'd for $C_{25}H_{34}O_6$: C, 69.72; H, 7.96.
Found: C, 68.15; H, 8.21.

SUMMARY

1. Cholic acid [3(α),7,12-trihydroxycholanic acid] (I) was degraded to etiocholic acid [3(α),7,12-trihydroxyetiocholanic acid] (VIII) and 3(α),7,12-trihydroxypregnane-20-one (V).

2. Etiocholic acid [3(α),7,12-trihydroxyetiocholanic acid] (VIII) was oxidized to a substance considered to be dehydroetiocholic acid (3,7,12-triketoetiocholanic acid) (IX).

3. 3(α),7,12-Trihydroxypregnane-20-one (V) was oxidized to pregnane-3,7,12,20-tetraone (VI).

4. 3(α),7,12-Triacetoxypregnane-20-one (IV) was partially saponified to 12-acetoxypregnane-3(α),7-diol-20-one (X). The latter compound was oxidized to 12-acetoxypregnane-3,7,20-trione (XI).

5. 12-Acetoxypregnane-3(α),7-diol-20-one (X) was selectively dehydrogenated with aluminum isopropoxide and cyclohexanone to 12-acetoxypregnane-7-ol-3,20-dione (XII). This substance was acetylated to 7,12-diacetoxypregnane-3,20-dione (XIII) and the latter converted by bromination to 4-bromo-7,12-diacetoxypregnane-3,20-dione (XIV). The bromo compound (XIV) was debrominated to 7,12-diacetoxy-4-pregnene-3,20-dione (7,12-diacetoxyprogesterone; 7,12-dihydroxyprogesterone diacetate, XV). The last two substances were obviously not pure.

PHILADELPHIA, PA.

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