

heated at reflux for two hours. The mixture was cooled, diluted with water and the solvent layer separated, washed with dilute potassium hydroxide, water and dried over magnesium sulfate. The mixture was filtered and the filtrate concentrated *in vacuo*. The crystalline material that separated from the residue on cooling was washed with cold alcohol, decolorized with Norite in benzene, 60° naphtha solution and recrystallized twice from ethanol to give 14.0 g. (47%) of VIII, m.p. 91.5–93°; $\lambda_{\text{max}}^{\text{alc}}$ 225 m μ (E 24,450), 276 m μ (E 19,500).

Anal. Calcd. for $C_{19}H_{20}O_3$: C, 77.03; H, 6.75. Found: C, 77.14; H, 6.56.

1-Ethyl-2-(*p*-methoxybenzyl)-6-methoxy-3,4-dihydronaphthalene (IX).—To a Grignard reagent made from 3.2 g. of ethyl bromide and 0.9 g. of magnesium turnings in 25 ml. of dry ether was added a solution of 6.0 g. of VIII in 30 ml. of dry benzene. The reaction was carried out at –5° in an argon atmosphere. After warming to room temperature and allowing to stand overnight, the reaction mixture was hydrolyzed and the product extracted with ether. On evaporating the solvent and distilling the residue, a yield of 5.1 g. (77%) of IX distilling at 180–197° (0.1 mm.), was obtained.

Anal. Calcd. for $C_{21}H_{24}O_2$: C, 81.82; H, 7.79. Found: C, 81.66; H, 7.82.

1-Ethyl-2-(*p*-methoxybenzyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (X).—A solution of 5.0 g. of IX in 50 ml. of sulfur-free benzene and 10 ml. of *n*-propanol was hydrogenated over 0.5 g. of 30% palladium–charcoal catalyst at atmospheric pressure until hydrogen uptake ceased. Approximately one mole of hydrogen was absorbed in six hours. The mixture was filtered and the filtrate evaporated and distilled *in vacuo*. A yield of 5.0 g. of X distilling at 175–177° (0.1 mm.) was obtained.

Anal. Calcd. for $C_{21}H_{26}O_2$: C, 81.29; H, 8.38. Found: C, 81.17; H, 8.32.

1-Ethyl-2-(*p*-hydroxybenzyl)-6-hydroxy-1,2,3,4-tetrahydronaphthalene (XI).—The ether X, 1.5 g., was cleaved by refluxing in 48% hydrobromic acid–acetic acid solution and the reaction mixture worked up as previously described.¹

The product was purified using the method employed with compound V. A yield of 1.1 g. of XI, m.p. 116–120°, was obtained.

Anal. Calcd. for $C_{19}H_{22}O_2$: C, 80.85; H, 7.80. Found: C, 80.94; H, 7.70.

The 1-Ethyl-2-(*p*-methoxybenzyl)-6-methoxynaphthalene (XII).—A mixture of 3.0 g. of X and 0.2 g. of 30% palladium–charcoal catalyst was heated to 210° in an argon atmosphere. The evolution of hydrogen slowed in 20 minutes and heating was continued for 10 minutes more. The mixture was cooled, taken up in ether, and filtered. The filtrate was concentrated, the residue dissolved in warm alcohol, treated with 2 g. of picric acid and the solution cooled to give 4.2 g. (81%) of the picrate, m.p. 80–81.5°. The picrates from several similar runs were combined and recrystallized from ethanol to give a purified product melting at 82–82.5°.

Anal. Calcd. for $C_{27}H_{26}O_5N_3$: N, 7.85. Found: N, 7.76.

Picrate totalling 8.8 g. was dissolved in benzene and passed through a column containing 22 g. of activated alumina (Fisher), and the column washed with benzene until the yellow zone approached the bottom. The eluate was concentrated and the residue distilled *in vacuo*. The distillate was recrystallized from methanol to give 3.8 g. (77%) of product, m.p. 71.2–72.5°.

Anal. Calcd. for $C_{21}H_{22}O_3$: C, 82.35; H, 7.19. Found: C, 82.52; H, 7.36.

The 1-Ethyl-2-(*p*-hydroxybenzyl)-6-hydroxynaphthalene (XIII).—The ether XII, 2.0 g. was cleaved by heating with 30 g. of pyridine hydrochloride and the reaction mixture worked up as previously described.¹ The crude product was boiled with benzene–60° naphtha solution to form a solid which was dissolved in reagent ether, decolorized twice with Norite, benzene added and the solution evaporated *in vacuo* until a solid separated. A yield of 1.0 g. of product, which darkened on exposure to air, was obtained, m.p. 164–166° (vac.).

Anal. Calcd. for $C_{19}H_{18}O_2$: C, 82.01; H, 6.47. Found: C, 82.14; H, 6.56.

MISSOULA, MONTANA

NOTES

A Specific Test Differentiating between α -Ketol and Dihydroxyacetone Groups of C_{21} -Steroids on Paper Chromatograms

BY L. R. AXELROD

RECEIVED MAY 5, 1953

The use of alkaline triphenyltetrazolium chloride solution to detect any side-chain containing a C_{17} α -ketol has had wide application in the chromatography of adrenal steroids.¹ This test however does not differentiate between the α -ketol side-chain and one which, in addition, contains a tertiary hydroxyl group at the C_{17} -position. If with the use of the above reagent a characteristic red spot appears on a strip from a paper chromatogram, the following test may then be applied to demonstrate the presence or absence of a dihydroxyacetone group (*i.e.*, an α -ketol with a C_{17} tertiary hydroxyl group).

Another strip from the same chromatogram is passed through aqueous 0.1 *N* NaOH and placed on a glass plate which has been heating on a Lindberg hot plate (surface temperature, 100°). The strip is covered with another glass plate and the heating continued for exactly three minutes after which time the topmost plate is removed and the strip allowed to dry on the heated plate. The strip is then passed through the usual alkaline triphenyltetrazolium solution and returned to the heated glass plate until maximum color production (about 15 sec.).

The appearance of a red color in the same position as on the first strip is evidence for an α -ketol side-chain without the added tertiary hydroxyl group, whereas no red color will appear if a dihydroxyacetone structure is present. This test is based on an observation by Mason, *et al.*,² that the dihydroxyacetone side-chain is very labile to dilute alkali, whereas the α -ketol is much more stable.

(1) R. Burton, A. Zaffaroni and E. H. Keutmann, *J. Biol. Chem.*, **188**, 763 (1951).

(2) H. L. Mason, W. M. Hoehn and E. C. Kendall, *ibid.*, **124**, 459 (1938).

Under the conditions of the above spot test, up to 40–50 γ of a steroid with a dihydroxyacetone side-chain per 1 cm. width of chromatogram will be destroyed in the allotted time. Exposure to higher temperatures than 100–110° or concentrations of alkali greater than 0.1 *N* will destroy some of the α -ketol group. The appearance of a light yellow-pink color after the test has been executed, as compared to the vivid red on the first strip, should be taken as a positive test for the dihydroxyacetone group.

This test has been used successfully on chromatograms in differentiating the side-chains of cortisone, hydrocortisone, substance S of Reichstein, and substance D of Reichstein from corticosterone, desoxycorticosterone and allopregnane-3 β ,21-diol-20-one.

DEPARTMENT OF RADIATION BIOLOGY
UNIVERSITY OF ROCHESTER
SCHOOL OF MEDICINE AND DENTISTRY
ROCHESTER, NEW YORK

Synthesis of Ethyl Ethoxybromoacetate and Ethyl Ethoxycyanoacetate¹

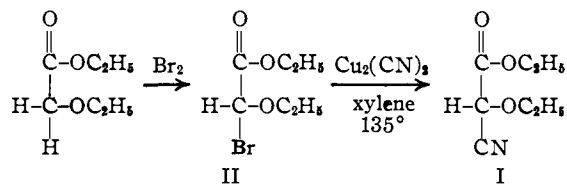
BY AARON BENDICH AND GRACE C. CLEMENTS

RECEIVED APRIL 15, 1953

Ethyl ethoxycyanoacetate (I) was required for the preparation of substituted pyrimidines² containing the ethoxy group at position 5. The carbethoxylation reaction of aliphatic nitriles with diethyl carbonate described by Wallingford³ was attempted on ethoxyacetone nitrile, but the desired ester I was obtained apparently together with its ethylated derivative ethyl α -ethoxy- α -ethylcyanoacetate. It has been pointed out previously⁴ that in such carbethoxylation reactions, simultaneous alkylation by the alkyl carbonate often occurs.

The alternate route, described below, affords the ester I in good yield. For this method, ethyl ethoxybromoacetate (II) was prepared by direct bromination of ethyl ethoxyacetate in carbon tetrachloride solution. The bromo ester II possesses an extremely reactive bromo atom which is easily hydrolyzed on brief contact with cold water. It also readily produces iodine upon treatment with aqueous potassium iodide.

Several unsuccessful attempts were made to convert the bromo ester II to the cyano ester I upon treatment with either potassium or cuprous cyanide in methanol, ethanol, diethyl ether or benzene. A



(1) This investigation was supported by grants from the National Cancer Institute, National Institutes of Health, United States Public Health Service, and from the Atomic Energy Commission, Contract No. AT(30-1)-910.

(2) A. Bendich, *Trans. N. Y. Acad. Sciences, Ser. II*, **15**, 58 (1952).

(3) V. H. Wallingford, D. M. Jones and A. H. Homeyer, *This Journal*, **64**, 576 (1942).

(4) V. H. Wallingford, A. H. Homeyer and D. M. Jones, *ibid.*, **63**, 2056 (1941).

55% yield of the cyano ester I was obtained upon refluxing a suspension of cuprous cyanide in a xylene solution of II.

Experimental

Ethyl Ethoxybromoacetate.—Ethyl ethoxyacetate (66 g., 0.5 mole) was dissolved in 65 ml. of carbon tetrachloride. The solution was stirred and kept refluxing while 80 g. (0.5 mole) of bromine was added at a rate such as to prevent the presence of excess bromine. The addition of bromine required about 3 hours. The HBr that had formed was removed by aeration and the residue was fractionated *in vacuo*. The fraction boiling 82–93° at about 10 mm. was redistilled; b.p. 94–95° (15 mm.) (197° at 750 mm.). The yield was 79 g. (75%).

Anal. Calcd. for $\text{C}_8\text{H}_{11}\text{O}_3\text{Br}$: C, 34.14; H, 5.25; Br, 37.86. Found: C, 33.93; H, 5.61; Br, 37.63.

Ethyl Ethoxycyanoacetate.—Ethyl ethoxybromoacetate (15 g., 0.071 mole) was dissolved in an equal volume of xylene (b.p. 135°) and 13.6 g. of cuprous cyanide (0.076 mole of $\text{Cu}_2(\text{CN})_2$) was added. The mixture was stirred vigorously and was refluxed for 5 hours at the end of which time it no longer released iodine upon treatment with aqueous potassium iodide. The insoluble salts were removed and the fluid was distilled *in vacuo*. The fraction boiling at 94–100° at 11 mm. was collected; yield 6.2 g. (55%). It was re-fractionated: b.p. 95.0–96.5° (11 mm.), 217–218° (750 mm.).

Anal. Calcd. for $\text{C}_7\text{H}_{11}\text{O}_3\text{N}$: C, 53.48; H, 7.05; N, 8.91; total OC_2H_5 , 57.33. Found: C, 53.46; H, 7.05; N, 8.81; total OC_2H_5 , 57.22.

Acknowledgment.—The microanalyses were performed by Dr. J. F. Alicino. The authors gratefully acknowledge the continued interest and support of Dr. George Bosworth Brown.

LABORATORIES OF THE SLOAN-KETTERING INSTITUTE FOR
CANCER RESEARCH
NEW YORK, 21, N. Y.

The Metabolic Fate of Imidazoleacetic(C^{14}OOH) Acid in the Rat

BY L. P. BOUTHILLIER AND GILLES LÉVEILLÉ

RECEIVED APRIL 10, 1953

It has been shown conclusively that imidazoleacetic acid is a product of oxidation of histamine in the intact rat.^{1–3} However, the metabolism of imidazoleacetic acid is as yet unknown and the question arises whether this substance can be broken down or not *in vivo*. In this paper, we wish to report the results of experiments which provide evidence that this metabolite does not undergo oxidation in the rat tissues. Single doses of imidazoleacetic (C^{14}OOH) acid were administered intraperitoneally to three rats. The respiratory carbon dioxide and urine were collected for a period of 24 hours and the radioactivity of each was determined. Our experimental data, summarized in Table I, show that nearly 90% of the injected radiocarbon was recovered as imidazoleacetic acid in the urine samples, through the use of the isotope dilution technique. However, no radioactivity could be measured in the expired carbon dioxide. Employing the ascending method, one-dimensional paper chromatograms of urine samples were prepared in *n*-butanol–glacial acetic acid—

(1) A. H. Mehler, H. Tabor and H. Bauer, *J. Biol. Chem.*, **197**, 475 (1952).

(2) H. Tabor, A. H. Mehler and R. W. Schayer, *ibid.*, **200**, 605 (1953).

(3) L. P. Bouthillier and Moe Goldner, *Arch. Biochem. Biophys.*, in press.

TABLE I

	Rat		
	1	2	3
Weight of animal, g.	51	52	55
Amount of imidazoleacetic acid injected, mg.	15.6	20.9	16.2
Total radioactivity injected, c.p.m.	1.56×10^5	2.09×10^5	1.62×10^5
Radioactivity of expired CO ₂	Nil	Nil	Nil
Total radioactivity of urine, c.p.m.	1.39×10^5	1.89×10^5	1.45×10^5
Total radioactivity of urinary imidazoleacetic acid, c.p.m.	1.41×10^5	1.81×10^5	1.42×10^5
Per cent. of injected radioactivity recovered in urine as imidazoleacetic acid	90.4	86.6	87.7

water as solvent system. The Pauly diazo reaction, carried out on a series of chromatograms, revealed the presence of only one imidazole compound; a single red-colored spot of R_F 0.34 appeared, corresponding to imidazoleacetic acid. Another series of chromatograms were cut into small segments and each segment was assayed for radioactivity. The average activity values, expressed in c.p.m. and corrected for background only, are presented in Fig. 1. A single radioactive peak was found which coincided with the imidazoleacetic acid spot.

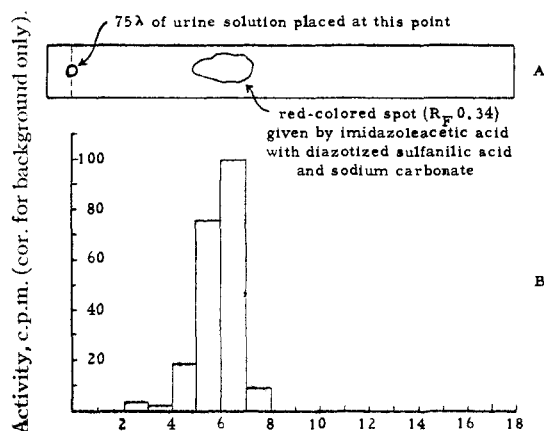


Fig. 1.—A, typical paper chromatogram of urine solution prepared with n -BuOH-AcOH-H₂O; B, radioactivity distribution on paper chromatogram of urine solution.

In the light of the data reported here, the conclusion is reached that imidazoleacetic acid is not metabolized to any measurable extent in the rat organism. In unpublished preliminary experiments carried out with ring-labeled imidazole-2-C¹⁴acetic acid, we have obtained results comparable to those given in this paper. We wish to draw attention to the report of Mehler, Tabor and Bauer¹ who "found that only one-third of a 246 μ M dose (40 mg.) of imidazoleacetic acid hydrochloride, injected intraperitoneally into a 250-g. rat, was found in the urine." The discrepancy which exists between their result and ours is for the moment unexplainable.

We wish to report also that purified imidazoleacetic acid hydrate produces toxic effects when injected to 50-g. rats at levels of 5 mg. or higher. It induces irregular respiration and nervous disorders accompanied by an increased sensitivity to noise. The toxic manifestations lasted for one

to three hours depending on the dose administered. No attempt was made to determine the lethal dose.

Experimental Part

Synthesis of Imidazoleacetic(C¹⁴OOH) Acid.—The method of Darby, Lewis and Totter⁴ was employed for the preparation of hydroxymethylimidazole picrate. Regeneration of hydroxymethylimidazole hydrochloride from the picrate was made according to the method of Koessler and Hanke.⁵ By reaction of hydroxymethylimidazole hydrochloride with phosphorus pentachloride,⁶ chloromethylimidazole hydrochloride was obtained. Employing the method of Pyman,⁶ 1 g. of the latter compound was made to react with 3 g. of KC¹⁴N (about 0.5 mc.) and the resulting nitrile was converted into ethyl imidazoleacetate and subsequently into imidazoleacetic(C¹⁴OOH) acid hydrochloride. Free imidazoleacetic acid was prepared by treatment of an aqueous solution of the hydrochloride with silver carbonate. The over-all yield in the synthesis, calculated on the basis of chloromethylimidazole hydrochloride employed, was about 18%. Pure crystals of imidazoleacetic acid monohydrate,⁶ melting with decomposition at 217–218° (uncor.), were obtained by crystallization of the synthetic product in a mixture of water and acetone. Analysis for C₅H₈O₂N₂ (anhydrous form obtained after treatment in an Abderhalden apparatus): N, calculated 22.22%; found, 21.69%. The specific activity was measured with a windowless flow counter and calculated to be 1.0×10^4 counts-minute-mg.

Administration of Labeled Imidazoleacetic Acid to Rats and Collection of Exhaled CO₂ and Urine.—Known amounts of the radioactive material (Table I) were dissolved in 1-ml. portions of water and the pH of each preparation was adjusted to 7.4 with sodium hydroxide. The solutions were administered to Wistar strain rats by way of intraperitoneal injection and each animal was placed in a glass metabolism cage for a period of 24 hours. The animals were allowed to drink water during the experimental period. The respiratory CO₂ was absorbed by sodium hydroxide solution and precipitated as barium carbonate. The 24-hour urine, preserved with thymol, was collected and completed to a volume of 25 ml. with the washings and distilled water.

Isolation of Urinary Imidazoleacetic Acid by the Carrier Method.—Into 5-ml. portions of diluted urine was dissolved 100 mg. of imidazoleacetic acid hydrate and 15 ml. of acetone was then added. The solutions were kept in a refrigerator until imidazoleacetic acid hydrate precipitated out. The product was recrystallized a few more times to constant radioactivity. The various samples obtained melted with decomposition at 218–220°.

Radioactivity Measurements.—Known quantities of barium carbonate and imidazoleacetic acid samples were uniformly spread on aluminum cups (7.2 cm.²) and small volumes (1 ml. or less) of the urine samples were evaporated to complete dryness on similar cups. The radioactivity of the contents of each cup was measured with a windowless flow counter and corrected for background and internal absorption.

Chromatography Assays of Urine.—Seventy-five microliters of the urine solutions were placed on each paper chromatogram (Whatman No. 1). The ascending method was employed using, as chromatographic solvent system, a mixture of n -butanol, 300 ml., glacial acetic acid, 60 ml., and water, 140 ml.⁷ Then the chromatograms were sprayed with a freshly diazotized sulfanilic acid solution (0.45%) and treated with finely powdered sodium carbonate. The appearance of a red-colored spot is characteristic of imidazole compounds (Pauly diazo reaction).

Another series of chromatograms was prepared and cut into half-inch-square segments. The radioactivity of each paper segment was measured with a thin mica window Geiger tube and the values were corrected for background only.

Acknowledgments.—This investigation was supported in part by a grant from the National Research Council of Canada, Division of Medical Research, and by the "Fondation Rhéaume." The

(4) W. J. Darby, H. B. Lewis and J. R. Totter, *THIS JOURNAL*, **64**, 463 (1942).

(5) K. K. Koessler and M. T. Hanke, *ibid.*, **40**, 1716 (1918).

(6) F. L. Pyman, *J. Chem. Soc.*, **99**, 668 (1911).

(7) J. L. Auclair and J. B. Maltais, *Nature*, **170**, 1114 (1952).

authors are indebted also to the Scientific Research Bureau, Department of Trade and Commerce, Province of Quebec, for a studentship granted to one of us (G.L.).

DEPARTMENT OF BIOCHEMISTRY
UNIVERSITY OF MONTREAL
MONTREAL, P. Q., CANADA

Aromatic Substitution at Ortho-Positions

BY R. D. BROWN

RECEIVED JANUARY 9, 1953

The interpretation of aromatic substitution in benzene derivatives in terms of the simple LCAO molecular-orbital approximation has now attracted the attention of a number of authors.¹⁻⁸ Early attempts^{1,2} were concerned only with a demonstration that the theory points to *o*-, *p*-substitution for some kinds of derivatives, and *m*-substitution for others, in general agreement with observation. Dewar⁴ considered the more sophisticated problem of *o*:*p* ratios. His results indicated that only in cases where the benzene substituent is very electronegative would the *p*-position be electronically more activated than *o*-, with the inference that the observed preponderance of *p*-substitution is occasioned in part at least by steric factors.⁹ Additional weight is lent to Dewar's results because he was able to account qualitatively for trends in the *o*:*p* ratio as the nature of the substituent is varied.

If however the benzene substituent is a conjugated hydrocarbon system, as in biphenyl and styrene, the uncertainty about the electronegativity parameter disappears and the molecular-orbital approximation provides an unequivocal prediction of the electronic activities. For biphenyl the *o*-positions are predicted⁵ to be appreciably more reactive than the *p*-positions. In this

TABLE I
ATOM LOCALIZATION ENERGIES^s ($-\beta$)

	Biphenyl	Styrene	1-Phenyl- butadiene
Ortho	2.400	2.370	2.313
Para	2.447	2.424	2.377

case, then, the observed low *o*:*p* ratio must be ascribed to steric factors. This result is not peculiar to biphenyl; similar relative electronic reactivities of *o*- and *p*-positions are predicted for vinyl- and 1-butadienyl substituents, as shown in Table I, and indeed there seems little doubt that for any conjugated hydrocarbon system as substituent the MO approximation will ascribe a greater electronic reactivity to the *o*-position as has been

suggested by Roberts and Streitwieser. The results of Table I strictly apply only for the completely planar molecules. It is known¹⁰ that biphenyl is on the average non-planar in the vapor phase, and presumably also in solution, and this would effectively reduce the disparity in the *o*:*p* reactivities, but it will not affect the qualitative relationship.

The attribution of the observed superior reactivity of the *p*-position in biphenyl to steric effects rather than to a failure in the MO theory is supported by some further theoretical work of Dewar.⁶ He has computed approximate atom localization energies for a considerable number of polycyclic aromatic hydrocarbons. In all cases where the position of substitution is known experimentally it coincides with the position which theory predicts to be electronically most reactive, with the single exception of triphenylene. But in this molecule the 1-position, which has a steric environment analogous to an *o*-position in biphenyl, is predicted to be the most active, while substitution is observed¹¹ to occur in the 2-position. In all other cases considered by Dewar the most reactive positions predicted by theory have steric environments much more favorable for chemical attack.

Since the only two molecules for which substitution occurs predominantly at positions other than those predicted by the MO localization theory are those for which the steric environments of the electronically most reactive positions are unfavorable for substitution, it seems justifiable to attribute the predominant *p*-substitution in biphenyl to steric hindrance of the *o*-positions.

Remick¹² has suggested, in terms of the qualitative electronic theory, that the superior reactivity of the *p*-position in biphenyl is to be anticipated solely on electronic grounds, using the principle that "the electromeric effect will operate more readily the more extended the conjugation becomes." However if this principle is applied to biphenyl in the same way in which Remick applies it¹³ to explain the α -activation of pyrrole, furan and derivatives, it would point to *o*-activation; indeed Remick has noticed just this kind of difficulty¹⁴ in applying the principle to other benzene derivatives.

Finally it should be observed that the data for styrene in Table I differ considerably from the figures recently published by Roberts and Streitwieser.¹⁵ Both the absolute values of the localization energies and their relative values (their data indicate a greater *p*- than *o*-reactivity) are in error. The correct values, together with values of the free valences ($N_{\max} = \sqrt{3}$) for comparison,⁸ are listed in Table II. It will be observed that the free valences confirm the superior electronic reactivity of the *o*- as compared with the *p*-position.

(1) G. W. Wheland and L. Pauling, *THIS JOURNAL*, **57**, 2086 (1935).

(2) G. W. Wheland, *ibid.*, **64**, 900 (1942).

(3) C. Sandorfy, *Bull. soc. chim.*, **16**, 615 (1949).

(4) M. J. S. Dewar, *J. Chem. Soc.*, 463 (1949).

(5) R. D. Brown, *Experientia*, **6**, 376 (1950).

(6) M. J. S. Dewar, *THIS JOURNAL*, **74**, 3357 (1952).

(7) J. D. Roberts and A. Streitwieser, *ibid.*, **74**, 4723 (1952).

(8) For an account of the correlation of localization energies and free valences with chemical reactivities see R. D. Brown, *Quart. Rev.*, **6**, 63 (1952).

(9) More than this cannot be said because the appropriate electronegativity parameters for the various substituents are very uncertain.

(10) O. Bastiansen, *Acta Chem. Scand.*, **4**, 926 (1950).

(11) E. Clar, "Aromatische Kohlenwasserstoffe," Springer Verlag, Berlin, 1941, p. 104.

(12) A. E. Remick, "Electronic Interpretations of Organic Chemistry," John Wiley and Sons, Inc., New York, N. Y., 1943, p. 103.

(13) Reference 12, pp. 104-105.

(14) Reference 12, p. 104.

(15) Dr. Roberts has kindly informed the author of his agreement with the present figures for styrene, and that the incorrect data in ref. 7 were due to errors in transcription.

TABLE II

MOLECULAR-ORBITAL DATA FOR STYRENE					
Position	A(-β)	F	Position	A(-β)	F
β	1.704	0.821	m	2.546	0.395
α	2.424	.415	p	2.424	.415
o	2.370	.443			

WILLIAM RAMSAY AND RALPH FORSTER LABORATORIES
UNIVERSITY COLLEGE
LONDON, W.C.1, ENGLAND

Metathetical Reactions of Silver Salts in Solution. III. The Synthesis of Nitrate Esters¹

BY ARTHUR F. FERRIS, KATHARINE W. MCLEAN, IRMA G. MARKS AND WILLIAM D. EMMONS

RECEIVED APRIL 27, 1953

It has been found in this Laboratory that the use of silver nitrate in acetonitrile is a very convenient method for preparing laboratory quantities of extremely pure nitrate esters. The method has an additional advantage in that the reaction may be conveniently followed by periodic weighing of the silver halide precipitated.

The reaction of alkyl halides with silver nitrate under heterogeneous conditions has been used for many years as a preparative method for alkyl nitrates. Experiments wherein ethanol was used as a solvent for the reaction² have led largely to nitric acid and the mixed ethyl alkyl ether derived from the alkyl halide. The enormous solubility of silver nitrate in acetonitrile is well known,³ and the use of silver nitrate in acetonitrile to prepare 2,4,6-trinitrobenzyl nitrate from the corresponding bromide has been described.⁴ It would appear, however, that the virtues of silver nitrate in acetonitrile for synthesis of nitrates have not been generally recognized, since in even very recent work⁵ nitrates have been prepared by the heterogeneous reaction.

Most primary and secondary alkyl iodides, many bromides and active chlorides react rapidly enough at room temperature or slightly above to be useful in preparative work. The following nitrates were prepared in the yields indicated: *n*-hexyl nitrate from *n*-hexyl bromide (77%), and from *n*-hexyl iodide (67%), *n*-octyl nitrate from *n*-octyl iodide (61%), benzyl nitrate from benzyl chloride (64%), methallyl nitrate from methallyl chloride (45%), 2-octyl nitrate from 2-octyl iodide (46%), 2-nitrate-ethanol from 2-bromoethanol (70%), nitrate-acetonitrile from iodoacetonitrile (32%), ethyl lactate nitrate from ethyl α-bromopropionate (59%), and ethyl hydracrylate nitrate from ethyl β-bromopropionate (58%). These yields undoubtedly do not represent the optimum obtainable, since most of the experiments were carried out on a small scale with consequent large mechanical losses.

(1) This work was carried out under Army Ordnance Contract W-01-021-ORD-334.

(2) K. A. Burke and F. G. Donnan, *J. Chem. Soc.*, **85**, 555 (1904); J. W. Baker, *ibid.*, 987 (1934).

(3) A. Seidell, "Solubilities of Inorganic and Metal Organic Compounds," Third Ed., D. Van Nostrand Co., Inc., New York, N. Y., 1940, p. 68.

(4) L. F. Fieser and W. von E. Doering, *THIS JOURNAL*, **68**, 2252 (1946).

(5) J. W. Baker and D. M. Easty, *J. Chem. Soc.*, 1193 (1952).

Experimental⁶

The procedures described herein for ethyl hydracrylate nitrate and methallyl nitrate are typical of those used for the preparation of the other esters. All boiling points are uncorrected.

Ethyl Hydracrylate Nitrate.—To a solution of 20.0 g. (0.118 mole) of silver nitrate in 100 ml. of dry, distilled acetonitrile was added a solution of 9.1 g. (0.05 mole) of ethyl β-bromopropionate in 25 ml. of acetonitrile. After three days at room temperature 9.0 g. (96%) of silver bromide was recovered by filtration. The filtrate was poured into a liter of ice-water, and the oil which separated extracted into two 50-ml. portions of methylene chloride. After drying, the solvent was removed by distillation at atmospheric pressure, and the residue was distilled at reduced pressure to yield 4.7 g. (58%) of ethyl hydracrylate nitrate, b.p. 60–64° (1.5 mm.), *n*_D²⁵ 1.4258, *d*₄²⁰ 1.262.

Anal. Calcd. for C₅H₉O₂N: C, 36.81; H, 5.56; N, 8.59. Found: C, 37.11; H, 5.72; N, 8.46.

Methallyl Nitrate.—To a solution of 18.7 g. (0.11 mole) of silver nitrate in 30 ml. of dry acetonitrile was added 9.1 g. (0.10 mole) of methallyl chloride. After five days at room temperature a total of 13.1 g. (92%) of silver chloride was collected on a filter. The filtrate was worked up as described above, and the residue was fractionated through a short packed column to give 5.3 g. (45%) of methallyl nitrate, b.p. 83–88° (215 mm.), *n*_D²⁵ 1.4221, *d*₄²⁰ 1.064.

Anal. Calcd. for C₄H₇O₂N: C, 41.02; H, 6.03; N, 11.96. Found: C, 41.51; H, 6.40; N, 12.19.

(6) We are indebted to Mr. Al Kennedy and Miss Annie Smelley for analytical data.

ROHM AND HAAS COMPANY
JOSIAH GORGAS LABORATORY
REDSTONE ARSENAL RESEARCH DIVISION
HUNTSVILLE, ALABAMA

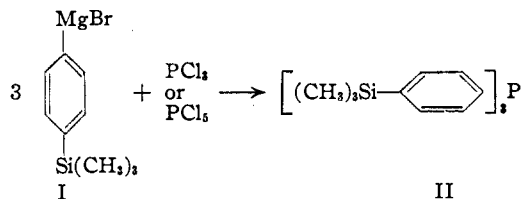
Silicon-containing Aromatic Phosphorus Derivatives

BY KURT C. FRISCH¹ AND HAROLD LYONS

RECEIVED APRIL 15, 1953

The purpose of this investigation was the preparation of aromatic silanes containing nuclear substituted phosphorus groups. The presence of phosphorus groups in aromatic silanes should impart certain physical properties useful in applications such as plasticizers, lubricants and oil additives. This paper deals with the preparation of some model compounds of this type.

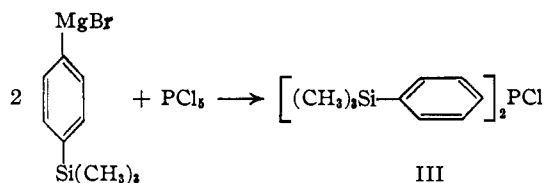
p-Trimethylsilylphenylmagnesium bromide (I) was treated with phosphorus tri- and pentachloride, using equimolecular amounts of the reactants. In both cases, the main product consisted of tris-(*p*-trimethylsilylphenyl)-phosphine (II)



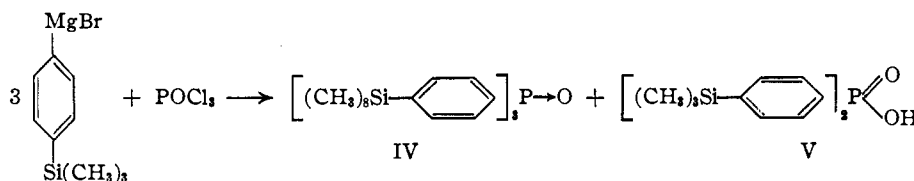
In the reaction with phosphorus pentachloride, in addition to the above described crystalline phosphine (II), another liquid product was obtained which is presumably bis-(*p*-trimethylsilyl)-chlorophosphine (III).

Tris-(*p*-trimethylsilyl)-phosphine (II) is very resistant to oxidation. Refluxing the phosphine

(1) E. F. Houghton & Co., Philadelphia, Penna.



(II) with potassium permanganate in aqueous and in pyridine solution did not result in the formation



of the corresponding phosphine oxide. This result is not surprising in view of the well-known resistance of aromatic phosphines toward oxidation.

p-Trimethylsilylphenylmagnesium bromide (I) when treated with phosphorus oxychloride yields both the phosphine oxide (IV) as well as the diposphonic acid (V). The procedure was essentially that of Kosolapoff.²

Experimental

p-Trimethylsilylphenylmagnesium bromide (I) was prepared from 12.2 g. of magnesium turnings, 114.5 g. of *p*-bromophenyltrimethylsilane and 550 cc. of anhydrous ether. The reaction was initiated by means of a small amount of ethylmagnesium bromide.

Tris-(*p*-trimethylsilylphenyl)-phosphine (II). (A).—In a three-necked flask, equipped with stirrer, reflux condenser and dropping funnel, were placed 34.4 g. of phosphorus trichloride and 100 cc. of ether. Half of the above prepared Grignard solution was added gradually through a dropping funnel. Afterwards the mixture was refluxed for three hours. The inorganic precipitate was filtered off and washed with ether. The solvent was then removed from the filtrate. The weight of the residual material was 68.1 g. On standing in the refrigerator, crystals formed which were recrystallized from alcohol, yielding colorless needles, m.p. 95–96° (uncor.).

B.—Half of the above described Grignard solution was added slowly to a solution of 52.1 g. of phosphorus pentachloride in 100 cc. of ether. The product was worked up in the same way as described in A. The residual material weighed 63 g. It was vacuum distilled. Tris-(*p*-trimethylsilylphenyl)-phosphine (II) distilled at 112–117° at 31 mm. It was recrystallized from alcohol, yielding colorless needles, m.p. 95–96° (uncor.). A mixed melting point taken with the products obtained by procedures A and B showed no depression, establishing thereby the identity of the two materials. The yields of the pure product ranged from 35–45%.

Anal. Calcd. for $\text{C}_{27}\text{H}_{39}\text{PSi}_3$: Si, 17.6; P, 6.5. Found: Si, 17.2; P, 6.8.

In the above distillation, another fraction was isolated, distilling at 72° at 43 mm. as a colorless liquid.

Anal. Calcd. for $\text{C}_{18}\text{H}_{24}\text{ClPSi}_2$: Si, 15.4; P, 8.5. Found: Si, 13.1; P, 8.9.

While this compound evidently was not pure, it probably contained bis-(*p*-trimethylsilylphenyl)-chlorophosphine (III). The presence of chlorine was proven by means of a qualitative test.

Tris-(*p*-trimethylsilylphenyl)-phosphine Oxide (IV).—*p*-Trimethylsilylphenylmagnesium bromide, prepared from 57 g. of *p*-bromophenyltrimethylsilane, was added gradually to a solution of 38 g. of phosphorus oxychloride in 300 cc. of ether which was brought to reflux before the addition. The reaction mixture was then refluxed for 15 hours. After cooling, the yellow liquid was decanted from the residual solid. The solid was hydrolyzed in ice-water forming a

white precipitate. The yellow liquid was concentrated on the steam-bath and formed a yellowish-white solid. Both the white precipitate and the residual solid obtained from the liquid portion of the reaction mixture were combined and washed first with dilute sodium hydroxide and then with water. The residual product was extracted with ether and the ether extract dried over anhydrous sodium sulfate. After removal of the ether, the remaining solid was recrystallized from alcohol, yielding a colorless, crystalline product, m.p. 259° (uncor.). The yield was 30%.

Anal. Calcd. for $\text{C}_{27}\text{H}_{39}\text{OPSi}_3$: Si, 17.0; P, 6.3. Found: Si, 17.4; P, 6.8.

Bis-(*p*-trimethylsilylphenyl)-phosphonic Acid (V).—The sodium hydroxide extract from the combined solid products of the reaction of *p*-trimethylsilylphenylmagnesium bromide and phosphorus oxychloride

was acidified with dilute hydrochloric acid, resulting in a colorless, crystalline product, m.p. 213–214.5° (uncor.). The yield was 15%.

Anal. Calcd. for $\text{C}_{18}\text{H}_{27}\text{O}_2\text{PSi}_2$: Si, 15.5; P, 8.6. Found: Si, 16.5; P, 8.9.

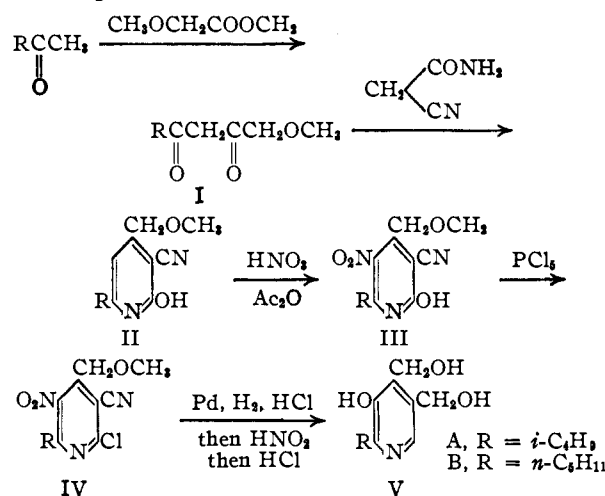
NEW PRODUCTS DEVELOPMENT LABORATORY
GENERAL ELECTRIC COMPANY
PITTSFIELD, MASS.

Chemistry of Vitamin B₆. X. Some Homologs of the Vitamin B₆ Group

BY DOROTHEA HEYL, EILEEN LUZ, STANTON A. HARRIS AND KARL FOLKERS

RECEIVED APRIL 22, 1953

An ethyl homolog of pyridoxine, 2-ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine, was reported previously.¹ Two higher homologs have been prepared; the corresponding isobutyl and *n*-amyl derivatives. These compounds were synthesized in general by the sequence of reactions which was used for preparation of the ethyl homolog, the main difference being that several of the intermediates were not isolated. The compounds actually isolated are represented by the formulas I through V.

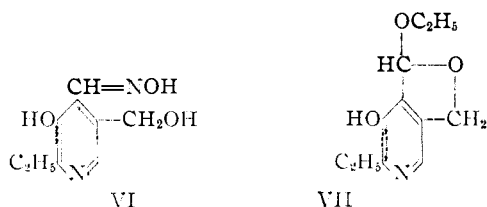


2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine¹ was oxidized to 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine, which was isolated as the oxime VI. The latter was con-

(2) G. M. Kosolapoff, *THIS JOURNAL*, **64**, 2982 (1942).

(1) S. A. Harris and A. N. Wilson, *THIS JOURNAL*, **63**, 2526 (1941).

verted to the monoethyl acetal VII. These reactions are analogous to those previously described for the corresponding pyridoxal derivatives.^{2,3}



Experimental⁴

The reactions carried out for the preparations of 2-isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine and 2-*n*-amyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine were similar to reactions previously described.^{1,5} Only the physical properties of the intermediates and products are listed here.

2-Isobutyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIA) was prepared from 1-methoxy-7-methyl-2,4-heptanedione (IA) (b.p. 113° (24 mm.), n_D^{20} 1.4596). After one recrystallization from ethyl alcohol, the product melted at 204–205°.

Anal. Calcd. for C₁₂H₁₆N₂O₂: C, 65.43; H, 7.32; N, 12.72. Found: C, 65.68; H, 7.25; N, 12.71.

2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIIA) was purified by two recrystallizations from ethyl alcohol, accompanied by decolorization with Darco; m.p. 167–168°.

Anal. Calcd. for C₁₂H₁₅N₃O₄: C, 54.33; H, 5.70; N, 15.84. Found: C, 54.62; H, 5.50; N, 15.83.

2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (IVA) was recrystallized three times from petroleum ether (b.p. 30–60°). It melted at 42–43°.

Anal. Calcd. for C₁₂H₁₄N₃O₂Cl: C, 50.80; H, 4.96; N, 14.82. Found: C, 50.82; H, 5.12; N, 15.08.

2-Isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride (VA) was recrystallized from hot water, with decolorization with Darco; m.p. 213–214°.

Anal. Calcd. for C₁₁H₁₈N₂O₃Cl: C, 53.33; H, 7.32; N, 5.66. Found: C, 53.35; H, 7.25; N, 5.90.

1-Methoxy-2,4-nonanedione (IB).—Condensation of methyl methoxyacetate with methyl *n*-amyl ketone yielded 1-methoxy-2,4-nonanedione; b.p. 138° (28 mm.). n_D^{20} 1.4602.

Anal. Calcd. for C₁₀H₁₈O₃: C, 64.48; H, 9.74. Found: C, 64.50; H, 9.72.

2-*n*-Amyl-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIB) was recrystallized twice from absolute alcohol; m.p. 131–132°.

Anal. Calcd. for C₁₃H₁₈N₂O₂: C, 66.64; H, 7.74; N, 11.96. Found: C, 66.74; H, 7.64; N, 12.05.

2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-hydroxypyridine (IIIB) was recrystallized twice from alcohol and once from dilute alcohol. It melted at 161–162°.

Anal. Calcd. for C₁₃H₁₇N₃O₄: C, 55.90; H, 6.14; N, 15.05. Found: C, 56.25; H, 5.79; N, 15.24.

2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (IVB) was recrystallized twice from petroleum ether (b.p. 30–60°); m.p. 42–43°.

Anal. Calcd. for C₁₃H₁₆N₃O₂Cl: C, 52.44; H, 5.42; N, 14.11. Found: C, 52.16; H, 5.00; N, 14.20.

2-*n*-Amyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride (VB) was recrystallized from alcohol containing a trace of hydrogen chloride. The product melted at 186–187°.

Anal. Calcd. for C₁₂H₂₀N₂O₃Cl: C, 55.05; H, 7.70; N, 5.35. Found: C, 54.93; H, 7.82; N, 5.47.

(2) D. Heyl, *ibid.*, **70**, 3434 (1948).

(3) S. A. Harris, D. Heyl and K. Folkers, *ibid.*, **66**, 2088 (1944).

(4) We are indebted to Mr. Richard Boos and his associates for the microanalyses.

(5) S. A. Harris and K. Folkers, *THIS JOURNAL*, **61**, 1248, 3207 (1939).

Oxime of 2-Ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine (VI).—2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride¹ (10.7 g.) was oxidized with manganese dioxide and sulfuric acid in a manner exactly analogous to the preparation of pyridoxal oxime.² The yield of the oxime of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine was 4.8 g. (50%). After one recrystallization from water-alcohol and one from alcohol, the oxime melted at 225–226°.

Anal. Calcd. for C₉H₁₂N₂O₃: C, 55.09; H, 6.17; N, 14.28. Found: C, 55.22; H, 6.00; N, 14.12.

Monoethyl Acetal of 2-Ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine Hydrochloride (VII).—Conversion of 3.4 g. of the oxime of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine (VI) to the corresponding monoethyl acetal was carried out in the manner previously described for the conversion of pyridoxal oxime.³ The yield of the monoethyl acetal of 2-ethyl-3-hydroxy-4-formyl-5-hydroxymethylpyridine hydrochloride was 1.66 g. (39%); m.p. 137.5–138.5°. After one recrystallization from alcohol-ether containing a little hydrogen chloride and another recrystallization from alcohol containing a little hydrogen chloride, the material melted at 132–133°.

Anal. Calcd. for C₁₁H₁₆N₂O₃Cl: C, 53.77; H, 6.56; N, 5.70. Found: C, 54.00; H, 6.29; N, 5.63.

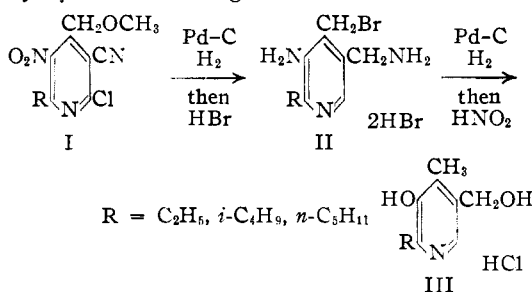
RESEARCH LABORATORIES
MERCK AND CO., INC.
RAHWAY, NEW JERSEY

Chemistry of Vitamin B₆, XI. Homologs of 4-Desoxypyridoxine

BY DOROTHEA HEYL, EILEEN LUZ, STANTON A. HARRIS AND KARL FOLKERS

RECEIVED APRIL 22, 1953

4-Desoxypyridoxine was shown to be a potent vitamin B₆ inhibitor.¹ Because of the biological interest in this compound, the preparation of homologs for further biological study was undertaken. Three homologs, represented by structure III, in which the methyl group in position 2 of 4-desoxypyridoxine has been replaced by ethyl, isobutyl and *n*-amyl groups, have now been prepared by synthesis through the intermediates I and II.



2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride and 2-isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride have also been prepared by the direct hydrogenolysis of the 2-ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride² and 2-isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride.³ Hydrogenolysis of pyridoxine hydrochloride to form 4-desoxypyridoxine hydrochloride was described previously.⁴

(1) W. H. Ott, *Proc. Soc. Exp. Biol. Med.*, **61**, 125 (1946); W. W. Cravens and S. B. Snell, *ibid.*, **71**, 73 (1949).

(2) S. A. Harris and A. N. Wilson, *THIS JOURNAL*, **63**, 2526 (1941).

(3) D. Heyl, E. Luz, S. A. Harris and K. Folkers, *ibid.*, **78**, 4079 (1953).

(4) S. A. Harris, *ibid.*, **68**, 3208 (1940).

Experimental⁶

2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-Ethyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I, 25.6 g.) was shaken with palladium-Darco and hydrogen in a solution containing hydrochloric acid under 2-3 atmospheres of pressure until 6 moles of hydrogen had been absorbed. The reduction was finished in 21 hours. After removal of the catalyst, the solution was concentrated under reduced pressure to a thick oil. This oil was heated with 400 ml. of 40-42% hydrobromic acid, and about 250 ml. distilled at atmospheric pressure. The black color was removed with Darco. The solution, after further concentration under reduced pressure, was diluted with alcohol, which caused crystallization of 27.1 g. of crude 2-ethyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II); m.p. 217-220° dec. Concentration of the filtrate left an oil which was again subjected to the hydrobromic acid treatment. Another 3.8 g. of product brought the yield to 76%.

A solution of 18.0 g. of this material in 600 ml. of water was shaken with 3 g. of 5% palladium chloride on Darco catalyst under 2-3 atmospheres of hydrogen. There was almost no hydrogen uptake for about an hour; then one mole was rapidly absorbed. The catalyst was removed by filtering, and the solution, combined with the reduction product of another 12 g. of bromomethyl compound II, was concentrated under reduced pressure to about 100 ml., and then shaken with 48 g. of silver chloride for several hours. The solid material was removed by filtering. The resulting solution containing 2-ethyl-3-amino-4-methyl-5-aminomethylpyridine dihydrochloride was diluted to 450 ml. and heated to 85°. A solution of 11.2 g. of sodium nitrite in 150 ml. of water, and 15 ml. of 12 *N* hydrochloric acid were added simultaneously over a period of 20 minutes. After an additional 10 minutes of stirring at 85°, the solution contained no nitrous acid, and was decolorized with Darco and concentrated to dryness under reduced pressure.

The residue, dissolved in a minimum amount of warm water, was treated with an excess of sodium bicarbonate and extracted continuously with chloroform for two days. After removal of the chloroform under reduced pressure, the residue was dissolved in alcohol and treated with an excess of alcoholic hydrogen chloride. 2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (III) was obtained in a yield of 5.2 g. (35%, based on 30 g. of crude 2-ethyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide); after two recrystallizations from alcohol the m.p. was 174-176°.

Anal. Calcd. for C₉H₁₄NO₂Cl: C, 53.07; H, 6.93; N, 6.88. Found: C, 52.81; H, 6.64; N, 7.13.

2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III) by Hydrogenolysis of 2-Ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine Hydrochloride.—A mixture of 1.0 g. of 2-ethyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine hydrochloride,³ 1 ml. of 6 *N* hydrochloric acid, 1 g. of 5% palladium on Darco catalyst and 125 ml. of water was shaken under 2-3 atmospheres of hydrogen for one hour. Approximately one mole of hydrogen was absorbed. After removal of the catalyst, the solution was concentrated to 3 ml., treated with an excess of sodium bicarbonate, and extracted continuously with chloroform for 17 hours. 2-Ethyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride (0.19 g., 21%) was isolated as described in the preceding experiment; the m.p., 178-179°, was not lowered when this material was mixed with a sample prepared by the method described above.

2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-Isobutyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine³ (I, 13.4 g.) was hydrogenated in the manner described for the ethyl homolog. The reduction required 5 hours. The gummy residue, after concentration of the filtrate, was treated with 200 ml. of 40-42% hydrobromic acid. After removal of one third of the solution by distillation at atmospheric pressure, the dark color was removed by treatment with Darco, and the resulting solution concentrated under reduced pressure to 25 ml. Crystalline 2-isobutyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II), m.p. 211-213° dec., was obtained in a yield of 6.73 g. The yield was increased to 14.3 g. (69%) after further concentration of the filtrate.

(5) We are indebted to Mr. Richard Boos and his associates for the microanalysis.

A mixture of 6.7 g. of this material, 1.5 g. of 10% palladium on Darco and 125 ml. of water was shaken with hydrogen under 2-3 atmospheres of pressure. One mole of hydrogen was consumed in several minutes. After removal of the catalyst, the solution was concentrated to dryness under reduced pressure. The white, crystalline residue was slurried with alcohol and collected on a filter. Two fractions, totaling 4.8 g., of 2-isobutyl-3-amino-4-methyl-5-aminomethylpyridine dihydrobromide were obtained. A solution of this material in 78 ml. of water was heated to 85° and treated simultaneously with 5.2 ml. of 6 *N* hydrochloric acid, and 1.95 g. of sodium nitrite dissolved in 26 ml. of water. The additions required 10 minutes and were followed by 10 minutes of stirring at 85°. After decolorization with Darco, the solution was concentrated to dryness under reduced pressure. The residue, dissolved in a small amount of water, was treated with an excess of sodium bicarbonate and extracted continuously with chloroform for 19 hours. The product, 2-isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride, was isolated and purified as described above for the ethyl homolog; yield 1.00 g. (28%, based on 6.7 g. of 2-isobutyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide); m.p. 163-165°.

Anal. Calcd. for C₁₁H₁₈NO₂Cl: C, 57.01; H, 7.83; N, 6.05. Found: C, 56.85; H, 7.79; N, 6.13.

2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride by Hydrogenolysis of 2-Isobutyl-3-hydroxy-4,5-bis-(hydroxymethyl)-pyridine Hydrochloride.—The hydrogenolysis was carried out on 3.0 g. of material exactly as described for the ethyl homolog, with the exception that the mixture was shaken with hydrogen for 2.5 hours. 2-Isobutyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride, m.p. 160-162°, was obtained in a yield of 0.77 g. (27%) after isolation as described for the ethyl homolog.

2-*n*-Amyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine Hydrochloride (III).—2-*n*-Amyl-3-nitro-4-methoxymethyl-5-cyano-6-chloropyridine (I, 29.8 g.) was hydrogenated and heated with hydrobromic acid as described for the ethyl homolog. 2-*n*-Amyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide (II), m.p. 215-218°, was obtained in a yield of 5.0 g. Concentration of the filtrate and further treatment with hydrobromic acid yielded another 11.4 g. raising the yield to 37%.

This material (5.0 g.) was subjected to hydrogenation and diazotization as described for the ethyl homolog, and the product was isolated in the same manner. 2-*n*-Amyl-3-hydroxy-4-methyl-5-hydroxymethylpyridine hydrochloride was obtained in a yield of 1.46 g. (53%, based on 5.0 g. of 2-*n*-amyl-3-amino-4-bromomethyl-5-aminomethylpyridine dihydrobromide). After one recrystallization from alcohol, the material had a m.p. of 125.0-125.5°.

Anal. Calcd. for C₁₂H₂₀NO₂Cl: C, 58.64; H, 8.20; N, 5.70. Found: C, 58.72; H, 8.13; N, 5.95.

RESEARCH LABORATORIES
MERCK & Co., INC.
RAHWAY, NEW JERSEY

Chloro-substituted Alkenyl Dithiocarbamates

BY MARION W. HARMAN AND JOHN J. D'AMICO

RECEIVED APRIL 13, 1953

Although a number of alkyl esters of substituted dithiocarbamic acids have been prepared, no reference to the preparation of chloro-substituted alkenyl dithiocarbamates has been found.¹⁻⁷ The purpose of this investigation was the synthesis of compounds of this type.

The compounds were prepared by treating either sodium dimethyldithiocarbamate, sodium diethyl-

- (1) R. Conrad and F. Salomon, *J. prakt. Chem.*, **10**, 28 (1874).
- (2) S. M. Delepine, *Bull. soc. chim. France*, **27**, 588 (1902).
- (3) M. T. Bogert, *This Journal*, **25**, 290 (1903).
- (4) J. V. Braun, *Ber.*, **50**, 1573 (1923).
- (5) W. H. Davies and W. A. Sexton, *Biochem. J.*, **40**, 881 (1946).
- (6) P. Briesley, *Florists Exchange*, **100**, 13 (1947).
- (7) M. W. Harman, U. S. Patent 2,418,917.

metal oxide catalysts in vapor phase hydrogenation and dehydrogenation reactions. It is known that cycloolefins undergo a complete hydrogen disproportionation to cycloparaffins and aromatics on the surface of metal catalysts (*i.e.*, platinum, palladium and nickel).

In the present work, cyclohexene was subject to the action of pure vanadium trioxide at temperatures of 250–450° in an atmosphere of hydrogen and of nitrogen. The obtained results were compared with theoretical calculations.

Theoretical equilibrium concentrations of benzene and cyclohexane as a function of temperature were calculated from the equilibrium constants as presented by Rossini,² *et al.* Benzene and cyclohexane would be expected to form by one or more of three reactions, namely, hydrogenation, dehydrogenation or disproportionation. Figure 1 presents the theoretical concentrations of products from these reactions together with the experimental results. The theoretical concentrations were calculated on the basis of the initial partial pressure of cyclohexene being 0.12 atmosphere to that of hydrogen being 0.88 atmosphere, as used in this experimentation. It can be seen from Fig. 1 that, theoretically, hydrogenation would be the major reaction below 250°, both hydrogenation and dehydrogenation in temperature range 250–300° and dehydrogenation above 300°. The disproportionation reaction is possible throughout these temperatures. The experimental results have shown that cyclohexene in the presence of hydrogen, when passed at various temperatures (250–450°) over vanadium trioxide catalyst, shows no hydrogen disproportionation, but direct hydrogenation and dehydrogenation reactions approaching the theoretical values.

This fact is in line with the interpretation of edgewise adsorption of the organic molecule on the surface of metal oxide catalysts *versus* flat adsorption on the surface of metals.

Experimental Part

Cyclohexene (Eastman Kodak Co.) b.p. 82.5–83.5°, n_D^{20} 1.4468, was vaporized in the stream of hydrogen at a constant rate into a glass tube filled with catalyst and placed in an electrically heated oven. The constancy of cyclohexene/hydrogen ratio (0.12:0.88 atmosphere) was maintained by a flowmeter (for hydrogen) and temperature of the evaporator (for cyclohexene). The liquid hourly space velocity was maintained between 0.015–0.017. The products were collected in receivers cooled with water and Dry Ice. Analysis was by distillation, chromatographic adsorption (silica gel) and determination of physical constants. The catalyst was prepared and activated as before.¹

The experimental results are presented in Table I. It can be seen from the results obtained at lower temperatures that the activity of vanadium trioxide is extremely low. This was to be expected, since in the earlier work³ with the same catalyst on hydrogenation of olefins its activity was at its maximum at higher temperatures (around 400°), which goes parallel with hydrogen adsorption and the amount of vanadium trioxide present. At higher temperatures the catalyst exhibits high activities and the reaction of dehydrogenation to benzene approaches the theoretical values. It is of importance for this discussion that in no case was there an excessive formation of cyclohexane and this consequently indi-

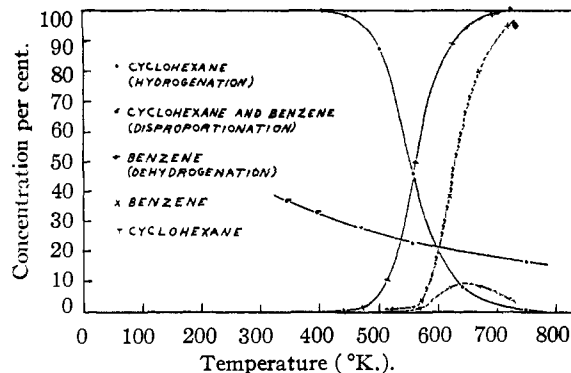


Fig. 1.—Reaction of cyclohexene and hydrogen. Theoretical equilibrium concentrations (solid lines) and experimental results (dotted line) over vanadia catalyst.

cates there is no hydrogen disproportionation reaction. Experiments carried out in an atmosphere of nitrogen showed similar results, the per cent. of dehydrogenation being somewhat higher than in experiments in hydrogen.

TABLE I

REACTION OF CYCLOHEXENE IN THE PRESENCE OF HYDROGEN AND OF NITROGEN (1:8 RATIO) OVER VANADIUM TRIOXIDE CATALYST. LIQUID HOURLY SPACE VELOCITY 0.015–0.017

Temp., °C.	n_D^{20} of the product	Chromatographic analysis ^a of the product (%)		
		C ₆ H ₁₂	C ₆ H ₆	C ₆ H ₁₀
A. Hydrogen experiments				
250	1.4465	98.5	1.5	0.5
300	1.4471	91.5	5.0	3.5
350	1.4583	53.8	38.5	7.7
400	1.4886	11.0	81.0	8.0
450	1.5010	0.0	97.0	3.0
B. Nitrogen experiments				
300	1.4473	100.0	0.0	0.0
350	1.4538	44.5	55.0	>0.5
400	1.4730	15.5	84.0	>0.5

^a Initial boiling point of all products was 80° which clearly indicated that no isomerization to methylcyclopentane or methylcyclopentene took place.

CATALYSIS LABORATORY
DEPARTMENT OF CHEMICAL ENGINEERING
ILLINOIS INSTITUTE OF TECHNOLOGY
CHICAGO 16, ILLINOIS

The Reaction between Periodate and Cobaltous Ions¹

BY RALPH E. JENTOFT AND REX J. ROBINSON²

RECEIVED MARCH 23, 1953

During a study of the determination of potassium as the metaperiodate, chemical evidence was obtained which indicated an oxidation–reduction reaction between periodic acid and divalent cobalt as a function of the hydrogen ion concentration. This reaction does not appear to be clearly indicated in the literature. Gmelin's "Handbuch"³ leaves the matter an open question in citing two papers with

(1) This work was partly supported by the Office of Naval Research under Contract No. N8onr-520/III with the University of Washington.

(2) Correspondence should be addressed to Rex J. Robinson.

(3) "Gmelin's Handbuch der anorganischen Chemie," No. 58 Cobalt, Part A, Sect. 2, 8th ed., Verlag Chemie G.m.b.h., Berlin, 1932, p. 317.

(2) M. B. Epstein, K. S. Pitzer and F. D. Rossini, *J. Research Natl. Bur. Standards*, **48**, 379 (1949).

(3) V. I. Komarevsky and J. R. Coley, *THIS JOURNAL*, **70**, 4163 (1948).

opposing views. More recently other workers^{4,5} have reported the existence of certain cobaltous periodates in complete variance with the present findings.

Some revealing information regarding this question is obtained through a consideration of oxidation potentials. In Fig. 1 are shown portions of the potential-*p*H diagram for iodine and cobalt constructed from the data of Latimer⁶ as described by Delahay, Pourbaix and Van Rysselberghe.⁷ (Although the potential of the periodate-iodate couple is based upon purely chemical evidence, it represents a close approximation). Thus it is seen that the stability of a strongly acid solution of cobaltous and periodate ions is indicated, whereas in weakly acid solution the reduction of periodate by the cobaltous ion appears possible.

The chemical evidence indicating this reaction was the production of gelatinous, greenish-brown cobaltic hydroxide and iodate ions when solutions of divalent cobalt and periodic acid were mixed. The cobaltic hydroxide was identified on the basis of its physical properties and the knowledge of the reactants and possible products. After filtration of the cobaltic hydroxide, iodate was identified in the filtrate with silver nitrate solution by the formation of white, curdy silver iodate, difficultly soluble in nitric acid (brown silver periodate is soluble). At a *p*H of about 2 this reaction proceeded very slowly, traces of the reaction products appearing after about 15 minutes. Many hours later the reaction was still far from complete as judged by the small amount of cobaltic hydroxide formed. In more acid solution the reaction did not go at all. However at *p*H 6 it was instantaneous even in dilute solutions.

Quantitative tests were performed to firmly establish the existence of this reaction. Cobaltous acetate solution in excess reacted with a known amount of potassium metaperiodate in solution. The oxidation state of the iodine after reaction was established iodometrically. Cobaltic ion in an acid solution is an oxidizing agent and would interfere in the iodometric procedure. Removal of the gelatinous cobaltic hydroxide was not practical so the cobalt was converted to the cobaltous state. This reduction occurred spontaneously when the cobaltic hydroxide was dissolved by heating in a 0.1 *N* sulfuric acid solution. A few drops of ethylenediamine were added to assist, through its complexing action with cobalt, in the solution of the difficultly soluble cobaltic hydroxide. Controls were run with identical treatments except that the solutions were acidified before mixing to prevent the reaction under study from occurring. The results are shown in Table I.

The ratio of the average number of oxidation equivalents found after reaction to the number of oxidation equivalents taken is 0.740 compared to the theoretical value of 0.750 if the equivalents of

(4) R. K. Bahl, S. Singh and N. K. Ball, *J. Indian Chem. Soc.*, **20**, 227 (1943).

(5) R. C. Sahney, S. L. Aggarwal and M. Singh, *ibid.*, **24**, 193 (1947).

(6) W. M. Latimer, "Oxidation Potentials," 2nd ed., Prentice-Hall, Inc., New York, N. Y., 1952, pp. 210-213.

(7) P. Delahay, M. Pourbaix and P. Van Rysselberghe, *J. Chem. Education*, **27**, 688 (1950).

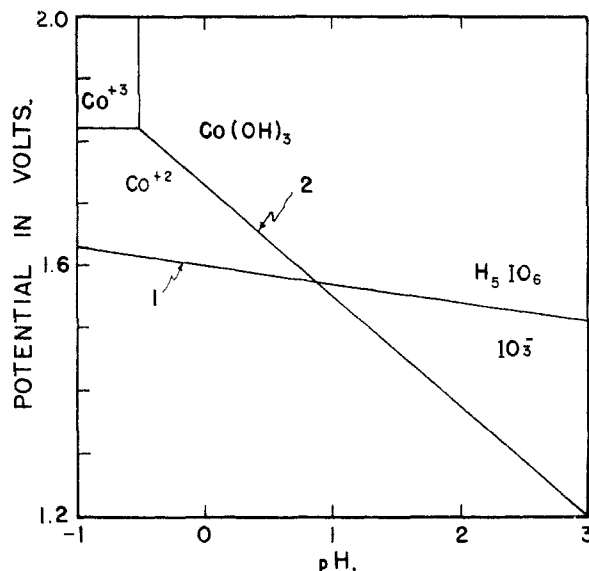


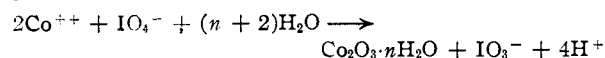
Fig. 1.—A portion of the potential-*p*H diagram for the $\text{Co}(\text{OH})_3\text{-Co}^{++}$ and the $\text{H}_5\text{IO}_6\text{-IO}_3^-$ couples.

periodate were all reduced to iodate. The same ratio for the controls is 0.988 compared to the theoretical value of 1.000 if the periodate solution had not reacted.

TABLE I
ANALYTICAL DATA FOR THE REACTION BETWEEN Co^{++} AND IO_4^-

Taken	Oxidation equivalents	
	Found after reaction	Found in controls
0.656	0.493	0.654
	.495	.650
	.474	.635
	.479	.652
	.484	
	Av. 0.485	0.648

It is believed that the above facts clearly establish the existence of an oxidation-reduction reaction between periodate and divalent cobalt. The probable reaction is indicated by the equation.



It is of interest to note that in agreement with the postulated formation of hydrogen ions here, a decrease in *p*H has been noted after the reaction of solutions originally at *p*H 6.

CHEMISTRY AND OCEANOGRAPHY DEPARTMENTS
UNIVERSITY OF WASHINGTON
SEATTLE 5, WASHINGTON

Peptides Isolated from a Partial Hydrolysate of Steer Hide Collagen

BY THOMAS D. KRONER, WILLIAM TABROFF AND JOHN J. MCGARR

RECEIVED APRIL 18, 1953

In the work on the determination of the structure of collagen being performed in these laboratories, we have been concerned with the sequences of the amino acid residues in the polypeptide chains of

this fibrous protein. We wish to report several peptides isolated in the form of dinitrophenyl (DNP) derivatives from the neutral fraction of an acid partial hydrolysate of steer hide collagen.

Experimental

The collagen was prepared from steer hide by the method of Highberger,¹ except that repeated extraction with 10% sodium chloride solution was substituted for the treatment with trypsin. The protein contained 18.56% nitrogen on a moisture- and ash-free basis.

The partial hydrolysate was obtained by hydrolyzing the collagen for four days at 37° with concentrated hydrochloric acid using a ratio of acid to protein of 20:1. The excess acid was removed in a Craig type evaporator² by concentration to a thick sirup six times.

The acid digest was separated into aromatic, neutral, basic and acidic fractions by use of charcoal (treated with 20% acetic acid) and ion-exchange resins. The basic fraction was obtained by adsorption on the resin XE-64 (Rohm and Haas Co.) buffered at pH 6.0 with ammonium acetate and the acidic fraction was adsorbed on a column of IR-4B (Rohm and Haas Co.) treated with acetic acid and washed until the effluent remained constant at pH 3.5. The neutral fraction obtained in this manner contained 67.5% of the nitrogen of the hydrolysate. The nitrogen content of the neutral fraction appears to be high because of incomplete adsorption of the acidic fraction on the IR-4B column. Acidic peptides have been found in the neutral fraction, but their composition has not been completely resolved.

The dinitrophenyl derivatives of the neutral fraction were prepared by the method of Sanger.³ During the ether extraction, it was observed that some of the yellow color remained in the acid phase. This would indicate that there are neutral peptides containing both acidic and basic amino acid residues, and the basic amino acid is the N-terminal amino acid since the basic DNP-amino acids are acid soluble. This fraction will be investigated in the future.

The DNP derivatives were separated on 10-g. columns of buffered Super-cel⁴ (Johns-Manville Corp.) using ethyl acetate saturated with water as the primary mobile phase. Occasionally, the varying methyl ethyl ketone-chloroform system of Mills⁵ was used and at other times, the columns were extruded and the resolved bands extracted with 2% sodium bicarbonate. In one or two instances, the columns failed to resolve a mixture of dipeptides and these were separated by paper chromatography.⁶ Redistilled solvents were used in the operation of the columns and redistilled hydrochloric acid for the hydrolysis of the peptides.

In the determination of the composition and sequences of the DNP peptides, aliquots of the sub-fractions were hydrolyzed with 6 *N* hydrochloric acid at 105° for various lengths of time. Partial hydrolysates were obtained by refluxing for a period of 0.5 or 1 hour. Four hours of refluxing was used for the complete liberation of the DNP-amino acids, and 16 hours in sealed tubes for complete hydrolysis. The aqueous extracts from the four-hour hydrolysates were hydrolyzed for a further 16 hours in sealed tubes. Extractions of the hydrolysates were made with ether or ethyl acetate. The liberated DNP-amino acids were identified by their rates both on columns and by paper chromatography.⁷ We have found the phenol-isoamyl alcohol-water system⁸ very useful for the identification of the DNP-amino acids on paper. The amino acid residues were identified by paper chromatography.⁹ The DNP-amino acids of the partial hydrolysates were identified by their rates both on columns and paper.

Results

The neutral fraction was first put through an

- (1) J. H. Highberger, *J. Am. Leather Chemists Assoc.*, **31**, 93 (1936).
- (2) L. C. Craig, J. D. Gregory and W. Haussmann, *Anal. Chem.*, **22**, 1462 (1950).
- (3) F. Sanger, *Biochem. J.*, **39**, 507 (1945).
- (4) J. C. Perrone, *Nature*, **167**, 513 (1951).
- (5) G. L. Mills, *Biochem. J.*, **50**, 707 (1952).
- (6) M. B. Williamson and J. M. Passmann, *J. Biol. Chem.*, **199**, 121 (1952).
- (7) S. Blackburn and A. G. Lowther, *Biochem. J.*, **48**, 126 (1951).
- (8) G. Biserte and R. Osteux, *Bull. soc. chim. biol.*, **33**, 50 (1951).
- (9) R. Conden, A. E. Gordon and A. J. P. Martin, *Biochem. J.*, **38**, 224 (1944).

ethyl acetate-pH 5.0 column and five main bands (A₁, A₂, A₃, A₄, A₅)¹⁰ were distinguished. The last band (A₅) moved very slowly and was eluted with 1% acetic acid in ethyl acetate. The fastest band (A₁) was the largest and it was resolved into 8 sub-fractions (A₁C₁ through A₁C₈) by passage through an ethyl acetate-pH 7.0 column. These sub-fractions were then resolved and purified on either ethyl acetate-pH 7.0, methyl ethyl ketone-chloroform-pH 7.0 columns or by paper chromatography.

As shown in Table I, we have isolated and identified six amino acids, eight dipeptides and one tripeptide as the DNP derivatives. The presence of H.Leu-Ala.OH in two different fractions may be attributed to the poor resolution of the fast moving DNP-amino acids and peptides on the ethyl acetate-pH 5.0 columns. Partial hydrolysis of the DNP-dipeptides resulted in the appearance of two bands. The faster band was the liberated DNP-amino acid and the second band retained the same rate as the DNP-peptide. In the instance of the tripeptide, H.Ala-Gly-Ala.OH, three bands were observed after partial hydrolysis.

TABLE I

SOME ETHER-SOLUBLE DNP-AMINO ACIDS AND DNP-PEPTIDES OF NEUTRAL FRACTION OF PARTIAL HYDROLYSATE OF STEER-HIDE COLLAGEN

Fraction	Amino acid or peptide ¹¹	Fraction	Amino acid or peptide ¹¹
A ₁ C ₁ M ₁ ^{a,b}	Leucine	A ₁ C ₆	H. Ala-Gly-Ala.OH
A ₁ C ₁ M ₂ ^b	H. Leu-Ala.OH	A ₁ C ₇ -I ^c	H. Gly-Pro.OH
A ₁ C ₁ M ₃ ^b	Methionine	A ₁ C ₇ -II ^c	H. Gly-Ala.OH
A ₁ C ₂ M ₁ ^b	H. Leu-Ala.OH	A ₁ C ₈ M ₁ ^d	H. Gly-Gly.OH
A ₁ C ₃ M ₂ ^c	H. Val-Gly.OH	A ₁ C ₈ M ₂ ^d	H. Thr-Gly.OH
A ₁ C ₄ M ₁ ^d	Proline	A ₂ M ₁ ^e	Serine
A ₁ C ₄ M ₂ ^d	Alanine	A ₂ M ₁ ^{e,g}	H. Ser-Gly.OH
A ₁ C ₅	Glycine	A ₂ M ₂ ^g	H. Hypro-Gly.OH

^a The DNP-amino acids and DNP-peptides were separated on columns of 20 mm. diameter containing 10 g. of Super-cel and buffer.⁴ A represents a column treated with 0.5 *M* phosphate buffer and developed with ethyl acetate saturated with water. C is an ethyl acetate-pH 7.0 (0.4 *M* phosphate buffer) column. M is the same as C, but developed with 30-75% methyl ethyl ketone-chloroform⁶ saturated with water (m-e-k-chloroform). ^b Eluted with 30% m-e-k-chloroform. ^c Eluted with 45% (m-e-k-chloroform). ^d Eluted with 60% m-e-k-chloroform. ^e Paper chromatography—Whatman No. 1 paper developed with phenol-isoamyl alcohol-water^{6,8} (1:1:1) at 22°. ^f Eluted with 75% m-e-k-chloroform. ^g Developed with 75% m-e-k-chloroform, and then extracted with 2% sodium bicarbonate after column extrusion.

Discussion

Schroeder, Honnen and Green¹² recently reported the following peptides from a partial hydrolysate of gelatin: -H. Thr-Gly.OH, H. Glu-Gly.OH, H. Glu-Ala.OH, H. Gly-Glu.OH, H. Ser-Gly.OH, H. Hypro-Gly.OH, H. Ala-Gly.OH. Grassman and Riederle¹³ isolated the tripeptide, H. Lys-Pro

(10) See footnote to Table 1 for designation of columns and fractions.

(11) The amino acid residues are abbreviated as suggested by Brand and Edsall, (*Ann. Rev. Biochem.*, **16**, 224 (1947)). The convention of Erlanger and Brand is used to denote peptides of known sequences, (*THIS JOURNAL*, **73**, 3508 (1951)). Thus, alanylglycine is written H. Ala-Gly.OH. Unknown sequences, whose N-terminal amino acid is known and the order of the other residues is unknown, are written in the form, H. Gly-(Ala,Leu).

(12) W. A. Schroeder, L. Honnen and F. C. Green, *Proc. Nat. Acad. Sci.*, **39**, 23 (1953).

(13) W. Grassman and K. Riederle, *Biochem. Z.*, **264**, 177 (1953).

Gly.OH, from a partial hydrolysate of gelatin. In an alkaline partial hydrolysate of gelatin, Heyns, Anders and Becker¹⁴ found H.Glu-Gly.OH, H.Ala-Gly.OH, H.Gly-Asp.OH, H.Ala-Ala-Gly.OH, H.-Ala-(Gly,Glu). Of the twenty or more dipeptides and tripeptides reported present in partial hydrolysates of collagen and gelatin, only five fit the collagen sequence -P-G-R-P-G-R- suggested by Astbury¹⁵ and Pauling and Corey¹⁶ where P represents either proline or hydroxyproline, G is glycine and R stands for one or other of the remaining residues. The five which fit are H.Lys-Pro-Gly.OH (Grassman and Riederle), H.Gly-Asp.OH (Heyns, *et al.*), H.Gly-Glu.OH and H.Hydro-Gly.OH (Schroeder, *et al.*), and H.Gly-Ala.OH (this paper). All of the peptides, except H.Gly-Gly.OH, conform to the -G-R-P-G-R-R- sequence suggested by Bergmann and Niemann¹⁷ for the structure of gelatin. However, this formula was based on Bergmann's value of 19.7% proline¹⁸ in gelatin which is much higher than the currently accepted values for proline of 14.8-15.1%.^{19,20} Schroeder, *et al.*,¹² have pointed out that in view of these more reliable values for proline only three-fourths of the collagen structure could have the sequence suggested by Astbury.¹⁵ A similar consideration would apply to the Bergmann-Niemann¹⁷ sequence. The isolation of H.Gly-Gly.OH (present work) would indicate that other sequences in addition to those suggested must be present. At present, sufficient data have not been accumulated to justify any conclusion as to the reliability of any proposed structure of collagen.

(14) K. Heyns, G. Anders and E. Becker, *Z. physiol. Chem.*, **287**, 120 (1951).

(15) W. T. Astbury, *J. Intern. Leather Trades' Chemists*, **24**, 69 (1940).

(16) L. Pauling and R. B. Corey, *Proc. Nat. Acad. Sci.*, **37**, 272 (1951).

(17) M. Bergmann and C. Niemann, *J. Biol. Chem.*, **115**, 77 (1936).

(18) M. Bergmann, *ibid.*, **110**, 471 (1935).

(19) A. C. Chibnall, *J. Intern. Leather Trades' Chemists*, **30**, 1 (1946).

(20) J. H. Bowes and R. H. Kenten, *Biochem. J.*, **43**, 358 (1948).

RESEARCH DIVISION
UNITED SHOE MACHINERY CORPORATION
BEVERLY, MASSACHUSETTS

Pyridazinemonocarboxylic Acids and Derivatives

BY W. J. LEANZA, H. J. BECKER AND E. F. ROGERS

RECEIVED MARCH 10, 1953

In connection with recent studies of nitrogen heterocyclic amides¹ and hydrazides, new syntheses of pyridazine-3-carboxylic acid and pyridazine-4-carboxylic acid were developed. Gabriel and Colman² first made pyridazine-3-carboxylic acid by the permanganate oxidation of 3-*p*-hydroxyphenylpyridazine.

In the present work two alternate routes to the 3-acid were explored. Permanganate oxidation of 3-hydroxymethylpyridazine and reductive dehalogenation of 6-chloropyridazine-3-carboxylic acid were found to give identical yields of the desired acid. The choice of the route depends, therefore, upon the availability of intermediates. 3-Hydroxy-

methylpyridazine can be prepared in two steps and 33% over-all yield from furfuryl acetate according to Clauson-Kass,³ and we have confirmed this. Our yield of 6-chloropyridazine-3-carboxylic acid from levulinic acid in five steps was 40%. Pyridazine-3-carboxamide and pyridazine-3-carbohydrazide were prepared from the acid *via* the ethyl ester.

Partial decarboxylation of pyridazine-4,5-dicarboxylic acid⁴ gave 4-carboxypyridazine. This new acid was converted to the ethyl ester, amide and hydrazide.

The pK_a values of the isomeric 3- and 4-carboxypyridazines are 3.0 and 2.8, respectively. Data on the basicities and reduction potentials of the corresponding amides have been previously reported.¹

The hydrazides were tested for antituberculous activity in a standardized mouse assay by Dr. M. Solotorovsky of the Merck Institute for Therapeutic Research and found to be inactive.

Experimental

6-Chloropyridazine-3-carboxylic Acid.—The route to this acid involves the following steps, all previously described: preparation of 6-hydroxy-3-methylidihydropyridazine,⁵ dehydrogenation to 6-hydroxy-3-methylpyridazine,⁶ conversion to 6-chloro-3-methylpyridazine^{7,8} and oxidation to 6-chloropyridazine-3-carboxylic acid.⁹ The yields obtained for the reactions were 94, 76, 80 and 60%, respectively.

Two details deserve special mention. In synthesis of 6-chloro-3-methylpyridazine, the temperature of the reaction mixture containing phosphorus oxychloride is critical and should not exceed 100°. In workup of the 6-chloropyridazine-3-carboxylic acid preparation, the product must be extracted immediately after pouring the reaction mixture onto ice. Failure to observe these precautions results in very poor yields.

Pyridazine-3-carboxylic Acid. A. By Dehalogenation of 6-Chloropyridazine-3-carboxylic Acid.—Thirty grams of 6-chloropyridazine-3-carboxylic acid and 25 g. of Raney nickel were added to a cooled solution of 15.9 g. of sodium hydroxide in 330 ml. of water. The mixture was shaken at once with hydrogen at 40 p.s.i. Reduction was completed in two hours. The catalyst was removed by filtration and washed with water, then the combined filtrate and washings were concentrated to 80 ml. The concentrate was cooled to 35° and acidified to pH 2.5 with hydrochloric acid. After two hours standing at 0°, the product was removed by filtration and washed with a little water. When recrystallized from 525 ml. of boiling water, 19.0 g. (81%) of off-white acid, m.p. 195° (dec.), was obtained. A second recrystallization gave 13.4 g. of colorless product, m.p. 201° (dec.), and a second crop, 5.0 g., m.p. 194° (dec.). The reported melting point of pyridazine-3-carboxylic acid is 200-201°. The lower melting material obtained was satisfactory for ester preparation.

Anal. Calcd. for C₅H₄N₂O₂: N, 22.57. Found: N, 22.36.

B. By Oxidation of 3-Hydroxymethylpyridazine.—A solution of 22.4 g. of 3-hydroxymethylpyridazine (m.p. 60°) in 1 l. of water was added with stirring to a solution of 48 g. of potassium permanganate in 2 l. of water at 75° over a period of 10 minutes. After an additional 5 minutes all of the purple color of permanganate had disappeared. The manganese dioxide was filtered off and the filtrate evaporated to 500 ml., acidified to pH 2.5 and cooled. The precipitate

(3) N. Clauson-Kass, *Acta Chem. Scand.*, **1**, 619 (1947).

(4) S. Gabriel and F. Muller, *Ber.*, **28**, 1830 (1895); S. Gabriel, *ibid.*, **36**, 3378 (1903).

(5) L. Wolff and C. Weiland, *Ann.*, **394**, 98 (1912).

(6) O. Poppenberg, *Ber.*, **34**, 3263 (1901).

(7) O. Poppenberg, *ibid.*, **34**, 3265 (1901).

(8) W. G. Overend and L. F. Wiggins, *J. Chem. Soc.*, 242 (1947).

(9) R. F. Homer, H. Gregory, W. G. Overend and L. F. Wiggins, *ibid.*, 2198 (1948).

(1) E. F. Rogers, *et al.*, *Science*, **116**, 253 (1952).

(2) S. Gabriel and A. Colman, *Ber.*, **32**, 408 (1899).

of pyridazine-3-carboxylic acid was collected and air-dried, m.p. 201° (dec.), yield 22 g. (81%).

Pyridazine-4-carboxylic Acid.—A solution of 3.35 g. of pyridazine-4,5-dicarboxylic acid in 300 ml. of water was heated in a bomb at 200° for two hours. The resulting tan solution was boiled with Darco and filtered. The filtrate was evaporated to 70 ml., acidified to pH 2.5 and chilled, yielding a precipitate of pyridazine-4-carboxylic acid as white crystals, m.p. 230–235° (dec.); yield 1.4 g. (56%). An analytical sample recrystallized twice from water decomposed at 239–240° (slow heating).

Anal. Calcd. for $C_6H_4N_2O_2$: C, 48.39; H, 3.25; N, 22.57. Found: C, 48.78; H, 3.42; N, 22.40.

3-Carboxypyridazine.—Pyridazine-3-carboxylic acid (17.7 g.) was esterified by refluxing for six hours with 177 ml. of absolute alcohol and 18 ml. of concentrated sulfuric acid. The reaction mixture was concentrated *in vacuo* to 75 ml. and poured into a cold saturated solution of sodium carbonate. The ester was extracted from the aqueous solution with benzene and crystallized from benzene-petroleum ether. Recrystallization from absolute alcohol gave 11.1 g. of product, m.p. 68.0–68.5°, and a second crop of 2.8 g., slightly yellow, m.p. 65–67° (64% yield).

Anal. Calcd. for $C_6H_5N_2O_2$: C, 55.25; H, 5.30; N, 18.41. Found: C, 55.52; H, 5.01.

4-Carboxypyridazine.—Pyridazine-4-carboxylic acid (6.5 g.) was esterified in a similar manner. The ester was obtained as a straw-colored oil which was distilled under vacuum; b.p. 125° (13 mm.), yield 4 g. (60%).

Anal. Found: C, 55.78; H, 4.97; N, 18.33.

Pyridazine-3-carboxamide.—A suspension of 109 g. of 3-carboxypyridazine in 800 ml. of absolute alcohol was treated with anhydrous ammonia. The mixture became warm, the ester dissolved and amide began to deposit. Gas introduction was halted after three hours when the reaction mixture had cooled to room temperature. The filtered crystals were recrystallized from water with charcoaling, giving 83.6 g. (95%) of colorless amide, m.p. 182–182.5°.

Anal. Calcd. for $C_6H_5N_3O$: C, 48.78; H, 4.09; N, 34.13. Found: C, 49.17; H, 3.92; N, 34.03.

Pyridazine-4-carboxamide.—Treatment of an alcoholic solution of 4-carboxypyridazine with ammonia gave the corresponding amide which when recrystallized from water melted at 191–192°.

Anal. Found: C, 48.77; H, 3.83; N, 33.96.

Pyridazine-3-carbohydrazide.—A mixture of 6 g. of 3-carboxypyridazine, 4.6 g. of 85% hydrazide hydrate and 35 ml. of alcohol was refluxed for one hour, then cooled. The hydrazide deposited as pale yellow crystals, m.p. 151–152°, yield 5.2 g. (95%). After recrystallization from alcohol, the product was cream-colored; the melting point was unchanged.

Anal. Calcd. for $C_6H_6N_4O$: C, 43.47; H, 4.38; N, 40.56. Found: N, 39.73.

Pyridazine-4-carbohydrazide.—Reaction of 4-carboxypyridazine with hydrazine hydrate as above gave the hydrazide, m.p. 124–125° (recrystallized from alcohol).

Anal. Found: C, 43.99; H, 4.13; N, 40.52.

RESEARCH & DEVELOPING DIVISION
MERCK & CO., INC.
RAHWAY, NEW JERSEY

Characterization of Some Alkylbenzenes through their Phthalic Anhydride Derivatives¹

BY GEORGE F. LEWENZ AND KASPER T. SERIJAN²

RECEIVED FEBRUARY 27, 1953

The identification of aromatic hydrocarbons has generally been possible only by physical methods such as examination of absorption spectra and comparison of the physical properties of unknown with authentic compounds. Identification based on the

(1) Presented at the Buffalo meeting of the American Chemical Society, March 24, 1952.

(2) Armour and Company, Chicago, Illinois.

melting points of solid derivatives offers several advantages, especially in those instances where sufficient quantities of the hydrocarbons or equipment necessary for physical examination are unavailable. Consequently, an investigation of solid derivatives of aromatic hydrocarbons was begun at this Laboratory in order to ascertain the usefulness of certain derivatives in identifying the hydrocarbons.

While several types of solid derivatives of aromatic hydrocarbons are known, most of them have proved to be unsuitable for identification purposes, for one reason or another. Picric acid derivatives are frequently unstable,³ while styphnic acid⁴ and 2,4,7-trinitrofluorenone⁵ derivatives have been prepared only from fused ring aromatics. The mono- and diacetamino as well as the benzamino derivatives have been prepared only from monoalkylbenzenes.^{6,7} Trinitrobenzene derivatives from fused ring aromatics are stable,⁴ but those from single-ring aromatics are not.⁸

The *o*-aroylbenzoic and *o*-aroyltetrachlorobenzoic acids, prepared by the condensation of aromatic hydrocarbons with phthalic and tetrachlorophthalic anhydride, respectively, have been proposed by Underwood and Walsh⁹ as suitable crystalline derivatives for the identification of aromatic hydrocarbons. In the present investigation phthalic anhydride derivatives of 25 mono-, di- and trialkylbenzenes have been prepared, and the melting points of the derivatives have been compared to determine the usefulness of these compounds in distinguishing the hydrocarbons. The keto acid of *i*-propylbenzene could not be obtained in sufficient purity. In addition the 1,4-substituted alkylbenzenes formed derivatives only with difficulty and none could be obtained in the cases of the *o*-aroylbenzoic acid derivatives of 1-methyl-4-ethylbenzene and 1,4-diethylbenzene.

The melting points, carbon-hydrogen analyses and neutralization equivalents of 25 *o*-aroylbenzoic acids are presented in Table I; fourteen of these keto acids are reported for the first time. All the derivatives were recrystallized until successive recrystallizations gave no significant change in melting point. The melting points available from the literature are indicated in the tables and are generally in good agreement with the values obtained in the present work. In those instances where the melting points of derivatives of isomeric hydrocarbons were similar, mixed melting points were determined. In this way it was found that a common derivative was obtained from the three isomeric methyl-*t*-butylbenzenes.

In two other cases the mixed melting points taken with the derivatives of two isomeric hydrocarbons showed slight depressions; however, the degree of depression was not sufficient to permit a definite conclusion as to whether rearrangement of the hy-

(3) O. L. Baril and E. S. Hauber, *THIS JOURNAL*, **53**, 1087 (1931).

(4) W. J. Hickinbottom, "Reactions of Organic Compounds," 2nd Edition, Longmans Green and Co., London, 1948, p. 76.

(5) M. Orchin and E. O. Woolfolk, *THIS JOURNAL*, **68**, 1727 (1946).

(6) V. N. Ipatieff and L. Schmerling, *ibid.*, **59**, 1056 (1937).

(7) V. N. Ipatieff and L. Schmerling, *ibid.*, **60**, 1476 (1938).

(8) L. Triandaf, *Ann. sci. Univ. Jassy*, **26**, I, 155 (1940).

(9) H. Underwood, Jr., and W. Walsh, *THIS JOURNAL*, **57**, 940 (1935).

TABLE I
 THE *o*-AROYL BENZOIC ACID DERIVATIVES OF BENZENE AND VARIOUS MONO-, DI- AND TRIALKYLBENZENES

<i>o</i> -Aroylbenzoic acid	Molecular formula	Analyses, %				Neut. equiv.		Melting point (°C.)	
		Carbon		Hydrogen		Calcd.	Found	Obsd.	Lit.
		Calcd.	Found	Calcd.	Found				
Benzene	C ₁₄ H ₁₀ O ₃	74.34	74.46	4.46	4.50	226	225	129.2-130.0	127-128 ⁹
Toluene	C ₁₅ H ₁₂ O ₃	74.98	75.07	5.03	5.04	240	239	139.6-140.5	137-138 ⁹
Ethylbenzene	C ₁₆ H ₁₄ O ₃	75.57	75.40	5.55	5.62	254	254	130.7-131.6	122 ¹⁶
1,2-Dimethylbenzene	C ₁₆ H ₁₄ O ₃	75.57	75.65	5.55	5.64	254	251	166.7-168.1	162 ¹⁷
1,3-Dimethylbenzene	C ₁₆ H ₁₄ O ₃	75.57	75.51	5.55	5.64	254	254	142.5-142.8	
1,4-Dimethylbenzene	C ₁₆ H ₁₄ O ₃	75.57	75.71	5.55	5.63	254	256	148.0-149.1	149 ¹⁸
<i>n</i> -Propylbenzene	C ₁₇ H ₁₆ O ₃	76.10	75.84	6.01	5.97	268	263	125.4-126.2	125-126 ⁹
1,2,3-Trimethylbenzene	C ₁₇ H ₁₆ O ₃	76.10	76.05	6.01	5.84	268	268	173.4-173.8	
1,3,5-Trimethylbenzene	C ₁₇ H ₁₆ O ₃	76.10	75.92	6.01	6.19	268	267	216.3-216.9	211-212 ⁹
1,2,4-Trimethylbenzene	C ₁₇ H ₁₆ O ₃	76.10	75.99	6.01	5.98	268	261	148.9-150.5	
1-Methyl-2-ethylbenzene	C ₁₇ H ₁₆ O ₃	76.10	76.16	6.01	5.99	268	269	129.8-131.4	
1-Methyl-3-ethylbenzene	C ₁₇ H ₁₆ O ₃	76.10	76.34	6.01	6.09	268	268	104.1-105.7	
1,2-Diethylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.30	6.43	6.34	282	283	141.8-142.7	
1,3-Diethylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.66	6.43	6.38	282	276	121.8-122.5	114-116 ⁹
<i>n</i> -Butylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.62	6.43	6.29	282	282	100.8-101.8	97-98 ⁹
<i>s</i> -Butylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.84	6.43	6.74	282	282	129.0-129.6	
<i>i</i> -Butylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.26	6.43	6.46	282	272	125.2-126.8	
<i>t</i> -Butylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.47	6.43	6.44	282	277	143.8-144.7	
1,3-Dimethyl-5-ethylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.29	6.43	6.42	282	287	210.1-212.1	
1-Methyl-4- <i>i</i> -propylbenzene	C ₁₈ H ₁₈ O ₃	76.57	76.49	6.43	6.47	282	282	125.8-126.6	123-124 ⁹
1-Methyl-2- <i>t</i> -butylbenzene	C ₁₉ H ₂₀ O ₃	77.00	76.84	6.80	6.80	296	293	134.3-135.5	
1-Methyl-3- <i>t</i> -butylbenzene	C ₁₉ H ₂₀ O ₃	77.00	76.82	6.80	6.78	296	292	135.6-136.4	
1-Methyl-4- <i>t</i> -butylbenzene	C ₁₉ H ₂₀ O ₃	77.00	76.72	6.80	6.91	296	295	136.0-136.8	
1-Methyl-3,5-diethylbenzene	C ₁₉ H ₂₀ O ₃	77.00	76.89	6.80	6.80	296	298	145.2-146.7	
1,3,5-Triethylbenzene	C ₂₀ H ₂₂ O ₃	77.39	77.42	7.15	7.12	310	306	(19)	129.5-130.5 ⁹

drocarbon had or had not occurred. Compounds in this category were the keto acids of *s*- and *i*-butylbenzene.

One derivative was also observed to have at least two crystalline modifications, and the change from one modification to another could be seen at certain temperatures on the hot stage of a microscope. The compound which was observed to exhibit this phenomenon was the keto acid of 1,3,5-triethylbenzene. An examination of the data of Table I shows that the keto acids of the three trimethylbenzenes, the two methylethylbenzenes, the two diethylbenzenes, and three of the four butylbenzenes distinguish well between these isomeric hydrocarbons.

Experimental

General.—In preparing the *o*-aroylbenzoic acids, previously described procedures^{9,10,11} which involved the application of heat during the condensation reaction, were found to give poor yields of the acids, and often non-crystallizable products, especially where higher alkylated benzenes were involved. This may be due to the fact that on heating alkylbenzenes with aluminum chloride, rearrangement of the alkyl groups and isomerization can occur,^{12,13} changing the originally pure hydrocarbon to a mixture, so that the resulting derivatives would be difficult to crystallize and separate. By cooling the reaction flask in an ice-bath for the first 3 to 4 hours and then allowing the reactants to warm to room temperature until the evolution of hydrogen chloride had ceased, these difficulties were alleviated. Although solvents such as benzene or mixtures of ethanol and water were tried for the recrystallization of the derivatives, the *o*-aroylbenzoic acids were most satisfactorily recrystallized from a mixture of toluene and petroleum ether.

Starting Materials.—The hydrocarbons used in this investigation were of 99 mole % purity or better and had pre-

viously been prepared and purified in conjunction with a program concerned with the evaluation of aviation fuel components at this Laboratory.¹⁴ The aluminum chloride used was J. T. Baker Reagent grade, anhydrous, sublimed, and the phthalic anhydride was Eastman Kodak Co. Reagent grade.

***o*-Aroylbenzoic Acids.**—As a typical preparation the synthesis and purification of *o*-benzoylbenzoic acid is given. A mixture of 14.8 g. (0.1 mole) of phthalic anhydride (m.p. 130.8-131.6°) and 29.4 g. (0.22 mole) of aluminum chloride¹⁵ was intimately ground in a mortar, and the mixture then placed in a 500-ml. 2-necked flask which was equipped with a stirrer and a small reflux condenser. The flask was cooled in an ice-bath while 39.1 g. (0.5 mole) of benzene was added with stirring, the excess of hydrocarbon serving as solvent. The reaction mixture was vigorously stirred at the ice-bath temperature for 3 to 4 hours, during which time a continuous evolution of hydrogen chloride was observed. The ice-bath was then removed and stirring continued until the evolution of gas ceased. The product was hydrolyzed by gradually pouring the reaction mixture into a beaker containing dilute hydrochloric acid and ice. The hydrolyzed mixture was refrigerated at about 0° for 5 hours and the solid product was filtered off, washed several times with petroleum ether, and dried in a vacuum oven at 50°. The

(14) (a) L. Gibbons, *et al.*, *THIS JOURNAL*, **68**, 1130 (1946); (b) J. Karabinos, K. Serijan and L. Gibbons, *ibid.*, **68**, 2107 (1946); (c) K. Serijan, H. Hipsher and L. Gibbons, *ibid.*, **71**, 873 (1949); (d) T. Reynolds, *et al.*, *Ind. Eng. Chem.*, **40**, 1751 (1948); (e) E. Ebersole, "Natl. Advisory Comm. Aeronaut.," Tech. Note 1020, January 1946; (f) C. Buess, *et al.*, *ibid.*, 1021, June 1946; (g) J. Karabinos and J. Lamberti, *ibid.*, 1019, January 1946; (h) unpublished work.

(15) Careful adjustment of the quantities of the reactants and control of other factors helps to avoid the formation of substituted phthalides, as discussed in detail by C. Thomas in "Anhydrous Aluminum Chloride in Chemistry," American Chem. Soc. Monograph Series No. 87, Reinhold Publ. Corp., New York, N. Y., 1941, pp. 511-548, and by P. Groggins, *Ind. Eng. Chem.*, **23**, 152 (1931).

(16) R. Scholl, J. Potschewauscheg and J. Lenko, *Monatsh.*, **32**, 687 (1912).

(17) H. Limpricht, *Ann.*, **312**, 99 (1900).

(18) E. de Barry Barnett and J. A. Low, *Ber.*, **64B**, 49 (1931).

(19) Two crystalline modifications were observed: (1) 122.8-123.6°, (2) 131.0-132.0°.

(10) C. R. Rubidge and N. C. Qua, *THIS JOURNAL*, **36**, 732 (1914).

(11) W. A. Lawrence, *ibid.*, **43**, 2577 (1921).

(12) J. F. Norris and D. Rubinstein, *ibid.*, **61**, 1163 (1939).

(13) D. V. Nightingale, *Chem. Revs.*, **25**, 347 (1939).

material could not be crystallized and was probably a mixture of Ia and IIa.

The Reaction of Cyclohexylidene Diphenylmethane (IIa) with Peracetic Acid.—To 2.5 g. (0.01 mole) of cyclohexylidene diphenylmethane (IIa) in 20 ml. of glacial acetic acid was added 0.3 g. of anhydrous sodium acetate in 2.5 g. of 45% peracetic acid. The mixture was stirred for two hours at which time all of the solid starting material was in solution. The reaction mixture was poured into 10 ml. of a saturated salt solution in water and the solid which precipitated was filtered by suction. The yield of cyclohexylidene diphenylmethane oxide was 2.5 g. (95%) and, on recrystallization from ethanol, melted 120.5–121°. This material was identical with that obtained from the peracid oxidation of the retropinacolone rearrangement product.

2,2-Diphenylcyclohexanol (Ib).—A suspension of 0.8 g. (0.021 mole) of lithium aluminum hydride in 40 ml. of dry ether was prepared in a 200-ml. three-necked flask equipped for anhydrous conditions. To this mixture was added a solution of 5 g. (0.02 mole) of 2,2-diphenylcyclohexanone⁶ in 15 ml. of ether. Very little heat was generated by the reaction. The mixture was stirred for one hour and water was added dropwise until no further reaction occurred. The mixture was then acidified with dilute sulfuric acid and the ether layer removed. The aqueous layer was extracted with an additional 25 ml. of ether and the organic layers combined and dried over sodium sulfate. On evaporation of the ether 4.6 g. (92%) of solid remained which, after recrystallization from ethanol, melted 82.5–83°. Because of the similarity in melting point with that of the starting material a mixture melting point was determined giving a value of 60–67°.

Anal. Calcd. for C₁₈H₂₀O: C, 85.67; H, 7.99. Found: C, 85.15; H, 7.91.

Dehydration of 2,2-Diphenylcyclohexanol (Ib). a. **With Phosphorus Tribromide.**—On treatment of 5.3 g. (0.021 mole) of molten 2,2-diphenylcyclohexanol (Ib) with 4.1 g. (0.015 mole) of phosphorus tribromide as described in (b) above, 3.8 g. (75%) of oil, b.p. 175–180° at 8 mm., was obtained. A portion of this oil was crystallized from petroleum ether using a Dry Ice–acetone bath. Recrystallization produced a white solid, m.p. 60.8–61.2°. These physical constants agree with those reported⁷ for cyclopentylidene diphenylmethane (IIb), lit. b.p. 180–181° at 6–7 mm., m.p. 62–62.5°.

b. **Attempted Dehydration on Distillation at Atmospheric Pressure.**—After three consecutive distillations at atmospheric pressure 5 g. of Ib gave 4.68 g. of oil from which 3.71 g. (74%) of 2,2-diphenylcyclohexanol (Ib) was recovered.

The ultraviolet spectra of IIa and IIb were determined using a Beckmann Model DU quartz spectrophotometer. The concentrations of the solutions of IIa and IIb were 1.73 × 10⁻⁵ and 2.22 × 10⁻⁵ M, respectively, in 95% ethanol.

Acknowledgment.—The authors wish to express appreciation to Buffalo Electro-chemical Company, Inc., for generous supplies of peracetic acid used in this research.

(7) G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publ. Corp., New York, N. Y., 1946, p. 456.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF NEW HAMPSHIRE
DURHAM, NEW HAMPSHIRE

The Reaction of Sodium with Ethyl Trifluoroacetate

By E. T. MCBEE, O. R. PIERCE, H. W. KILBOURNE¹ and J. A. BARONE¹

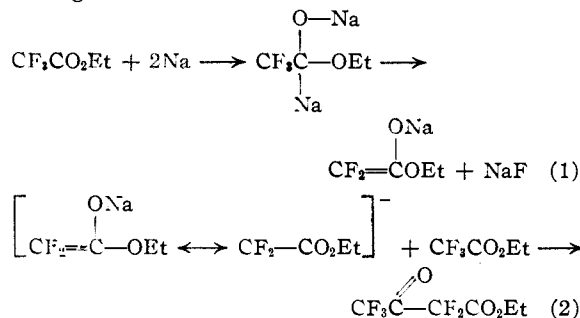
RECEIVED MARCH 30, 1953

In an attempt to prepare a fluorine-containing acyloin, it was found that sodium reacted with ethyl trifluoroacetate in anhydrous ether yielding, on hydrolysis of the reaction mixture, ethyl γ,γ,γ-trifluoroacetoacetate in yields of 25–30%. A similar

(1) Abstracted, in part, from the doctoral theses of H. W. Kilbourne and J. A. Barone, Purdue University.

observation was made by Haszeldine² but no experimental details of explanations were offered. None of the expected acyloin was obtained and the only other products observed were unidentifiable high boiling materials, thought to be polymeric forms of 1,1,1,4,4,4-hexafluoroacetoin.

In an effort to delineate the reaction mechanism, ethyl pentafluoroacetoacetate³ was treated with sodium under similar conditions and found to yield ethyl γ,γ,γ-trifluoroacetoacetate. This would indicate a possible reaction sequence which involves the formation of an intermediate acetoacetic ester. The latter compound could be obtained in the following manner



Corroborating evidence may be found in the fact that sodium fluoride was isolated from the reaction mixture in appreciable quantities and that only two moles of sodium per mole of ester was readily consumed.

Experimental

Ethyl Trifluoroacetate and Sodium in Anhydrous Ether.—A 500-ml., 3-necked flask was equipped with a sealed stirrer, a reflux condenser and an addition funnel with a side-arm pressure equalizer tube. The apparatus was flame-dried in a stream of dry nitrogen and one mole of sodium sand and 200 ml. of anhydrous ether were placed in the flask. One-half mole of ethyl trifluoroacetate (b.p. 60.5°, *n*_D²⁰ 1.3073) was added dropwise to the stirred mixture of ether and sodium sand. After the first few ml. of ester had been added, the ether solution became dark red and the ether began to reflux vigorously. The remaining portion of the ester was added at such a rate that a steady reflux was maintained. After all the ester had been added, the mixture was stirred for an additional 2 hours. The ether solution was then poured over a mixture of 200 g. of crushed ice and 60 g. of concd. sulfuric acid. The ether layer was separated and the aqueous solution was extracted with ether. The ether solution was dried with anhydrous sodium sulfate and Drierite. After distillation of the ether, 20 g. of ethyl trifluoroacetate was recovered and 14 g. of ethyl γ,γ,γ-trifluoroacetoacetate was obtained boiling at 131–132°. A copper chelate was prepared, m.p. 188–189°. The γ,γ,γ-trifluoroacetoacetic ester yielded 1,1,1-trifluoroacetone (b.p. 22°) upon hydrolysis with 30% sulfuric acid. A 2,4-dinitrophenylhydrazone was prepared, m.p. 139°.⁴

Anal. Calcd. for C₆H₇F₃N₄O₄: C, 37.0; H, 2.39. Found: C, 37.09; H, 2.52.

Sodium and Ethyl Pentafluoroacetoacetate in Anhydrous Ether.—A mixture of 70 ml. of anhydrous ether and 4.6 g. of sodium sand was placed in a 200-ml., 3-necked flask. A solution of 23 g. of ethyl pentafluoroacetoacetate and 50 ml. of anhydrous ether was added dropwise to the ether-sodium mixture. The ether solution was stirred for 6 hours and then poured over a mixture of 100 g. of crushed ice and 20 g. of concd. sulfuric acid. The ether layer was separated and the aqueous solution was extracted with ether.

(2) R. N. Haszeldine, *Nature*, **168**, 1028 (1951).

(3) E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, *This Journal*, **75**, 3152 (1953).

(4) A. L. Henne, L. L. Quill, M. S. Newman and R. A. Stanforth, *ibid.*, **69**, 1819 (1947).

The ether solutions were combined and dried with Drierite and then distilled. Twelve grams of a mixture of pentafluoro- and trifluoroacetoacetic esters was obtained boiling at 130–133°. The presence of the trifluoroacetoacetic ester was shown by the formation of a copper chelate, m.p. 188–189°⁴ and by hydrolysis to trifluoroacetone which gave a 2,4-dinitrophenylhydrazone, m.p. 139°.⁴

Acknowledgment.—The authors express their appreciation to the Westinghouse Electric Corporation which supported this work.

DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

1,3,3,3-Tetrafluoropropylene Oxide

BY E. T. MCBEE, O. R. PIERCE AND H. W. KILBOURNE¹
RECEIVED MARCH 30, 1953

It was of interest to prepare an epoxide containing a fluorine atom substituted on a bridge carbon atom for a study of the orientation effect of fluorine in epoxide ring opening. Only two fluorine-containing propylene oxides have been previously reported² and no compound having fluorine substituted directly on the epoxide ring has been described.

The synthesis of the desired epoxide was based on bromotetrafluoroacetone. It was found that this material could be obtained directly in excellent yield by treating ethyl $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate³ with a mixture of sulfuric acid and bromine at moderate temperatures. The bromotetrafluoroacetone obtained was reduced with lithium aluminum hydride at 0° in an excess of the ketone to produce 3-bromo-1,1,1,3-tetrafluoro-2-propanol in 80% yield. Dehydrobromination of the alcohol was accomplished by reaction with hot 50% sodium hydroxide and 1,3,3,3-tetrafluoropropylene oxide was obtained in 96% yield.

It was first thought that bromination probably occurred during the decarboxylation reaction in accordance with the postulates of other researchers.⁴ However, it was found that use of excess bromine produced 3,3-dibromo-1,1,1,3-tetrafluoroacetone in high yield. This would indicate that the introduction of the first bromine atom took place before decarboxylation since any further bromination of the ketone formed would be extremely difficult under these conditions.⁵ In support of this postulate, ethyl α -bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate was prepared and found to undergo ready hydrolysis and decarboxylation yielding the monobromoketone. If this reaction was conducted in the presence of bromine, the principal product was the dibromoketone.

The properties of the compounds prepared are given in Table I.

(1) Abstracted, in part, from the doctoral thesis of H. W. Kilbourne, Purdue University.

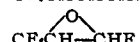
(2) (a) E. Gryskiewicz-Trochimowski, A. Sporzynski and J. Wnuk, *Rec. trav. chim.*, **66**, 413 (1947); (b) E. T. McBee and T. M. Burton, *THIS JOURNAL*, **74**, 3022 (1952).

(3) E. T. McBee, O. R. Pierce, H. W. Kilbourne and E. R. Wilson, *ibid.*, **75**, 3152 (1953).

(4) L. P. Hammett, "Physical Organic Chemistry," First Ed., McGraw-Hill Book Co., Inc., New York, N. Y., p. 362.

(5) E. T. McBee and T. M. Burton, *THIS JOURNAL*, **74**, 3902 (1952).

TABLE I
NEW COMPOUNDS

Formula	B.p., °C.	Analyses, %			
		Carbon		Hydrogen	
		Calcd.	Found	Calcd.	Found
CF ₃ COCHFBr	65	17.20	17.01	0.48	0.60
CF ₃ COCFBr ₂	81	12.50	12.81	0.00	0.10
CF ₃ CHOHCHFBr	124	17.10	17.12	1.43	1.54
	37	27.70	27.78	1.53	1.89
CF ₃ COCFBrCO ₂ C ₂ H ₅	51 at 15 mm.	25.60	25.90	1.78	1.81

Experimental

3-Bromo-1,1,1,3-tetrafluoroacetone.—A solution of 40% sulfuric acid (200 ml.) was prepared in a 500-ml., round bottomed flask which was equipped with a reflux condenser, a sealed stirrer and an addition funnel. Ethyl $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate (86 g.) was added to the aqueous acid and the mixture was heated to 80–90°. While the mixture was being stirred vigorously, bromine (75 g.) was added dropwise and at such a rate that only a light red color was maintained in the solution. After all the bromine had been added, the mixture was heated and stirred for an additional two hours. The cooled mixture was diluted with 100 ml. of water and extracted with ether. The ether solution was dried with Drierite and then distilled. When the pot temperature reached 50°, the distillation was stopped and the residue was cooled in an ice bath. An equal volume of concd. sulfuric acid was added to the flask and the contents were mixed. Distillation was then continued and 87 g. (95%) of ketone was obtained. The material had an unpleasant odor similar to that of 3-bromo-1,1,1-trifluoroacetone.^{2b}

3,3-Dibromo-1,1,1,3-tetrafluoroacetone.—A solution of 40% sulfuric acid (100 ml.) was prepared in the reaction flask. Ethyl $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate (20 g.) was added to the flask and the mixture was heated to 90°. Bromine (30 g.) was added to the hydrolysis mixture over a period of 30 minutes. The bromine concentration in the reaction flask was high at all times as shown by the dark red color in the flask. An additional two hours of heating and stirring was required to remove all the bromine color from the solution. The aqueous mixture was cooled and extracted with ether. The ether solution was dried with Drierite and then distilled until the pot temperature reached 50°. The residue was mixed with an equal volume of concd. sulfuric acid and distillation was continued. The monobromo compound (4 g.) was obtained boiling at 65–67°, the temperature then rose to 81° and 23 g. (80%) of the dibromoketone was obtained.

3-Bromo-1,1,1,3-tetrafluoroisopropyl Alcohol.—Anhydrous ether (500 ml.) and lithium aluminum hydride (3.8 g.) were mixed in a 1000-ml., 3-necked flask which was equipped with a reflux condenser, a sealed stirrer, and an addition funnel. The flask was immersed in an ice-bath and a solution of 3-bromo-1,1,1,3-tetrafluoroacetone (41 g.) in anhydrous ether (80 ml.) was added dropwise over a period of 8 hours. The reaction was stirred at 0° for an additional 6 hours and then permitted to stand at room temperature for 8 hours. Absolute ethanol (3 ml.) was added to decompose any unreacted lithium aluminum hydride and the mixture was then poured over a mixture of concd. sulfuric acid (50 g.) and crushed ice (500 g.). The ether solution was separated and the aqueous solution was extracted with ether. The ether solution was dried with Drierite and then distilled. Phosphorus pentoxide (2 g.) was added to the mixture and distillation was continued. The bromoketone (4 g.) was recovered boiling at 60–70° and 33.5 g. (91%) of 3-bromo-1,1,1,3-tetrafluoroisopropyl alcohol was obtained.

1,3,3,3-Tetrafluoropropylene Oxide.—A solution of water (50 g.) and sodium hydroxide (50 g.) was prepared in a 300-ml., 3 necked flask. The reaction flask was equipped with a sealed stirrer, an addition funnel and a side arm distilling head. The side arm of the distilling head was connected to an ice-cooled trap followed by a Dry Ice-cooled trap. A thermometer was inserted through the distilling head into the aqueous sodium hydroxide so that the temperature of the reaction mixture could be checked at all times.

The reaction mixture was heated to 95–100° and 3-bromo-1,1,1,3-tetrafluoroisopropyl alcohol (21 g.) was added dropwise over a period of 3 hours. The bromohydrin was added

slowly due to the tendency for the mixture to froth. The epoxide was condensed in the ice-cooled trap and no material was condensed in the Dry Ice-cooled trap. The epoxide was then cooled in Dry Ice, the water which had been carried over from the aqueous solution was frozen out, the epoxide was decanted, dried and rectified. The yield was 12.5 g. (96%).

Ethyl α -Bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate.—Ethyl $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate (42 g.) was dissolved in carbon tetrachloride (150 ml.) and the mixture was heated to 70°. Bromine (40 g.) was added dropwise over a period of 12 hours and the mixture was then stirred and heated for an additional 12 hours. The carbon tetrachloride and a small amount of bromine was distilled out of the mixture, and the pressure was reduced to 15 mm., and distillation was continued. Ethyl α -bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate (50 g., 72%) was obtained boiling at 51–52° at 15 mm.

Hydrolysis of Ethyl α -Bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate.—A mixture of ethyl α -bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate (14 g.) and 50% sulfuric acid (100 ml.) was refluxed for 6 hours. The aqueous solution was then cooled and extracted with ether. The ether extract was dried with sodium sulfate and distilled. When the pot temperature reached 50°, the residue was mixed with 50 ml. of concd. sulfuric acid and distillation was continued. 3-Bromo-1,1,1,3-tetrafluoroacetone (9 g., 90%) was obtained boiling at 65–66°.

Hydrolysis and Bromination of Ethyl α -Bromo- $\alpha,\gamma,\gamma,\gamma$ -tetrafluoroacetoacetate.—The ester (28 g.) and 50% sulfuric acid (150 ml.) were mixed in a 500-ml., 3-necked flask which was equipped with a reflux condenser, a sealed stirrer and an addition funnel. The mixture was heated to 90° and bromine (16 g.) was added dropwise. Heating and stirring was continued for an additional two hours and then the aqueous solution was cooled and extracted with ether. The ether extract was dried with anhydrous sodium sulfate and distilled. After distillation of the ether, the residue was mixed with concd. sulfuric acid (50 ml.) and distillation was continued. 3,3-Dibromo-1,1,1,3-tetrafluoroacetone (25 g., 83%) was obtained boiling at 81–82°.

Acknowledgment.—The authors wish to express their thanks to the Westinghouse Electric Corporation for the financial support of this work.

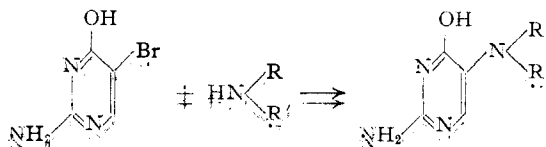
DEPARTMENT OF CHEMISTRY
PURDUE UNIVERSITY
LAFAYETTE, INDIANA

Reactivity of 5-Bromoisocytosine with Some Amines

BY ARTHUR P. PHILLIPS

RECEIVED APRIL 30, 1953

The reactivity of 5-bromouracil with amines permitted the preparation of a series of 5-substituted aminouracils for chemotherapeutic testing.¹ In order to obtain other 5-substituted aminopyrimidines bearing additional amino groups, the reactivity of 5-bromoisocytosine toward amines has now been examined.



The bromine of 5-bromoisocytosine is active for replacement reactions with amines but apparently less so than that of 5-bromouracil. Piperidine and morpholine reacted rapidly with 5-bromoisocytosine to give high yields of the 5-substituted amino derivatives. On the other hand, *n*-butylamine,

(1) A. P. Phillips, *THIS JOURNAL*, **73**, 1061 (1951).

ethylamine and methylbenzylamine either gave no reaction or no good product was isolated even when more strenuous reaction conditions were employed than were necessary to produce excellent yields with 5-bromouracil.

For example when a mixture of 0.1 mole of 5-bromouracil and 0.3 mole of *n*-butylamine was refluxed for three hours on a steam-bath a 90–100% yield of 5-*n*-butylaminouracil was obtained. But when 0.1 mole of 5-bromoisocytosine in 0.4 mole of *n*-butylamine was refluxed for 24 hours on the steam-bath a nearly quantitative recovery of unchanged 5-bromoisocytosine resulted.

Experimental

5-Piperidinoisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 25 cc. (21 g., 0.25 mole) of piperidine was refluxed in a metal-bath at 140–150° for four hours. The reaction mixture was washed out with 100 cc. of hot water and a little acetic acid was added bringing the pH to 8–8.5. After cooling, filtration gave 19 g. (100%) of white crystals. The product was purified by several reprecipitations from dilute hydrochloric acid solution by the addition of aqueous ammonia to pH 8 and then melted at 278–280°.

When 5-piperidinoisocytosine was treated with an excess of methanolic hydrogen chloride the dihydrochloride was formed. This salt was purified by several recrystallizations from methanol-ethyl acetate mixtures; m.p. 269–270° (dec.).

Anal. Calcd. for C₉H₁₆Cl₂N₄O: C, 40.4; H, 6.0. Found: C, 40.8; H, 5.8.

5-Morpholinouisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 25 cc. (22 g., 0.25 mole) of morpholine was refluxed in a metal-bath at 150–160° for four hours. The reaction product was taken up in about 80–90 cc. of hot water, the pH was adjusted to 6–7 with dilute acetic acid, and on cooling there was obtained 18 g. (90–95%) of white crystals. After recrystallization from hot water the product melted at 275–276° (dec.). The analytical sample was dried *in vacuo* at 120°.

Anal. Calcd. for C₈H₁₂N₄O₂: C, 48.9; H, 6.1. Found: C, 48.7; H, 6.1.

Attempted Reaction of *n*-Butylamine and 5-Bromoisocytosine.—A mixture of 19 g. (0.1 mole) of 5-bromoisocytosine and 35 cc. (25 g., 0.35 mole) of *n*-butylamine was refluxed on the steam-bath for 24 hours. The bulk of the *n*-butylamine was removed by evaporation. The residue was purified by reprecipitation from alkali solution by the addition of acid to pH 7–8. In this way 16–18 g. of solid was recovered which, upon purification both as the base and as the hydrochloride, was proved by analyses to be the original 5-bromoisocytosine. The recovery of unreacted bromo compound represents 85–95%.

Similar reactions were attempted with a number of other amines, ethylamine, methylbenzylamine, etc., but either the bromoisocytosine was recovered unchanged or no good product was readily isolable.

Acknowledgment.—The author is indebted to S. W. Blackman for the microanalyses included.

THE WELLCOME RESEARCH LABORATORIES
TUCKAHOE 7, NEW YORK

The Preparation of Free Hydroxylamine and Deutero-hydroxylamine

BY R. E. NIGHTINGALE AND E. L. WAGNER

RECEIVED APRIL 10, 1953

During a study of the infrared spectrum of crystalline hydroxylamine,¹ it was felt that additional information was needed which might be provided by deutero-hydroxylamine. It is well known that

(1) R. E. Nightingale and E. L. Wagner, submitted to *J. Chem. Phys.*

spectra of isotopic molecules, particularly of deuterio compounds when they are available, are valuable aids in the interpretation of infrared data.

The compound D_2NOD has not been reported in the literature. The usual method for the preparation of H_2NOH involves the neutralization of hydroxyammonium chloride by sodium butoxide in a hydrogen-rich solvent such as butanol.² This is obviously not suited for the preparation of D_2NOD using reasonable amounts of D_2O . Moreover, our attempts to make D_2NOD by successive exchanges of H_2NOH with D_2O have been unsuccessful. It appears that a stable hydrate is formed which makes it impossible to recover the exchange water from the mixture, H_2NOH-H_2O , by a vacuum distillation. Another method of preparation of D_2NOD was attempted and proved to be successful. Uhlenhuth,³ in 1900, prepared free hydroxylamine by the thermal decomposition of tertiary hydroxyammonium phosphate at reduced pressure. We have prepared H_2NOH by a modification of this procedure, which, when followed by two or three fractional sublimations resulted in a product melting at 32–33°, the same as that ascribed to pure hydroxylamine. Infrared spectra of this material in the region 500–4000 cm^{-1} were identical with those of H_2NOH prepared in the usual manner.

This method was adapted to the preparation of D_2NOD . The salt $(H_3NOH)_3PO_4$ was first converted to $(D_3NOD)_3PO_4$ by exchange with heavy water and this was followed by thermal decomposition to D_2NOD . The material was collected in a tube in the vacuum system, fractionally sublimed, and finally sublimed onto the rocksalt sample support of an infrared low-temperature cell.⁴ In addition to offering a simple method for the preparation of D_2NOD using small amounts of D_2O , this method also has some obvious advantages for the preparation of small amounts of H_2NOH . A sample may be prepared and used on the same day. The melting point may be checked easily in the vacuum system by subliming a small amount into a capillary tube. All transfers are carried out *in vacuo*, thereby eliminating the danger of reaction with atmospheric vapors. Finally, the material may be conveniently purified by fractional sublimation.

Experimental Procedure

$(H_3NOH)_3PO_4$ was prepared by precipitation from a hot solution of H_3NOHCl and Na_3PO_4 . This was filtered and dried in a vacuum desiccator over H_2SO_4 .

For the preparation of D_2NOD , 0.7 g. $(H_3NOH)_3PO_4$ was introduced into a flask on the vacuum line. Enough D_2O (5.5 ml.) was added to dissolve the salt at 80°. The mixture was evaporated to dryness at reduced pressure and room temperature. The system was brought back to atmospheric pressure with dry nitrogen and a second portion of D_2O was added. Three more exchanges were made and the salt was finally dried by pumping at 0.015 mm. for several hours followed by a final heating to 110–120° at 13 mm. pressure.

The distillation of the D_2NOD from the salt was carried out at 13 mm. and 135–150°. Heating was done with a glycerol-bath which could be removed rapidly if necessary, and was carried out with the protection of a safety glass explosion screen. A bleeder valve between the pump and

the vacuum system was employed in order to add dry nitrogen to maintain the pressure at 13 mm. during distillation. Reaction began at about 130° at this pressure. The D_2NOD was collected in a portion of the apparatus at 0° and kept there until needed. Deutero-hydroxylamine prepared in this manner had a deuterium purity, as estimated from its infrared spectrum, of about 97%.

DEPARTMENT OF CHEMISTRY
STATE COLLEGE OF WASHINGTON
PULLMAN, WASHINGTON

The Melting Transition of Polymethylene¹

By L. MANDELKERN, M. HELLMANN, D. W. BROWN, D. E. ROBERTS AND F. A. QUINN, JR.

RECEIVED APRIL 14, 1953

Polymethylene, a linear polymeric hydrocarbon of high molecular weight, serves ideally as a model polymer in various physicochemical studies, because of the simplicity of its structure. It is particularly well suited for an investigation of the crystallization behavior of chain molecules, and in this connection we should like to present the results of a study of its volume-temperature behavior, and its melting temperature, T_m .

In Fig. 1, the relative volume of polymethylene (relative to that at 137°), as determined dilatometrically, is plotted as a function of temperature. A well defined first-order transition, or melting temperature, characterized by the disappearance of the last traces of crystallinity, occurs at 136.5 ± 0.5°, and 70% of the melting occurs in only a three to four degree interval. For comparative purposes similar data for a commercial sample of polyethylene, which is known to be highly branched,^{2,3} are also plotted in Fig. 1. The melting temperature is lowered to 115° for the branched polymer and the melting range considerably extended in comparison with the linear one. The lowering of T_m and broadening of the melting range by branch units is in agreement with the predictions of the statistical equilibrium theory of crystallization in polymers.^{4,5}

The melting temperature observed for polymethylene, 136 to 137°, is very close to the convergence temperature of 135° predicted for a high molecular weight *n*-paraffin by King and Garner⁶ from an analysis of thermodynamic data for low molecular weight paraffins. This again illustrates the asymptotic relation between T_m and molecular weight in linear polymers.^{4,5}

Recently a melting temperature of 132° has been reported⁷ for a polymethylene prepared in a similar but not identical manner. This lower T_m may probably be attributed to the rapid heating rate (0.5°/min.) used in its determination. It has been

(1) The work reported here was supported by the Office of Naval Research and the Office of the Quartermaster General.

(2) R. B. Richards, *J. Applied Chem.*, **1**, 370 (1951).

(3) I. Harris, *J. Polymer Sci.*, **8**, 353 (1952).

(4) P. J. Flory, *J. Chem. Phys.*, **17**, 223 (1949).

(5) R. D. Evans, H. R. Mighon and P. J. Flory, *THIS JOURNAL*, **72**, 2018 (1950).

(6) A. M. King and W. E. Garner, *J. Chem. Soc.*, 1449 (1934); 1368, 1372 (1936).

(7) S. W. Kantor and R. C. Osthoff, *THIS JOURNAL*, **75**, 931 (1953).

(2) C. D. Hurd, *Inorganic Syntheses*, **1**, 87 (1939).

(3) R. Uhlenhuth, *Ann.*, **311**, 117 (1900).

(4) E. L. Wagner and D. F. Hornig, *J. Chem. Phys.*, **18**, 296 (1950).

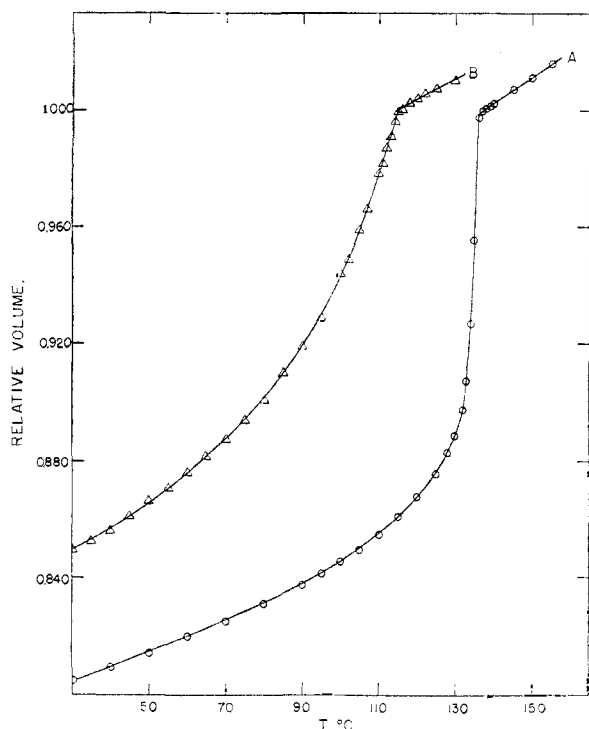


Fig. 1.—Relative volume-temperature curves: curve A for polymethylene O; curve B for polyethylene Δ .

demonstrated^{5,8,9} that to obtain reliable values of T_m in polymers, the heating in the vicinity of the melting temperature must be gradual and should occur over a period of several days. Other observers^{10,11} have reported the decomposition of polymethylene around 300° without noting any indication of melting at lower temperatures. If visual methods were employed, the true melting point was probably obscured by the very high viscosity of the polymer. Both the branched and linear polymers supercool, the amount of supercooling, of course, depending on the cooling rate.

Experimental.—Polymethylene was prepared according to the method described by Buckley and Ray¹⁰ by means of the decomposition of diazomethane, using trimethyl borate as catalyst. The infrared absorption spectrum of thin films of the polymer was identical with that reported by these authors,¹⁰ indicating the absence of methyl groups and hence a linear molecule. Its intrinsic viscosity in units of 100 ml./g., was 8.6 ± 0.1 , in freshly distilled xylene at 100°, so that our polymer is of high molecular weight.³ The polyethylene was obtained from the Bakelite Corporation and is designated as DYNH resin. Its physical properties have been described in the literature.³

The dilatometric samples were films approximately 0.2–0.3 mm. thick prepared from a 1% xylene solution held at 110° in an atmosphere of nitrogen at reduced pressure. After the bulk of the solvent was removed, the films were dried *in vacuo* at 70° for 28 hours. The dilatometric procedure, using mercury as a confining fluid, has been described previously.⁸ Observations were made in the order of ascending temperature and in the melting region, the temperature was raised only 1° per 24 hours. A considerable amount of recrystallization, as has been observed in other polymers,^{5,8,9} occurred.

NATIONAL BUREAU OF STANDARDS
WASHINGTON 25, D. C.

(8) P. J. Flory, L. Mandelkern and H. K. Hall, *ibid.*, **78**, 2352 (1951).

(9) L. Mandelkern, R. R. Garrett and P. J. Flory, *ibid.*, **74**, 3949 (1952).

(10) G. D. Buckley and N. H. Ray, *J. Chem. Soc.*, 3701 (1952).

(11) H. Meerwein, *Angew. Chem.*, **60**, 78 (1948).

cis- and *trans*-Propenylbenzene and their Azeotropes with *n*-Decane

By R. Y. MIXER,^{1a} R. F. HECK,^{1b} S. WINSTEIN AND WILLIAM G. YOUNG

RECEIVED DECEMBER 5, 1952

Samples of pure *cis*- and *trans*-propenylbenzene were desired during the course of two independent investigations in these laboratories. The propenylbenzenes were needed as spectral standards for the infrared spectrographic analyses of olefins resulting from solvolysis of 2-phenyl-1-propyl and 1-phenyl-2-propyl *p*-bromobenzenesulfonates. They were also desired for testing azeotrope-formation with *n*-decane. These azeotropes were found during the distillation of the products from the reactions of sodium allylbenzene in pentane with methanol and various halides.²

Attempts to separate the pure *cis*-isomer from the propenylbenzenes obtained by isomerization of allylbenzene³ were unsuccessful even though columns of ca. 100 theoretical plates were used. The propenylbenzene obtained in this manner was predominantly the *trans*-isomer.⁴ Catalytic hydrogenation of 1-phenyl-1-propyne gave the *cis*-propenylbenzene which was satisfactorily purified by a precision distillation through a 112-theoretical-plate center-rod column. The *trans*-propenylbenzene was obtained without difficulty and free of the *cis*-isomer from the methanolysis of sodium allylbenzene in pentane. The small amount of the *cis*-isomer found in this reaction presumably was separated as the *n*-decane azeotrope.

TABLE I

PHYSICAL PROPERTIES AND ULTRAVIOLET ABSORPTION MAXIMA OF <i>cis</i> - AND <i>trans</i> -PROPENYLBENZENE			
Isomer	<i>cis</i>	<i>trans</i>	
B.p., °C. (20 mm.)	64.5	73.5	
n_D^{25}	1.5400	1.5473	
d_4^{25}	0.9107	0.9019	
<i>M</i> R _D , calcd.	39.69	39.69	
found	40.69	41.56	
exaltation	1.00	1.87	

Ultraviolet absorption maxima in 95% ethanol

λ , m μ	ϵ_m	λ , m μ	ϵ_m
240.6	13800	250	17300
279	Shoulder	284	1100
290	120	293	780

The physical and optical properties of the *cis*- and *trans*-propenylbenzenes (Table I) clearly show the effects of steric inhibition of resonance in the *cis*-isomer due to interference between the ortho-hydrogen of the benzene ring and the methyl hydrogens in the side chain. This produces a reduction of 0.87 in the exaltation of the molecular refraction, and similar reductions are displayed by

(1) (a) Standard Oil Company of California Fellow in Chemistry 1950–1952; (b) research supported by Office of Naval Research.

(2) The results of these investigations are reported elsewhere.

(3) M. Tiffeneau, *Comp. rend.*, **139**, 482 (1904).

(4) The Am. Pet. Inst., "Selected Values of Properties of Hydrocarbons," Vol. III, Table 13p gives the following free energies of formation (ΔF°_{298} kcal.): *cis*-propenylbenzene, 51.84 and *trans*-propenylbenzene 51.08. From these values, the composition of the thermal equilibrium mixture is estimated to be 21.7% *cis*- and 78.3% *trans*-propenylbenzene.

TABLE II
MOLAR REFRACTIONS AND EXALTATIONS FOR VARIOUS STYRENES

$\begin{array}{c} \text{C}_6\text{H}_5 \\ \diagdown \\ \text{C}=\text{C} \\ \diagup \\ \text{R}_1 \end{array} \begin{array}{c} \text{R}_2 \\ \diagup \\ \text{C} \\ \diagdown \\ \text{R}_3 \end{array}$					
R ₁	R ₂	R ₃	MR _D	Exaltation	Ref.
H	H	H	36.44	1.37	5
Me	H	H	40.63	0.94	5
H	Me	H	40.70	1.00	a
H	H	Me	41.57	1.87	a
Me	Me	H	45.14	0.83	6
Me	H	Me	45.02	0.70	6
Me	Me	Me	49.62	0.59	7

^a This work.

various substituted styrenes (Table II). The values in Table II illustrate the reductions of molecular refraction due to the placement of a β -group *cis* to phenyl rather than *trans* to it, and due to an α -methyl group, especially when it is *cis* to the β -methyl group.⁸

The physical properties for the propenylbenzene now in the literature^{6,9} appear to be mainly those for the *trans*-propenylbenzene.

The infrared spectra of the propenylbenzenes (Table III) contain several features which lend strong support to the correctness of the *cis*-*trans*-assignment. A band at 1412 cm.⁻¹ of medium intensity, characteristic of the hydrogen in plane deformation of *cis*-disubstituted ethylenes,¹⁰ appears only in the spectrum of the *cis*-propenylbenzene. The corresponding band in the *trans*-substituted molecules is usually weak and occurs at about 1300 cm.⁻¹. Such a band is found at 1309 cm.⁻¹ for the *trans*-compound. One of the most characteristic

TABLE III
PRINCIPAL INFRARED ABSORPTION BANDS OF *cis*- AND *trans*-PROPENYLBENZENES

s = strong, m = medium, and w = weak intensities.

Frequency, cm. ⁻¹			
<i>cis</i>	<i>trans</i>	<i>cis</i>	<i>trans</i>
702 s	694 s	1445 s	1445 s
	736 s	1495 s	1495 s
769 s		1582 w	1582 w
808 s	812 s	1608 m	1608 m
917 s	912 m	1650 w	1650 w
939 m	948 s	1667 w	1667 m
	962 s	1721 w	1779 w
971 w	980 s	1815 w	1799 w
1034 m	1034 m	1887 w	1887 w
1073 w	1073 m	1953 w	1957 w
1087 m		2924 m	2924 m
1190 w	1183 w	2976 s	2959 s
	1309 w	3067 s	3067 s
1372 s	1382 m	3106 s	3106 s
1412 m			

(5) Am. Pet. Inst. "Selected Values of Properties of Hydrocarbons," Table 13a,b.

(6) D. J. Cram, THIS JOURNAL, 71, 3883 (1949).

(7) K. von Auwers and F. Eisenlohr, J. prakt. Chem., [2] 84, 32 (1911).

(8) Styrene to α -methylstyrene gives a reduction of 0.43 and *trans*-propenylbenzene to *cis*-2-phenyl-2-butene gives a reduction of 1.17.

(9) G. Egloff, "Physical Constants of Hydrocarbons," Vol. III, Reinhold Publ. Corp., New York, N. Y., 1946, p. 191.

(10) N. Sheppard and D. M. Simpson, Quart. Rev., 6, 1 (1952).

bands in the infrared spectra of disubstituted ethylenes corresponds to the asymmetrical out-of-plane hydrogen deformations. These are found at around 965 cm.⁻¹ in the *trans*-molecules and in the *cis*-compounds from 690 to 820 cm.⁻¹,^{10,11} The spectrum of *trans*-propenylbenzene shows a strong band at 962 cm.⁻¹ while there is no such strong band for the *cis*-compound in the same vicinity. The corresponding vibration of the *cis*-propenylbenzene may correspond to the strong band at 769 cm.⁻¹,¹² The lowering of the C=C stretching frequencies from 1667 to 1653 cm.⁻¹ in going from *trans*- to *cis*-propenylbenzene agrees well with an average shift of 17 cm.⁻¹ in the same direction observed for a series of *cis*- and *trans*-olefins.¹⁰ The published¹³ infrared spectrum of propenylbenzene (β -methylstyrene) agrees well with our spectrum for the *trans*-isomer except in the region around 1667 cm.⁻¹.

The azeotropes of the propenylbenzenes with *n*-decane were first discovered by an adsorption-displacement analysis using silica gel as the adsorbent and methanol as the desorber, and they were confirmed by distillation of synthetic mixtures. The *trans*-propenylbenzene azeotrope was obtained as a constant-boiling and constant-refractive index series of cuts. There is some doubt that the *n*-decane-*cis*-propenylbenzene mixtures formed an azeotrope as the boiling points of the mixture and *cis*-propenylbenzene were virtually the same by our temperature instrumentation. There was a small but definite plateau in the refractive index curve. This work could not be repeated with larger quantities because of the limited amount of *cis*-propenylbenzene available. Table IV contains the physical properties and composition of the *n*-decane-*trans*-propenylbenzene azeotrope along with the corresponding approximate values for the *n*-decane-*cis*-propenylbenzene azeotrope.

TABLE IV
PHYSICAL PROPERTIES OF THE *n*-DECANE AZEOTROPES WITH *cis*- AND *trans*-PROPENYLBENZENE

Isomer	<i>cis</i>	<i>trans</i>
B.p., °C. (20 mm.)	64.5	70
<i>n</i> ²⁵ _D	1.510	1.4553
Composition (by wt.)		
<i>n</i> -Decane, %	ca. 19	60.8
Propenylbenzene, %	ca. 81	39.2

Experimental Part¹⁴

cis-Propenylbenzene.—1-Phenyl-1-propyne¹⁵ (28.0 g.) was hydrogenated at atmospheric pressure in 300 ml. of dry ether with 2 g. of 5% palladium on Norite. After 4.5 hours, 6.1 liters of hydrogen had been taken up. The solution was filtered to remove the catalyst and the solvent was evaporated. The product was fractionated at atmospheric pressure through a center-rod column (112 theoretical plates) at a reflux ratio of 200:1. The center fractions (b.p. 168–169°, *n*²⁵_D 1.5398) were carefully redistilled at 20 mm. pressure using a twisted, stainless steel wire-gauze

(11) G. B. B. M. Sutherland, Rec. Chem. Progress, 13, 79 (1952).

(12) Professor W. F. Edgell (in a private communication) and Referee I suggested this assignment. However, Sheppard and Simpson¹⁰ and Sutherland¹¹ choose the region around 690 cm.⁻¹ for this vibration.

(13) Am. Pet. Inst. Infrared Spectrogram No. 330.

(14) All melting points and boiling points are uncorrected except where noted.

(15) K. N. Campbell and M. J. O'Connor, THIS JOURNAL, 61, 2897 (1939).

column,¹⁶ 5 mm. × 30 in., equipped with an electrically heated jacket over a vacuum jacket. The physical properties and ultraviolet absorption maxima (using a Cary Model 11 PMS Spectrophotometer) are given in Table I and the principal infrared absorption bands (using a Beckman IR-2 Spectrophotometer) of the pure liquid in Table III.

trans-Propenylbenzene.—This material was obtained as a constant boiling, constant refractive index series of cuts from the distillation of the products from the reaction of sodium allylbenzene in pentane with methanol. The distillation was carried out at 20 mm. pressure in an analytical manner using the twisted wire gauze column described above. The physical properties and ultraviolet absorption maxima are given in Table I and the infrared absorption bands in Table III.

The 2,4-dinitrobenzenesulfonyl chloride derivative, m.p. 91.5–92°, was prepared¹⁷ from another sample of *trans*-propenylbenzene, n_D^{25} 1.5468.

Anal. Calcd. for $C_{15}H_{13}SN_2ClO_4$: C, 51.06; H, 3.71. Found: C, 51.36; H, 3.87.

Azeotropes with *n*-Decane.—Synthetic mixtures of pure *n*-decane, n_D^{25} 1.4098, with *cis*-propenylbenzene and pure *n*-decane with *trans*-propenylbenzene were carefully distilled at 20 mm. pressure in the twisted wire-gauze column. Table IV contains the physical properties and compositions of the azeotropes. The compositions were determined by means of the non-linear, refractive index–composition curves which were based upon the indices of a number of synthetic mixtures.

Acknowledgment.—The authors gratefully acknowledge the assistance of Dr. Clair Birdsall of the Linde Air Products Company and Professor Walter F. Edgell of Purdue University in the interpretation of the infrared spectra.

(16) J. R. Bower and L. M. Cooke, *Ind. Eng. Chem., Anal. Ed.*, **15**, 290 (1943).

(17) D. I. Hagmann, Ph.D. Thesis, University of California, Los Angeles, 1950.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CALIFORNIA
LOS ANGELES, CALIFORNIA

Dynamic Structure of Oxide Cracking Catalyst

By A. G. OBLAD, S. G. HINDIN AND G. A. MILLS

RECEIVED APRIL 4, 1953

Recently, Milliken, Mills and Oblad¹ advanced the hypothesis that the catalytic activity of a silica–aluminum cracking catalyst depends for driving force upon the ability of the aluminum ion to undergo a reversible change in coordination number from six to four. This reversible shift in coordination of the aluminum would involve a movement of the oxygen ions of a few tenths of an ångström unit. The purpose of this note is to present experimental evidence that, at cracking conditions, the silica–alumina structure is extremely mobile in the presence of water and such a proposed coordination shift is easily possible.

The exchange of oxygen between water enriched in O^{18} and a silica–alumina cracking catalyst was measured under conditions which the catalyst experiences when used in cracking petroleum. Previous work on such water–oxide exchange^{2,3} has been carried out primarily at relatively low temperatures, 100°, and for long times, up to one

(1) T. H. Milliken, G. A. Mills and A. G. Oblad, *Paraday Society Discussions*, **8**, 279 (1950); also Vol. III "Advances in Catalysis," Academic Press, Inc., New York, N. Y., 1951.

(2) G. A. Mills and S. G. Hindin, *THIS JOURNAL*, **72**, 3549 (1950).

(3) E. Whalley and E. R. S. Winter, *J. Chem. Soc.*, 1175 (1950).

month. In commercial cracking, temperatures are of the order of 450°. Working at these latter temperatures using a flow system, it was found that remarkably fast exchange occurs so that between 50 and 100% of all oxygen of the silica–alumina structure will undergo exchange within a 20-minute period.

Experimental

A flow system was used, employing conventional apparatus as for catalyst testing.⁴ The silica–alumina catalyst was commercial pelleted Houdry Type S-45 previously described.² The procedure consisted of passing water enriched in O^{18} , at atmospheric pressure, at constant rate through the catalyst bed maintained at 450°, collecting the exit water in fractions, and measuring its O^{18} content by equilibrating with CO_2 which was then examined in a mass spectrometer. Experiments also were carried out in which oil was charged to the catalyst simultaneously with the water. In both sets of runs flow rates closely approximated those of commercial operation in which steam and oil are charged to the catalyst. Runs were for a 20-minute period, again conventional for cracking. Typical results are shown in Table I.

TABLE I

OXYGEN EXCHANGE BETWEEN WATER AND SILICA–ALUMINA AT 450°

Catalyst: Houdry Type S-45, 87.5% SiO_2 –12.5% Al_2O_3 , H_2O^{18} : 1.59 atom % O^{18} , normal isotopic concn., 0.20 atom % O^{18} .

Expt. no.	Flow period, min.	Oxygen in catalyst, g.	Oxygen charged, g.	Oxygen in water collected, g.	O^{18} in water fraction, atom %	% Oxygen of oxide in equil. with added H_2O^d
1	10	7.87	1.29		0.66	
	10		1.15		.91	Total 44
2	5	62.6	3.48	2.18	.21	
			3.02	2.65	.24	
			3.11	3.15	.39	
			3.73	3.75	.61	Total 67 ^b
3 ^c	20	62.6	13.3		.60	53

^a Values are incremental, not total. ^b In this experiment, 15.0 g. of water was charged during the run—only 13.2 g. was recovered. Averaging the data on a no loss basis disproportionately weights the data toward higher values for % exchange, as is evident from column six. Assuming the 1.8 g. loss showed no exchange, we would arrive at a value of 67% of the oxide oxygen equilibrating. It is reasonable to assume some exchange however, and so the true value for % oxygen equilibrating will be greater than 67%. ^c During this experiment, light East Texas gas oil was simultaneously charged to the catalyst at 1.5 liquid hourly space velocity. ^d For method of calculation see reference 2.

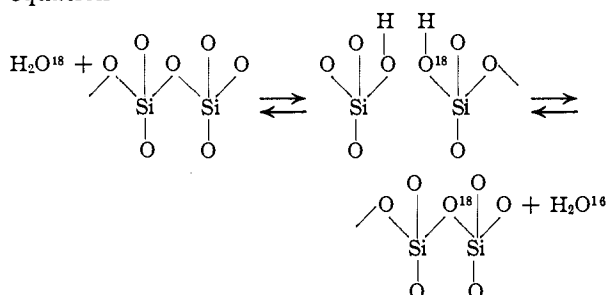
In view of these data, several static experiments were carried out at 450°. In these, catalyst and enriched water were sealed into an evacuated tube and heated at 450° for periods of 1.5 to 4.0 hours. Results in all cases indicated that all catalyst oxygen had equilibrated. Less exchange was reported previously (ref. 2, Table VIII). The reason for the lower results is not known, although less exchange may occur at the lower water vapor pressures used earlier.

Discussion

The data of Table I show that one-half or more of the catalyst oxygens exchange in a few minutes, a period in which the characteristic catalyst structure–area, pore-size distribution, does not alter measurably. For extensive loss of area to occur requires months of commercial operation. It should be noted that the figures indicate far more oxygens have exchanged than can be accounted for in the two uppermost surface layers—those together

(4) J. Alexander, *J. Proc. Am. Pet. Inst.*, **27** (III) 51, Nov. (1947).

total some 24% of all the oxide oxygens.² The exchange of the surface oxygens must be almost instantaneous at 450°. The exchange with surface oxygen seems likely to occur through reversible hydrolysis of metal-oxygen bonds as shown in the equation



For oxygens below the surface the situation is not obvious. With an oxygen defect structure, exchange could occur by oxygen moving into vacant lattice positions, with hole transfer. Silica-alumina catalyst in which the silica presumably has a cristobalite structure is not a semiconductor. However, it does have channels honeycombing the lattice—the diameter of these passages is just large enough to admit an oxygen ion. We believe that at temperatures of ~450° there may be sufficient lattice vibration to allow passage of water molecules (or hydroxyl ions) through this network of channels. It is during this period that the oxygen exchange can occur, with only momentary distortion of the lattice. Such exchange could show a chain-like effect if the incoming oxygen caused a “Walden-type” inversion of the tetrahedron with effects transmitted to adjoining tetrahedra. Further, these channels in which the oxygen molecule moves at high temperature are too small to accommodate a nitrogen molecule, and they are, therefore, not measured by the usual BET method. Polack, Segura and Walden⁵ have recently considered oxygen transfer at a catalyst surface and into the interior.

Exchange occurring in this fashion would not necessitate the slow loss of area reported by Ries⁶ and Holmes.⁷ The silicon ions shown in the equation are bound in a cross-linked structure. For area loss to occur would perhaps require simultaneous hydrolysis of three or four metal-oxygen bonds, allowing the —O—Si(OH)₃ to “flop over” to a new position with loss of area.

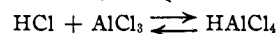
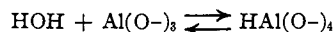
Perhaps the most important information to be derived from these experiments is the indication of the dynamic nature of the oxide structure. Although the over-all physical structure remains fixed, the high mobility of individual oxygen atoms testifies to the highly dynamic state of equilibrium. This mobility found experimentally in the presence of water indicates clearly that the small shift of oxygen position which was proposed¹ can occur easily.

(5) J. A. Polack, M. A. Segura and G. H. Walden, presented before the Division of Colloid Chemistry at the 120th meeting of the A.C.S., 1951.

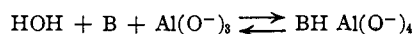
(6) H. E. Ries, “Advances in Catalysis,” Vol. III, Academic Press, Inc., New York, N. Y., 1952.

(7) J. Holmes and G. A. Mills, *J. Phys. Colloid Chem.*, **55**, 1302 (1951).

The catalytic system of silica-alumina with water as co-catalyst is believed to correspond to the aluminum chloride system with hydrogen chloride co-catalyst.

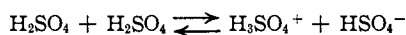


Just as HAlCl₄ has not been found to exist in the free state,⁸ so as stated earlier,¹ we do not believe the acid HAl(O⁻)₄ exists in the free state especially at high temperatures. However, in the presence of a Lewis base, B, for example, nitrogen compounds or olefins, the “salt” of the acid can be stabilized.

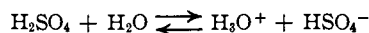


The formation of the stable salts as depicted involves a “coördination induction” or an “acid induction” through the influence of the silica on the alumina. Such a coördination induction can be likened to the “valence inductivity” described by Selwood.⁹ The latter effect, plus “valence oscillation” on the basis of the ideas proposed here, plays an important role in the catalytic action of semiconductor metal oxides and metals. This is described in greater detail by Cook and Oblad.¹⁰ The creation of active sites on catalyst surface by reactants also has been advanced by Taylor and Thon¹¹ from kinetic data.

Finally, it is of interest to examine the implications of a mobile catalyst surface in connection with problems such as effect of poisons on catalytic behavior. If the surface represents a two dimensional “fluid” acid, then similarities to other acids such as sulfuric and phosphoric become evident. For these homogeneous acids, relatively small amounts of bases such as water or nitrogen compounds are effective poisons. Considering 100% sulfuric acid which will ionize as



the presence of water gives rise to the following reaction



If the catalytic activity is proportional to the concentration of (H₃SO₄⁺) = $K(\text{H}_2\text{SO}_4)^2/(\text{HSO}_4^-)$, then a few per cent. of water or other Lewis bases will reduce the catalytic activity to a very low value, where K equals a small number. For example, since $K(\text{H}_2\text{SO}_4)^2 = 0.00073^{12}$ expressed on a molal basis, 1 wt. % water, corresponding to 0.57 molal, will introduce essentially 0.57 molal HSO₄⁻ and therefore decrease the H₃SO₄⁺ concentration from 0.03 to 0.001, a decrease of 30-fold. This great sensitivity to water “poisoning” has received a more exact treatment employing Hammett’s H_0 function to relate concentration of acid to catalytic activity.¹³ In a like manner, poisoning

(8) H. C. Brown and H. W. Pearsall, *THIS JOURNAL*, **73**, 4681 (1951).

(9) P. W. Selwood, *ibid.*, **70**, 883 (1948).

(10) M. A. Cook and A. G. Oblad, *Ind. Eng. Chem.*, **45**, 1456 (1953).

(11) H. A. Taylor and N. Thon, *THIS JOURNAL*, **74**, 4169 (1952).

(12) L. P. Hammett and A. J. Deyrup, *ibid.*, **54**, 2721 (1932).

(13) L. P. Hammett, “Phys. Org. Chem.,” McGraw-Hill Book Co., Inc., New York, N. Y., 1940, p. 277.

experiments with cracking catalysts do not necessarily prove heterogeneity of surface. We do not intend to imply by this that silica-alumina has a homogeneously active surface—there is considerable evidence for heterogeneity, and in theory we should expect such heterogeneity depending on the geometry of the aluminum and silicon atoms in the surface. We wish merely to indicate that by using the concept of the mobility of the surface, poisons need not be present in amounts stoichiometrically equivalent to the total active surface to cause essentially complete deactivation. The surface of cracking catalysts then behaves to a certain degree like a two-dimensional mobile acid.

HOUDRY PROCESS CORPORATION
MARCUS HOOK, PA.

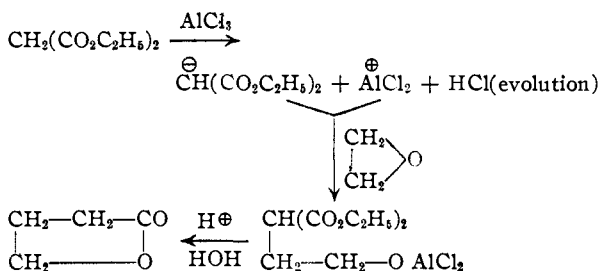
Alkylation of Malonic Ester by Ethylene Oxide Catalyzed by Anhydrous AlCl_3

BY CHITTARANJAN RAHA

RECEIVED DECEMBER 31, 1952

Available methods^{1-3,5-14} of synthesis of γ -butyrolactone are not easily workable and give poor yields. A consideration of the mechanism of reaction of ethylene oxide as discussed by Hammett¹⁵ suggested that the alkylation of malonic ester by ethylene oxide in the presence of anhydrous aluminum chloride might be an effective method for the preparation of γ -hydroxy acids. Breslow and Hauser⁴ have previously described the alkylation of acetoacetic ester with benzyl chloride in the presence of boron trifluoride.

The present reaction may be explained as



Experimental

Sixty-four grams (0.4 mole) of malonic ester dissolved in 50 ml. of absolute chloroform was added slowly to 34 g. (0.25 mole) of coarsely powdered anhydrous AlCl_3 ¹⁶ in a 3-

- (1) S. W. Chaikin and W. G. Brown, *THIS JOURNAL*, **71**, 122 (1949).
- (2) F. F. Blicke, S. B. Wright, Jr., and M. F. Zienty, *ibid.*, **63**, 2488 (1941).
- (3) W. L. Nelson and L. H. Cretcher, *ibid.*, **52**, 3702 (1930).
- (4) D. S. Breslow and C. R. Hauser, *ibid.*, **62**, 2358 (1940).
- (5) N. Fröschl and C. G. Danoff, *J. prakt. Chem.*, **144**, 217 (1936); *C. A.*, **30**, 3777⁴ (1936).
- (6) W. H. Bentley, E. Haworth and W. H. Perkin, Jr., *J. Chem. Soc.*, 161 (1896).
- (7) W. H. Perkin, Jr., and C. H. G. Sprankling, *ibid.*, 17 (1899).
- (8) S. S. Guhasarkar, *ibid.*, 898 (1928).
- (9) F. Fichter and A. Herbrand, *Ber.*, **29**, 1192 (1896).
- (10) Fittig, *Ann.*, **226**, 331 (1884).
- (11) *Ibid.*, **267**, 192, 200 (1892).
- (12) Saytzeff, *ibid.*, **171**, 266, 279, 282.
- (13) Traube and Lehmann, *Ber.*, **32**, 720 (1899); **34**, 1971, 1976 (1901).
- (14) Curtius, *ibid.*, **37**, 1277 (1904).
- (15) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., p. 1940, 301.
- (16) The yield depends on the freshness of anhydrous AlCl_3 .

necked flask fitted with a reflux condenser, a dropping funnel, an all-glass stirrer and a gas inlet tube. Hydrogen chloride was evolved. Ethylene oxide, generated by dropping 21 g. (0.26 mole) of ethylene chlorohydrin slowly on 20 g. (0.5 mole) of powdered sodium hydroxide under absolute toluene, was passed into the reaction mixture at room temperature with mechanical stirring. The rate of introduction of ethylene oxide was regulated so that the ether refluxed. After addition was complete, the mixture was cautiously acidified with 5 *N* hydrochloric acid, and then refluxed for five hours. The solid which separated on acidification dissolved within a few minutes. The light greenish mixture was then cooled, saturated with salt and extracted with benzene. The benzene extract was washed with a small amount of water, dried over anhydrous sodium sulfate and concentrated. The residual thin liquid was fractionated under reduced pressure.

The yield of γ -butyrolactone obtained as a colorless thin liquid, b.p. 85–110° (11 mm.); 105–120° (15 mm.), was quantitative (based on the ethylene chlorohydrin used).

Anal. Calcd. for $\text{C}_4\text{H}_6\text{O}_2$: C, 55.8; H, 6.9; neut. equiv., 86. Found: C, 55.42; H, 7.3; neut. equiv., 84, 86; n_D^{20} 1.3760.

The liquid γ -lactone which boiled usually over a range could be collected in two distinctly different fractions which had the same contents of carbon and hydrogen and same saponification equivalent. This property is possibly due to a dimorphism as suggested by Sueur.¹⁷

In one experiment the two fractions were: I, b.p. 85° (11 mm.), 105° (15 mm.), yield 5 g.; II, b.p. 130° (11 mm.), 140° (15 mm.), yield 17 g. In other experiments the relative proportions of the two fractions varied.

In more or less identical yield the two fractions gave a 2,4-dinitrophenylhydrazide, m.p. 93–94°.

Anal. Calcd. for $\text{C}_{10}\text{H}_{12}\text{N}_4\text{O}_8$: C, 42.26; H, 4.225; N, 19.72. Found: C, 42.48; H, 4.323; N, 19.59.

Acknowledgment.—Thanks are due to Dr. D. M. Bose, Director of the Bose Institute, for his encouragement and interest in this work. The author is indebted to Dr. S. K. Mukherjee, Department of Applied Chemistry, for his valuable help.

(17) Sueur, *Ann. Rept. Chem. Soc. (London)*, **9**, 90 (1912).

BOSE INSTITUTE
CALCUTTA, INDIA

Anhydrous AlCl_3 -Catalyzed Alkylation of Ethyl Cyanacetate by Ethyl Chloroacetate

BY CHITTARANJAN RAHA

RECEIVED MARCH 23, 1953

Breslow and Hauser¹ have observed that a reactive methylene compound, e.g., acetoacetic ester, can be ar-alkylated by benzyl chloride in the presence of an acid catalyst such as boron trifluoride. A similar reaction, viz., alkylation of cyanoacetic ester by means of ethyl chloroacetate in presence of anhydrous aluminum chloride, has been studied by the present author.

The yield of the alkylated product varied with the amount of catalyst used, but unlike a base-catalyzed reaction even a large amount of the acid catalyst failed to produce in a single step a di-condensation product. The results of comparative runs of experiments carried out in presence of an acidic catalyst and a basic catalyst are tabulated.

Experimental

Alkylation of Cyanoacetic Ester with Ethyl α -Chloroacetate to Yield the Monocondensation Product. Acid Cata-

- (1) D. S. Breslow and C. R. Hauser, *THIS JOURNAL*, **62**, 2385, 2389 (1940).

TABLE I

Reactive methylene compound	Alkylating agent	Catalyst	% Yield of product*
Cyanoacetic ester	Ethyl chloroacetate	1. 1 mole of AlCl ₃	50%
		2. 2 moles of AlCl ₃	Quantitative
		3. 1 mole of NaOC ₂ H ₅	50% mono-condensation product + 10% dicondensation product
		4. 2 moles of NaOC ₂ H ₅	35% dicondensation product + 10% mono-condensation product
α-Cyanosuccinic ester	Ethyl chloroacetate	5. 1-7 moles of AlCl ₃	Nil
		6. 1 mole of NaOC ₂ H ₅	30% dicondensation product

* The yield depends on the freshness of the AlCl₃.

lyst (1 M).—To 13 g. (0.1 mole) of coarsely powdered anhydrous aluminum chloride was added dropwise a solution of 11.3 g. (0.1 mole) of cyanoacetic ester and 12 g. (0.1 mole) of ethyl α-chloroacetate in 25 ml. of dry chloroform with constant shaking of the externally cooled reaction mixture. The addition of the solution was attended with evolution of hydrogen chloride followed by dissolution of the catalyst. The brown reaction mixture was left at room temperature till gas evolution had ceased. After careful decomposition of excess aluminum chloride with ice the reaction mixture was worked up in the usual manner. The residual liquid after removal of the solution was fractionated under vacuum.

The yield of colorless liquid product, b.p. 105° (10 mm.), was 11.5 g. (50%). *Anal.* Calcd. for C₂H₃NO₄: C, 54.27; H, 6.5; N, 7.03. Found: C, 53.97; H, 6.63; N, 7.32.

A portion (2 g.) of the distillate on hydrolysis with 20% hydrochloric acid and subsequent crystallization proved to be succinic acid (0.8 g.), m.p. 185°, singly and on admixture.

The catalyst even if increased to 2 moles or more always gave the above monocondensation product alone in quantitative yield but never any dicondensation product.

Sodium Ethoxide Catalyst.—To sodium ethoxide (prepared from 1 g. (less than 0.05 mole) of sodium metal and 12 ml. of absolute alcohol) was added 5.65 g. (0.05 mole) of cyanoacetic ester with constant shaking and external cooling. The sodio salt formed was left at room temperature for an hour or so after which 6 g. (0.05 mole) of ethyl chloroacetate in 5 ml. of absolute alcohol was dropped in with external cooling and constant shaking of the reaction mixture. Eight to ten hours reflux on a water-bath and subsequent working up in the usual manner gave 4.9 g. (50%) of the monocondensation product and 1.4 g. (10%) of a glycerol-like dicondensation liquid product, b.p. 145° (10 mm.). *Calcd.* for C₃H₅NO₆: C, 54.73; H, 6.66; N, 4.91. Found: C, 54.52; H, 6.77; N, 4.83.

Acid hydrolysis of the dicondensation product (3 g.) gave tricarballic acid (1.5 g.), m.p. 165°; on admixture with an authentic sample the m.p. was 164–165°.

As already pointed out the acid catalyst yielded no dicondensation product under any of the above experimental conditions. It could be prepared only when a base catalyst was employed as described below.

In One Step.—2.3 g. (0.1 mole) of sodium metal was dissolved in 30 ml. of absolute alcohol. To the cold sodium ethoxide was added 5.7 g. (0.05 mole) of cyanoacetic ester. The resulting mixture was intermittently warmed on a water-bath for about an hour. A solution of 12 g. (0.1 mole) of ethyl α-chloroacetate in 10 ml. of absolute alcohol was added dropwise to the cold sodio salt. After leaving overnight the mixture was refluxed on a steam-bath for 10 hours. The reaction mixture was cooled and worked up in the usual way to get 1 g. (10%) of monocondensation product, b.p. 105° (10 mm.), and 4.9 g. (35%) of dicondensation product, b.p. 145° (10 mm.).

Monocondensation to Dicondensation Product.—Three grams (0.025 mole) of ethyl α-chloroacetate was added to the sodio salt of ethyl α-cyanosuccinate prepared from 4.98 g. (0.025 mole) of the ester and 0.681 g. (0.025 mole) of sodium metal. The reaction mixture was colored violet. The usual processing gave (30%) of the ethyl α-cyanotricarballylate, b.p. 145° (10 mm.).

Acknowledgments.—The author expresses his thankful indebtedness to Dr. D. M. Bose, Director of the Bose Institute, and to Dr. S. K. Mukherjee, Lecturer in Physical Chemistry, Applied Chemistry Department, University College of Science

and Technology, Calcutta, for their interest in this work.

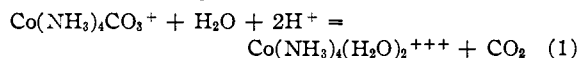
BOSE INSTITUTE
93 UPPER CIRCULAR ROAD
CALCUTTA 9, INDIA

Mechanism of Aquotization of Carbonato Complex Ions

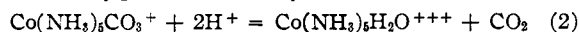
BY FRANZ A. POSEY AND HENRY TAUBE

RECEIVED FEBRUARY 20, 1953

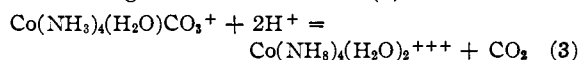
Stranks and Harris¹ have reported that there is no carbon isotope discrimination in the reaction



In an oxygen tracer study on a related reaction



Hunt, Rutenberg and Taube² showed that in release of carbonate, the Co–O bond is not severed, but rather the C–O bond. Since reaction (2) is analogous to what can reasonably be supposed to be a stage in the net reaction (1)



there is an apparent inconsistency in the two observations which, while it can be resolved by one of several assumptions, forces none as a conclusion. We have therefore undertaken an oxygen tracer study of reaction (1), for comparison with the results obtained in reaction (2), similar to that conducted for this reaction, but have increased the power of the tracer results by examining also the isotopic composition of the carbon dioxide liberated both in reactions (1) and (2). The method for isotopic assay of the water bound in Co(NH₃)₄(H₂O)₂⁺⁺⁺ was developed during the course of other research on the ion, and will be described more fully when these results are published.

Experimental

The salt (Co(NH₃)₄CO₃)NO₃·1/2H₂O was prepared according to the method of Grubitsch.³ The purity was checked by electrolytic determination of the cobalt content (calculated, 22.84%; observed, 22.86%). The salt (Co(NH₃)₅CO₃)NO₃·H₂O was part of a preparation used previously.²

The tracer experiments with (Co(NH₃)₄CO₃)NO₃·1/2H₂O were performed by preparing a solution of this compound in water enriched in H₂O.¹⁸ Perchloric acid in water of isotopic composition very near to that in the solution was

- (1) D. R. Stranks and G. W. Harris, *J. Phys. Chem.*, **56**, 906 (1952).
- (2) J. P. Hunt, A. C. Rutenberg and H. Taube, *THIS JOURNAL*, **74**, 268 (1952).
- (3) H. Grubitsch, "Anorganisch-präparative Chemie," Springer Verlag, Vienna, 1950, p. 441.

then added. During this operation, a rapid stream of nitrogen passed through the solution to carry off the carbon dioxide released. This was stripped from the gas by means of a trap immersed in liquid nitrogen. The ion $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$ was precipitated from the solution with $\text{Co}(\text{CN})_6^{4-}$, and the salt $(\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2)(\text{Co}(\text{CN})_6)$ was removed, washed, dried, and finally heated *in vacuo* to remove the complex-bound water. The isotopic composition of the water was determined by equilibrating it with carbon dioxide, and analyzing the carbon dioxide in a mass spectrometer. The necessary blank determinations were conducted as indicated by the procedures described. Separate experiments were also conducted in which the solid carbonate salts were dusted into perchloric acid in enriched water, and the carbon dioxide swept out with nitrogen as before.

All operations were performed as rapidly as possible to minimize exchange of $\text{Co}(\text{NH}_3)_4\text{CO}_3^+$ and $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$ with the environment. The solutions before addition of the acid were cooled to 0° , and maintained there for precipitation of $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2(\text{Co}(\text{CN})_6)$. In a typical experiment, 1.5 g. of salt was used in 30 ml. of solution.

Results

N represents the mole fraction of O^{18} in the species under consideration. All results were normalized to 2.000×10^{-3} as the mole fraction of O^{18} in a sample of ordinary CO_2 kept as a standard.

The method of isotopic assay of $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$ was tested by precipitating the cobaltcyanide from water enriched in O^{18} , after leaving the aquo ion in contact under conditions and for a time comparable to those obtaining in the experiments with the carbonate ion. The results were: $N \times 10^3$ for inner sphere water of $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$ precipitated from normal water = 2.235; $N \times 10^3$ for normal water = 1.928; $N \times 10^3$ for inner sphere water when precipitated from enriched solvent = 2.348; $N \times 10^3$ for H_2O in enriched solvent = 7.163. The results show 2.3% exchange of the aquo ion during the operation.

To learn the exchange to be expected for CO_2 liberated by acid under the conditions of our experiments, a solution of Na_2CO_3 (of normal isotopic composition) was added to enriched water containing acid, with the following results: $N \times 10^3$ for CO_2 from Na_2CO_3 in ordinary water = 1.996; $N \times 10^3$ for CO_2 from Na_2CO_3 in enriched water = 2.077; $N \times 10^3$ for enriched water = 5.985; exchange of CO_2 = 2.0%.

To provide the necessary base values for the interpretation of the tracer experiments, the aquotization of $\text{Co}(\text{NH}_3)_4\text{CO}_3^+$ was conducted in water of normal isotopic composition ($N \times 10^3 = 1.928$). $N \times 10^3$ for CO_2 from aquotization = 2.009; $N \times 10^3$ for inner sphere water = 1.985.

The results on the aquotization in enriched water are: $N \times 10^3$ for water in solution = 8.263; $N \times 10^3$ for inner sphere water = 5.147. Base value (1.985×10^{-3} corrected for exchange expected in this environment = 2.129×10^{-3}). Fraction of inner sphere water derived from environment = 0.493. The carbon dioxide collected in this experiment was found to have undergone 5.4% exchange with the environment, somewhat in excess of that observed using Na_2CO_3 . A third experiment proved this exchange not to be reproducible ($\sim 8\%$), and the method of adding the solid was adopted.

With $(\text{Co}(\text{NH}_3)_4\text{CO}_3)\text{NO}_3 \cdot \frac{1}{2}\text{H}_2\text{O}$, the results were: $N \times 10^3$ for H_2O in enriched solvent = 6.923; $N \times 10^3$ for CO_2 released = 2.069. The value 2.069 compared with 2.009 for the release of CO_2 in normal water shows 1.2% enrichment.

With $(\text{Co}(\text{NH}_3)_6\text{CO}_3)\text{NO}_3 \cdot \text{H}_2\text{O}$ the results were: $N \times 10^3$ for CO_2 released from normal water = 1.972; $N \times 10^3$ for CO_2 released from enriched water = 2.048; $N \times 10^3$ for H_2O in enriched solution = 5.665. In this experiment, the carbon dioxide underwent 1.5% exchange with the solvent.

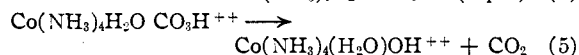
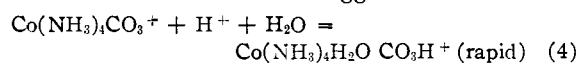
Discussion

It is necessary for the success of an experiment of this type that the resulting aquo ion not exchange rapidly with the solvent. The blank experiments with $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$, as well as proving the method of isotopic analysis of the bound water, prove the formula of this ion in water to be $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$, and demonstrate its ex-

change with the solvent to be sufficiently slow for the present purposes.

The experiments show that the ion $\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$, formed from $\text{Co}(\text{NH}_3)_4\text{CO}_3^+$, derives only $1/2$ of the oxygen from the solvent, the other $1/2$ being left by the carbonate when CO_2 is removed. The possibility that the 50% exchange appears equally distributed between the two positions, as an accidental value on the way to complete exchange, can be excluded by considering the isotopic composition of the liberated CO_2 . Such enrichment could only take place with some form of the carbonate ion ($\text{Co}(\text{NH}_3)_4(\text{H}_2\text{O})_2^{+++}$ does not exchange sufficiently rapidly) and would necessarily result in enrichment of the CO_2 which is liberated. The slight enrichment of the CO_2 observed ($\sim 1\%$) is attributable to exchange following its release.

Stranks and Harris have suggested the mechanism

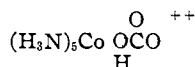


The stepwise feature of the mechanism is certainly reasonable, and is to some extent confirmed by providing an explanation for our oxygen tracer results. Applying our observations to this mechanism, it can be concluded that the Co-O bond is severed in step (4), otherwise CO_2 would appear at least 33% exchanged with solvent. Reaction 5, involving $\text{Co}(\text{NH}_3)_4\text{H}_2\text{O}^* \text{CO}_3\text{H}^{++}$, then takes place as demonstrated for the analogous ion $\text{Co}(\text{NH}_3)_5\text{CO}_3\text{H}^{++}$, severing the C-O bond. The fractionation experiments of Stranks and Harris, obtained for the reaction in acid, find an explanation if reaction (4) under these conditions is formulated not as an equilibrium, but as a rate determining step; no large carbon fractionation can be expected in step (4) since the Co-O bond is severed there, and none can take place in (5), since the ion is completely decomposed to products.

It is interesting to note that the major conclusions are indicated also by the experiments on aquotization in ordinary water, the isotopic composition of the inner sphere water (1.985×10^{-3}) lying fairly near the mean of that of the solvent (1.928×10^{-3}) and of the carbon dioxide (2.009×10^{-3}). The dependability of such a conclusion drawn from this experiment, however, is reduced not only because of the slight difference between the extreme values, but also because fractionation effects interfere. These can take place due to discrimination by Co(III) between O^{16} and O^{18} in water, and in the attached carbonate. The results show that a slight excess of O^{18} is left on the Co(III).

If it is assumed that precisely 50% of the H_2O in the inner sphere is derived from the solvent, the isotopic composition expected for this water in the experiment using enriched solvent is the mean of 8.263×10^{-3} and 2.009×10^{-3} or 5.136×10^{-3} . When this is corrected for the exchange to be expected for the aquo ion, the value 5.208×10^{-3} is obtained, to be compared with the experimental value of 5.147×10^{-3} . The result may indicate a slightly greater rate of reaction of H_2O^{16} compared to H_2O^{18} .

A conclusion about mechanism which applies to the results for CO_3^- attached as a chelate, bound at one position, or not bound at all, is that there is no transfer of oxygen from the solvent to C at any stage on the release of CO_2 . Thus it seems likely that the activated complex which in the case of $\text{Co}(\text{NH}_3)_5\text{CO}_3^+$ has the composition $\text{Co}(\text{NH}_3)_5\text{CO}_3\text{H}^{++}$, does not have the structure reasonable for this complex ion, but rather has the proton on the oxygen bridging cobalt and carbon



Since new Co(III) bonds are established during the release of CO_2 from $\text{Co}(\text{NH}_3)_4\text{CO}_3^+$, it will be of interest to learn whether groups besides water (e.g., Cl^- , SO_4^{2-}) can enter during this rapid process. It was this possibility that attracted interest to the aquation of $\text{Co}(\text{NH}_3)_5\text{CO}_3^+$, but could not be realized in this reaction since oxygen is left attached to Co(III).

Acknowledgments.—This work was supported by the Office of Naval Research under contract N6-ori-02026. The funds for the purchase of the mass spectrometer used in the research were supplied by the Atomic Energy Commission under contract At(11-1)-92.

DEPARTMENT OF CHEMISTRY
UNIVERSITY OF CHICAGO
CHICAGO, ILL.

Some Esters of Unsaturated Acids

By V. SATTA,¹ M. L. FEIN AND E. M. FILACHIONE

RECEIVED APRIL 6, 1953

In connection with a study of the preparation of co-polymers of acrylic esters, various esters of un-

fumarate⁵ have been most completely reported; for butyl fumarate, however, the previously reported constants and those of this paper are not in good agreement. The patent literature reports only the boiling point of 2-ethylhexyl maleate,³ and the refractive index for *n*-butyl aconitate⁶ and 2-ethylhexyl aconitate.⁷ This paper reports the preparation, boiling point, refractive index and density of various esters of several unsaturated acids.

Experimental

Samples of 2-chloroethyl crotonate, butyl maleate, 2-ethylhexyl maleate, butyl itaconate, butyl aconitate and 2-ethylhexyl aconitate were available commercially; these were redistilled and the constants determined.

The other esters of Table I were prepared by the usual esterification procedure, glass equipment with ground glass joints being employed.⁸ A mixture of acid or anhydride, an excess of the alcohol, sulfuric acid catalyst and entraining agent was refluxed, and water was continuously removed in a separating trap. Benzene or toluene was used as the entraining agent except in the preparation of the butyl esters, in which the excess of butyl alcohol served as the entraining agent. After esterification was complete, the catalyst was neutralized with sodium acetate, and the ester isolated by vacuum distillation. A 35-mm. by 50-cm. Vigreux or an alembic-type still,⁹ mounted to permit agitation of the still pot contents, was used in the distillation. Center fractions were collected for determination of the various constants. Results are shown in Table I.

EASTERN REGIONAL RESEARCH LABORATORY¹⁰
PHILADELPHIA 18, PENNSYLVANIA

(5) D. Vorländer, *Ann.*, **280**, 200 (1894).

(6) P. M. Kirk, U. S. Patent 2,375,563, May 8, 1945.

(7) E. R. Meincke, U. S. Patent 2,475,629, July 12, 1949.

(8) P. A. Shearer and A. M. Pardee, *Proc. S. Dakota Acad. Sci.*, **15**, 24 (1935); *C. A.*, **30**, 2550 (1936).

(9) W. P. Ratchford and C. E. Rehberg, *Anal. Chem.*, **21**, 1417 (1949).

(10) One of the laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, United States Department of Agriculture. Article not copyrighted.

TABLE I

PROPERTIES OF SOME ESTERS OF UNSATURATED ACIDS

Ester	Yield, %	B.p., °C.	B.p., mm.	n_D^{20}	d_4^{20}	Carbon, %		Hydrogen, %		Chlorine, %		Sapn. equiv.	
						Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.
2-Chloroethyl crotonate ^a		58-60	3.5	1.4599	1.1185					23.72	23.86		
<i>n</i> -Butyl maleate ^a		124-125	3.4	1.4451	0.9964								
<i>n</i> -Hexyl maleate	97	127	0.7	1.4499	.9583	68.20	67.57	10.48	9.92			142.1	142.2
2-Ethylhexyl maleate ^a		156	0.7	1.4548	.9437								
2-(2-Chloroethoxy)-ethyl maleate	86	197	1.0	1.4858	1.2738					21.70	21.54		
<i>n</i> -Butyl fumarate	80	117	2.5	1.4429	0.9775	63.12	63.13	8.77	8.77			113.9	114.1
2-Ethylhexyl fumarate	87	160	0.5	1.4370	0.9398	70.53	70.55	10.58	10.66			171.4	170.2
2-(2-Chloroethoxy)-ethyl fumarate	83	182	0.3	1.4863	1.2673					21.83	21.54		
<i>n</i> -Butyl chloromaleate	83	112	1.2	1.4558	1.0756	54.86	55.10	7.29	7.23	13.50	13.31		
2-Chloroethyl chloromaleate	75	138	1.2	1.4983	1.4047					38.44	38.60		
<i>n</i> -Butyl itaconate ^a		82	0.2	1.4450	0.9839								
<i>n</i> -Butyl aconitate ^a		155	.5	1.4553	1.0184								
2-Ethylhexyl aconitate ^a		170 ^b	.07 ^b	1.4620	0.9589								

^a The commercially available esters were redistilled. ^b Distilled in an alembic-type still.

saturated acids (listed in Table I) were required. Though several of these esters are available commercially, their physical properties are either not found in the permanent chemical literature or these are insufficiently reported. *n*-Butyl maleate^{2,3} and fumarate^{2,3} and 2-chloroethyl maleate⁴ and

(1) Foreign trainee from Italy.

(2) G. H. Jeffery and A. I. Vogel, *J. Chem. Soc.*, 658 (1948).

(3) W. O. Keayon and C. C. Unruh, U. S. Patent 2,448,531, September 7, 1948.

(4) M. E. Synerholm and A. Hartsell, *Contrib. Boyce Thompson Inst.*, **14**, 79 (1945); *C. A.*, **40**, 669 (1946).

Sulfatoalkyl Amines

By WILSON A. REEVES AND JOHN D. GUTHRIE

RECEIVED APRIL 13, 1953

Although a number of investigators have reported the preparation and use of 2-aminoethyl sulfuric acid^{1,2} other aminoalkyl sulfates have received very little attention. Apparently, most interest in these sulfates has been for the production of

(1) Sigmond Frankel and Martha Cornetas, *Ber.*, **51**, 1654 (1919).

(2) John D. Guthrie, *Textile Research J.*, **17**, 625 (1947).

TABLE I
 SULFATOALKYL AMINES

Name (formula)	M.P., °C.	Nitrogen, %		Sulfur, %		Potassium, %		Chloride, %	
		Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found
Sulfatoalkyl ethylenediamine hydrochloride (HO ₃ SOCH ₂ CH ₂ NHCH ₂ CH ₂ NH ₂ ·HCl)	192	12.70	13.19	14.53	14.20			16.07	16.18
2-Sulfato 1,3-diaminopropane hydrochloride [H ₂ NCH ₂ CH(OSO ₃ H)CH ₂ NH ₂ ·HCl]	270	13.56	13.71	15.52	15.00			17.17	17.20
Potassium (disulfatoethyl)-amine monohydrate (KO ₃ SOCH ₂ CH ₂ NHCH ₂ CH ₂ OSO ₃ H·H ₂ O)	127.5	4.37	4.36	19.90	19.73	12.17	12.16		
1-Sulfato-2-diethylaminopropane [HO ₃ SOCH ₂ CH(CH ₃)N(C ₂ H ₅) ₂]	228.5	6.60	6.61	15.08	14.85				
2-(2-Sulfatoethyl)-pyridine (HO ₃ SOCH ₂ CH ₂ NC ₅ H ₄)	167	6.90	6.73	15.76	15.31				
2-Sulfatoethyl dimethylamine hemihydrate [HO ₃ SOCH ₂ CH ₂ N(CH ₃) ₂ · ¹ / ₂ H ₂ O]	Anh. 253	7.90	7.90	18.05	18.15				
3-Sulfatopropylamine (HO ₃ SOCH ₂ CH ₂ CH ₂ NH ₂)	230.5	9.03	8.97	20.65	20.71				

either ethylenimine or substituted ethylenimines by the method of Wenker³ or similar methods.⁴ Saunders⁵ prepared a number of sulfuric acid esters of the simple monohydroxyethylarylamines. Aminized cotton is produced by allowing 2-aminoethylsulfuric acid to react with cotton in the presence of sodium hydroxide.⁶ A number of other sulfatoalkyl amines, some of which have not previously been reported, were made (see Table I) for use in determining their reactivity with cotton and evaluating the chemically modified cottons produced by such reactions.

In each case the sulfates were prepared from the corresponding aminoalkyl alcohol by allowing the alcohol to react with chlorosulfonic acid in carbon tetrachloride. With carbon tetrachloride as the solvent or as the suspending agent the solution or the mixture is stirred and maintained near 0°. A cooled mixture of chlorosulfonic acid in carbon tetrachloride is initially added dropwise and later aliquot additions are increased as the reaction becomes less vigorous. Under these conditions there is no charring, and the product separates out either as a viscous liquid or a granular mass. The monosulfato monoamines may be obtained as inner salts, and the monosulfato diamines are easily isolated as hydrochlorides, whereas the disulfato monoamines are readily crystallized as monosodium or potassium salts. These crystalline products generally contain some free sulfate ion, but this contamination can easily be removed by crystallizing from an appropriate aqueous ethanol solution. When the hydrochloride is to be crystallized, the ethanol solution should be acidified with hydrochloric acid.

Since the sulfation of each alcohol was carried out under similar conditions, only one typical preparation will be described.

Experimental

Potassium Acid Disulfatoethyl Amine.—Diethanolamine (210 g.) suspended in 270 ml. of carbon tetrachloride was cooled to near 0° in an ice-salt-bath. Chlorosulfonic acid (466 g.) was added to the cool diol while stirring. At first the addition of chlorosulfonic acid was dropwise and slow; the later additions were larger and more rapid. After all the chlorosulfonic acid had been added, the mixture was re-

moved from the cooling bath and stirred until the contents reached about room temperature. Much of the liberated hydrochloric acid had been removed at this stage. The crude granular disulfato compound separated out as an extremely deliquescent material. The neutral potassium salt was made by dissolving the acid in 500 ml. of water, then adding 30% potassium hydroxide in 50% ethanol until the solution had a pH of 7-8. Three liters of 95% ethanol was stirred in and when cooled, 550 g. (86% yield) of potassium acid disulfatoethyl amine separated. To get a highly purified sample, a portion of the above material was dissolved in a minimum of hot 67.5% ethanol and allowed to crystallize slowly.

Acknowledgment.—The authors wish to express their appreciation to the following members of this Laboratory: Lawrence E. Brown and Samuel M. Stark, Jr., for sulfur determinations; Vidabelle O. Cirino for nitrogen determinations; and Alva F. Cucullu for potassium determinations.

SOUTHERN REGIONAL RESEARCH LABORATORY⁷
NEW ORLEANS, LA.

(7) One of the Laboratories of the Bureau of Agricultural and Industrial Chemistry, Agricultural Research Administration, U. S. Department of Agriculture.

The Electrical Effect of the Trimethylsilyl Group. II.

BY JOHN D. ROBERTS AND CLARE M. REGAN

RECEIVED MARCH 25, 1953

In an earlier investigation,¹ we presented evidence based on Hammett² σ -constants that the trimethylsilyl [(CH₃)₃Si-] group is electron-donating in character as judged by the manner in which it influences the acidity of the carboxyl group in benzoic acid. Since the electrical influence of the group is not apparently clear-cut in other types of compounds³ we have reinvestigated the reactivities of the trimethylsilyl substituted benzoic acids and have prepared the corresponding ethyl esters and determined their alkaline saponification rates.⁴

(1) J. D. Roberts, E. A. McElhill and R. Armstrong, *THIS JOURNAL*, **71**, 2923 (1949).

(2) L. P. Hammett, "Physical Organic Chemistry," McGraw-Hill Book Co., Inc., New York, N. Y., 1940, Chap. VII.

(3) H. Soffer and T. DeVries, *THIS JOURNAL*, **73**, 5817 (1951).

(4) We have confined our attention to the acids and esters since Dr. R. A. Benkeser of Purdue University has measured the reactivities of a number of amine derivatives. **ADDED IN PROOF.**—R. A. Benkeser and H. R. Krysiak, *ibid.*, **75**, 2421 (1953). The results of these investigators with benzoic acid derivatives are in good agreement with those given in Table II.

(3) Henry Wenker, *THIS JOURNAL*, **57**, 2328 (1935).

(4) H. Schlapfer and A. Margot, U. S. Patent 2,558,273 (1951).

(5) K. H. Saunders, *J. Chem. Soc.*, **121**, 2667 (1922).

(6) Wilson A. Reeves and John D. Guthrie, *Textile Research J.*, in press.

TABLE I
APPARENT IONIZATION CONSTANTS, DIPHENYLDIAZOMETHANE REACTIVITIES AND ETHYL ESTER SAPONIFICATION RATES OF
SUBSTITUTED BENZOIC ACIDS

Substituent	Av. half-point ^{a, b}	$K_A \times 10^6$ ^c	Concn., moles/l. ^d	Half-life, ^d min.	Av. k_2 ^{b, d} l./mole min.	$k_2 \times 10^4$, ^{b, e} l./mole min.	$k_2 \times 10^3$ ^{b, f} l./mole min.
None	5.80 ± 0.01 (5.75) ^g	1.59	0.0487	13.21	1.08 ± 0.01 (1.04) ^g	28.7 ± 0.50	8.68 ± 0.50
			.0874	7.29			
			.0967	6.22			
<i>p</i> -(CH ₃) ₃ Si-	5.80 ± 0.01 (5.85) ^g	1.59	.0800	7.41	1.15 ± 0.01 (1.05) ^g	23.3 ± 0.6	9.98 ± 0.44
			.0823	7.35			
			.0440	13.71			
<i>m</i> -(CH ₃) ₃ Si-	6.00 ± 0.02 (6.01) ^g	1.00	.0810	7.72	1.10 ± 0.01 (1.07) ^g	12.6 ± 0.3	6.64 ± 0.08
			.0737	8.69			
			.0474	13.22			
<i>p</i> -CH ₃ -	6.00 ± 0.01 (5.94) ^g	1.00
<i>p</i> -CH ₃ O-	6.12 ± 0.02 (6.07) ^g	0.76

^a Reading on pH scale of pH meter calibrated for aqueous buffer solutions at half-neutralization point using glass and saturated calomel electrodes without correction for liquid junction potentials in 50% water-50% ethanol (by volume) solutions at 25°. ^b Standard deviations are appended to the average values. ^c Calculated assuming unit activities and readings of pH meter scale equal to logarithm of reciprocal of hydrogen ion concentrations. ^d For reaction of benzoic acids with diphenyldiazomethane in absolute alcohol solution at 30°. ^e Rate constants for saponification of ethyl esters in 56% acetone (by weight) at 24.9°, see ref. 5b. ^f Rate constants for saponification of ethyl esters in 87.83% ethanol (by volume) at 30.0°, see ref. 5a. ^g Values obtained previously¹ with different apparatus and materials.

The procedures have been described earlier in detail.¹⁻⁵ The ethyl esters of *m*- and *p*-trimethylsilylbenzoic acids were prepared in 50-57% yields by heating the silver salts of the acids¹ with a slight excess of ethyl iodide in ether; ethyl *m*-trimethylsilylbenzoate, b.p. 90-91° (1.5 mm.). *Anal.* Calcd. for C₁₂H₁₈O₂Si: C, 64.54; H, 8.12. Found: C, 64.84; H, 8.10. Ethyl *p*-trimethylsilylbenzoate, b.p. 105-106° (2.7 mm.). *Anal.* Calcd. for C₁₂H₁₈O₂Si: C, 64.54; H, 8.12. Found: C, 64.70; H, 8.11.

The experimental results for the trimethylsilyl derivatives along with those for some reference compounds are given in Table I. A summary of available σ -constant data is presented in Table II. Reasonable experimental agreement was found with the earlier investigation¹ and from all of the results it is clear that the net electrical effect of the trimethylsilyl group on the reactivities of benzoic acids or esters is essentially negligible in the para-position but rather electron-donating in the meta-position. The spread of the meta- σ -values is large compared with what is customarily found² and may be related to the bulkiness of the group.^{4,6}

TABLE II

 σ -CONSTANTS FOR THE TRIMETHYLSILYL GROUP

Reaction ^a	(Meta)	(Para)
Ionization constants in 50% ethanol at 25°	-0.155 (-0.208) ^b	-0.020 (-0.060) ^b
Diphenyldiazomethane rates in absolute ethanol at 30.0°	+0.025 (-0.018) ^b	+0.002 (-0.022) ^b
Alkaline hydrolysis in 87.83% ethanol at 30.0°	-0.040	+0.027
Alkaline hydrolysis in 56% acetone at 24.9°	-0.150	-0.040
Average	-0.080 ± 0.042 ^c (-0.113) ^b	-0.008 ± 0.014 ^c (-0.041) ^b

^a Data for log k_0 and ρ are given elsewhere.^{1,2} ^b Ref. 1. ^c Standard deviations.

DEPARTMENT OF CHEMISTRY AND LABORATORY
FOR NUCLEAR SCIENCE AND ENGINEERING
MASSACHUSETTS INSTITUTE OF TECHNOLOGY
CAMBRIDGE 39, MASSACHUSETTS

(5) (a) K. Kindler, *Ann.*, **450**, 1 (1926); (b) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1936).

(6) Cf. ref. 5 of J. D. Roberts, R. A. Clement and J. J. Drysdale, *THIS JOURNAL*, **73**, 2181 (1951); C. C. Price and D. C. Lincoln, *ibid.*, **73**, 5836 (1951).

Direct Synthesis of Organotin Halides. I. Preparation of Dimethyltin Dichloride¹

BY A. C. SMITH, JR.,² AND EUGENE G. ROCHOW

RECEIVED MAY 4, 1953

Organotin halides have been known for a hundred years,³ and many compounds of the type R_n-SnX_{4-n} have been synthesized. With the exception of two sealed-tube syntheses of iodides,^{4,5} all preparations have been by indirect and often difficult methods.⁶

The direct synthesis of organosilicon and organogermanium halides⁷ led to a study of the direct synthesis of organotin halides.⁸ The effects of several metals as catalysts was studied by placing each metal over a thin film of evaporated tin on a microscope slide and heating the slide in an atmosphere of methyl chloride for one-half hour at 300°. Any unusual reactivity of the metallic couple was indicated by reaction and removal of the tin at the junction of the two metals. Copper proved to be the most promising catalyst, with some activity also exhibited by silver and gold. Mercury, iron, selenium, arsenic, titanium, antimony, tellurium, calcium, magnesium, zirconium, aluminum, chro-

(1) From a thesis submitted by A. C. Smith, Jr., to the Graduate School of Arts and Sciences of Harvard University.

(2) Metal and Thermit Fellow at Harvard University 1949-1950.

(3) C. Lowig, *Ann.*, **84**, 309, 313 (1852).

(4) A. Cahours, *ibid.*, **114**, 373 (1860).

(5) Karantassis and Basileiados, *Compt. rend.*, **205**, 460 (1937).

(6) An extensive discussion is given in E. Krause and A. v. Grosse, "Die Chemie der metall-organischen Verbindungen," Chapt. V, Borntraeger, Berlin, 1937, pp. 311-372.

(7) E. G. Rochow, *THIS JOURNAL*, **67**, 963 (1945); **69**, 1729 (1947).

(8) The experiments reported herein were conducted in the period 1949 to 1951. After a full account had been prepared, U. S. Patent 2,825,559 in the same field, (Frederick A. Smith, assigned to Union Carbide and Carbon Corp.) appeared on Jan. 13, 1953. The present paper is a condensed version dealing almost entirely with those aspects of our work not touched upon by the F. A. Smith patent. Full details of our own work are available in the thesis of reference (1).

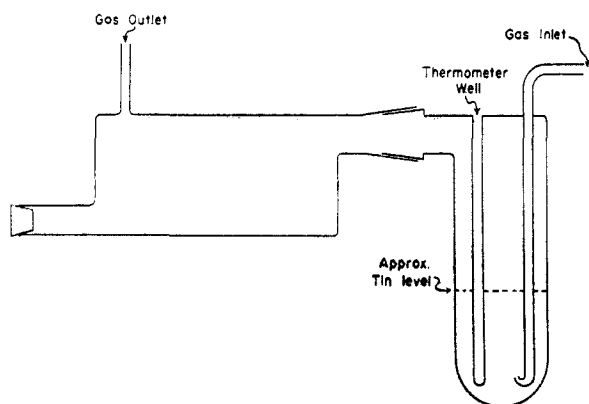


Fig. 1.—Dimensions: reaction chamber, 65 × 200 mm.; condenser (body), 80 × 200 mm.

mium, silicon, manganese, cobalt, nickel, zinc, cadmium, germanium, lead, bismuth and iodine gave no indications of being good catalysts, although the mercury dissolved the coating of tin.

Following this survey, methyl chloride was passed through molten tin⁹ at various temperatures, with various proportions of copper added to the tin as catalyst. Reaction occurred at the melting point of the tin (232°) and up to 450°, with the range of 300–350° being optimum. The product was practically pure dimethyltin dichloride,¹⁰ together with very small amounts of trimethyltin chloride and methyltin trichloride. At optimum conditions, a yield of 0.3 g. of dimethyltin dichloride per hour could be obtained from an input of 10 cc. per minute (1 g. per hr.) of methyl chloride, most of the excess methyl chloride being recoverable at the output.

Under the operating conditions employed, it could be expected that copper(II) chloride, copper(II) oxide, copper(I) oxide, tin(II) chloride, tin(II) oxide, and tin(IV) oxides might be present as impurities at the start or be formed to some extent during operation. Each of these substances was tested separately for its effect both on the induction period of the reaction and on its continued operation. Of these, only tin(II) oxide showed any marked effect, and that was to increase the induction period, an effect also noticed when the molten tin stood in contact with air before admitting methyl chloride. Treatment of the tin with hydrogen before admitting methyl chloride materially reduced the induction period.

The effects of zinc, lead, sodium, mercury and water on the starting and the progress of the reaction then were studied. Of these, only sodium showed any pronounced effect, and that was to cause an increased output of trimethyltin chloride and a corresponding retention of chlorine as sodium chloride in the reaction vessel.

The useful duration of the reaction was shortened by the accumulation of residues in the reaction mixture, particularly at the surface of the tin. When-

(9) Anal. 0.01% Fe, 0.01% Pb, 0.02% Zn, no As or Cu. Another source provided 99.981% pure tin containing 0.004% Pb, 0.001% Cu, 0.007% Sb, and 0.008% Fe, but this did not react readily with CH_3Cl until 0.2 to 1.0% of Zn was added.

(10) White crystals, easily sublimed at 20 to 50°, m.p. 106° (ref. 6 gives 90°). Anal. Calcd. for $\text{C}_2\text{H}_6\text{SnCl}_2$: C, 11.34; H, 2.84; Cl, 32.28. Found: C, 11.15; H, 3.00; Cl, 32.21.

ever considerable residue appeared, the yield of dimethyltin dichloride decreased and the product became increasingly contaminated with by-products and with tarry material. The residues were found to be composed chiefly of copper-tin intermetallic compounds and porous carbon. By operating the reaction between pure tin and methyl chloride at the optimum conditions determined with copper as catalyst, it was found that dimethyltin dichloride could be produced less dependably but in favorable yields without a catalyst. The accumulation of harmful residues was so greatly reduced that the reaction vessels did not become choked nor the reaction inhibited, but there was usually an induction period. The reaction was inhibited by tin(II) oxide, but relatively uninfluenced by tin(II) chloride. The reaction appears to be catalyzed or aided by the product, which, because of its volatility, escapes readily from the reaction zone. Before any product appears, very small amounts of inhibiting substances may divert the methyl chloride into other reactions. Such substances may very well be those which accelerate the pyrolysis of methyl chloride,¹¹ for if the reaction with tin is delayed in getting started the "right" way, the accumulation of carbon from pyrolysis of methyl groups accelerates further pyrolysis and keeps the reaction going in the "wrong" way. Experiments indicated that extended surface areas (of fritted glass distributors, finely-divided carbon, particulate residues, etc.) interfered in this way.

Many different reaction vessels were tried, but those using molten tin were preferred because they presented a fresh surface of the metal to the incoming methyl chloride. The most extreme attempt in this direction involved spraying a fine jet of molten tin into an atmosphere of methyl chloride at 300–350°. The reaction was successful in that dimethyltin dichloride was produced, but the yields were extremely low because a stream of two to four liters of gas per minute was necessary to atomize the liquid tin. This large volume gave a very short reaction time, and most of the tin agglomerated on the walls, which acted as baffles. A tower of large diameter and considerable length probably would be necessary to get high conversions.

The type of reaction vessel found to be most generally adaptable to laboratory experiments consisted of a vertical cylinder 6.5 × 20 cm., into which were sealed a gas delivery tube and a thermometer well. A horizontal outlet near the top connected through a 24/40 joint to an inclined air-cooled condenser 8 × 20 cm. in which the crystals collected. The product was removed by melting the crystals and collecting the liquid from a delivery tube at the lower end. The reaction chamber held approximately 1 kg. of tin; the condenser about 100 g. of product. Nearly a hundred experiments were carried out in such vessels, in the manner indicated below.

Experimental

Copper-catalyzed Reaction of Methyl Chloride with Tin.—In one example, a vessel of the type described was charged with 1400 g. of tin and 180 g. of copper powder, and was

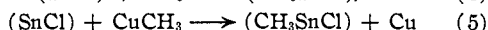
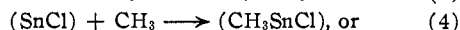
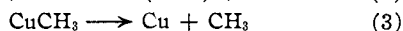
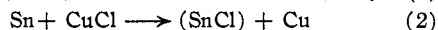
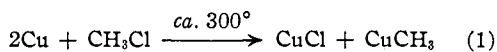
(11) K. Weisler, *Chem. Z.*, 52, 182 (1928).

heated to 305° under an atmosphere of methyl chloride. The temperature was raised to 370° to start the reaction, and then dropped to 315° after 1.5 hours. Methyl chloride was introduced at a rate of 30 cc./min. at room temperature. Crystals of dimethyltin dichloride formed in 12 minutes. Over an interval of 862 hours the rate of formation of (CH₃)₂SnCl₂ increased slowly to 3.3 g./hr., then declined after 250 hr. to 0.71 g./hr. The addition of fresh tin raised the rate to 2.1 g./hr. but after 400 hr. it declined to 0.81 g./hr. again. The average yield was 1.8 g./hr.

Uncatalyzed Reaction of Methyl Chloride with Tin.—In one example, a small reaction vessel of the same general type was charged with 170 g. of molten tin at 450° under an atmosphere of methyl chloride. The gas input was adjusted to 30 cc./min. Crystals of dimethyltin dichloride formed within 20 minutes, but the gas jet plugged intermittently for the first 120 hours and production during that period was low. Following this period operation was satisfactory at an average yield of 0.58 g./hr. for 774 hr.

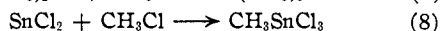
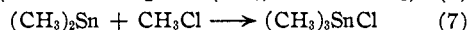
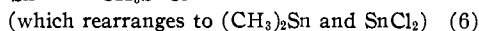
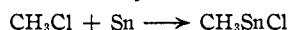
Discussion

The observed very high proportion of symmetrical dimethyltin dichloride follows a trend noted in the corresponding reactions with silicon and germanium^{7,12} and may be explained in the same way as those found in the case of silicon.¹³ A speculative mechanism for the catalyzed reaction is similar to the one proposed for silicon.¹⁴



and so on, until tetra-substitution has occurred. Rearrangement of methyl and chlorine groups at the reaction temperature then results in dimethyltin dichloride almost exclusively.

In the uncatalyzed reaction it could be assumed that tin can split methyl chloride in much the same manner as copper does. Alternatively, the "inert" 5s² electrons of tin allow divalent intermediates which are covalently unsaturated and may absorb more methyl chloride.



followed by rearrangement as before. In support of the latter mechanism, yellow polymeric dimethyltin and molten colorless tin(II) chloride have been observed in "uncatalyzed" reactions, and the feasibility of reaction (8) was demonstrated by passing methyl chloride into melted tin(II) chloride, yielding methyltin trichloride.

(12) E. G. Rochow, *THIS JOURNAL*, **70**, 436 (1948).

(13) P. D. Zeman and F. P. Price, *ibid.*, **70**, 4222 (1948).

(14) D. T. Hurd and E. G. Rochow, *ibid.*, **67**, 1057 (1945).

MALLINCKRODT LABORATORY
HARVARD UNIVERSITY
CAMBRIDGE 38, MASS.

New Preparative Methods for Organotin Halides

By ALBERT C. SMITH, JR., AND EUGENE G. ROCHOW

RECEIVED MAY 9, 1953

During the investigation of the preparation of organotin halides by the direct reaction of an alkyl

halide with metallic tin,¹ some new methods for preparing organotin halides were found which represent improvements over the previous methods.²

Tin oxide was found to impart an inhibiting effect to the direct reaction of methyl chloride with metallic tin.¹ In an attempt to determine the reasons for the inhibition, methyl chloride was passed through a Pyrex tube containing powdered tin oxide (either with or without copper powder) at 300°. In either case, at the start of the reaction a narrow yellow band formed at the gas-inlet end of the tube and progressed slowly down the tube to the outlet end. During the passage of this band along the tube, trimethyltin chloride was produced. From its color and the known reaction of diethyltin with ethyl chloride to produce triethyltin chloride,³ we conclude that the material was dimethyltin. Its formation can be postulated as



The insoluble, non-volatile dimethyltin then absorbs more methyl chloride to form volatile trimethyltin chloride



Only one-third of the tin thereby is converted to volatile product, leaving a powdered mixture of tin(IV) compounds and causing the reaction zone to move along the tube.

In a similar way trimethyltin bromide was prepared from methyl bromide and tin oxide, and although no pure trimethyltin iodide was isolated from the analogous reaction of methyl iodide, a small amount of liquid with the expected boiling and freezing ranges was obtained.

Pfeiffer and Heller⁴ previously have reported the preparation of compounds of the type RSnI₃ by the reaction of RI with tin diiodide. We have extended this method in the present investigation to the combination of methyl chloride and tin dichloride at 300° to give methyltin trichloride.⁵ Similarly, in testing the effect of tin dioxide on the reaction between methyl chloride and tin, some tin dioxide was mixed with 8% by weight of copper(II) oxide and treated with methyl chloride at 300°. Within a few hours a considerable quantity of dimethyltin dichloride containing small amounts of tin dichloride was obtained. It seems probable that the tin dioxide is reduced by the methyl chloride to tin oxide and tin dichloride, both of which are capable of reacting with methyl chloride to produce methyltin chlorides. Such a mixture of methyltin chlorides is known to rearrange at the reaction temperature to produce dimethyltin dichloride as the principal product.

Using a reaction vessel of the type described in reference (1) we have found that methyl bromide

(1) A. C. Smith, Jr., and E. G. Rochow, *THIS JOURNAL*, **76**, 4193 (1953).

(2) E. Krause and A. v. Grosse, "Die Chemie der metall-organischen Verbindungen," Chapt. V. Borntraeger, Berlin, 1937, pp. 311-372.

(3) P. Pfeiffer, *Ber.*, **44**, 1269 (1911).

(4) P. Pfeiffer and I. Heller, *ibid.*, **37**, 4619 (1904).

(5) This reaction was carried out on a half-kilogram scale by Mr. John W. Farnham while associated with us in this investigation, and he found that the addition of 10% by weight of copper powder to the melted SnCl₂ enabled the reaction to proceed more smoothly and rapidly.

will react with *metallic tin* to form dimethyltin dibromide, but methyl iodide undergoes pyrolysis at the temperatures used with methyl chloride (300–400°) to form free iodine and no detectable amount of dimethyltin diiodide. Instead, some tin diiodide is formed which reacts with methyl iodide to give trimethyltin iodide.³

Similar reactions were carried out using ethyl chloride as a reactant, both with and without copper as catalyst.¹ Under conditions similar to those used for the preparation of dimethyltin dichloride, diethyltin dichloride was formed in very small quantities. Lower operating temperatures gave better results, and it was found advantageous to remove the product from the hot reaction zone as rapidly as possible, as by passing a stream of dry nitrogen over the surface of the molten tin and into the condenser. A spray-type reaction vessel was devised in order to obtain the largest possible surface of molten tin for reaction and to remove the product rapidly from the reaction zone. In this apparatus a fine stream of molten tin was sprayed into an atmosphere of ethyl chloride at 350°, and diethyltin dichloride was condensed from the excess gas. The conversion of ethyl chloride was low, due in part to the necessity for blowing two to four liters of ethyl chloride per minute past the atomizing jet of molten tin in order to maintain an adequate spray of metal; only a small part of this ethyl chloride could react in the 2.8 by 60 cm. chamber following the jet.

In the preparation of phenylchlorosilanes⁶ it has been found advantageous to add dry hydrogen chloride to the chlorobenzene used. This modification was tested with ethyl chloride and molten tin, but no improvement in the reaction was noted.

The greater difficulty experienced in preparing diethyltin dichloride over that found in preparing dimethyltin dichloride indicated that higher members of the series might be even less readily obtained. Several attempts to prepare *n*-butyltin chlorides and bromides or phenyltin bromides by reactions in sealed tubes or in vessels of the type described in reference 1 were unsuccessful.

Experimental

Trimethyltin Chloride.—A stream of CH₃Cl at 15 cc./min. was passed through a mixture of 20 g. of SnO and 2 g. of Cu at 300°. (CH₃)₃SnCl was formed, which upon recrystallization from benzene gave a melting point of 37.5–39.5° (37° in ref. 2).

Anal. Calcd. for C₃H₉SnCl: C, 18.08; H, 4.55; Cl, 17.80. Found: C, 17.78; H, 4.63; Cl, 18.07.

Trimethyltin Bromide.—A stream of CH₃Br at 15 cc./min. was passed through a mixture of SnO and 10% by weight of Cu. The initial reaction temperature rose to 500°, but was dropped rapidly to 300°. About 20 cc. of liquid was collected in 7 hr. The product was fractionally distilled, and (CH₃)₃SnBr was obtained at 163–166° (165° in ref. 2) m.p. 26–27° (27° in ref. 2).

Anal. Calcd. for C₃H₉SnBr: C, 14.81; H, 3.70. Found: C, 15.19; H, 3.79.

Trimethyltin Iodide.—Two hundred grams of CH₃I was passed through a tube containing a mixture of SnO and 10% by weight of Cu heated to 350°, at a rate corresponding to 29 cc. of liquid per hour. About 20 cc. of liquid was collected in the receiving flask. The liquid was fractionally distilled giving mostly methyl iodide, but a small amount of

liquid boiling at 160–170° (b.p. (CH₃)₃SnI 170° in ref. 2). The freezing range of this fraction was –3 to –5°.

Methyltin Trichloride.—A stream of CH₃Cl at 30 cc./min. was bubbled through molten anhyd. SnCl₂ at 365°. About 70 g. of crystalline product was obtained in four days. The product was easily recrystallized from benzene and sublimed readily. An analytical sample was prepared by sublimation into an evacuated vial which was then sealed.

Anal. Calcd. for CH₃SnCl₃: C, 5.00; H, 1.25. Found: C, 5.37; H, 1.47.

Dimethyltin Dichloride.—A stream of CH₃Cl at 10 cc./min. was passed through a mixture of 50 g. of SnO₂ and 4 g. CuO at 300°. A condensate appeared in less than 18 hr., and at 48 hr. a considerable quantity of (CH₃)₂SnCl₂ containing some SnCl₂ was obtained.

Dimethyltin Dibromide.—A reaction vessel of the type described in ref. 1 was charged with 200 g. of tin at 395° under an atmosphere of CH₃Br. More CH₃Br was bubbled through the molten metal at a rate of 15 cc./min. until a total of 400 g. had been introduced. About 30 cc. of (CH₃)₂SnBr₂ was obtained, which was recrystallized from benzene and was found to melt at 75–77° (74–76° in ref. 2). The crystals sublimed at room temperature.

Anal. Calcd. for C₂H₆SnBr₂: C, 7.78; H, 1.94. Found: C, 7.79; H, 2.06.

Methyltin Triiodide.—Two hundred grams of CH₃I was bubbled through 200 g. of tin at 385° at a rate of 15 cc. of liquid per hour. Bright orange-red crystals of SnI₂ formed on top of the molten tin, and a suspension of yellow crystals of SnI₄ in a yellow liquid collected in the condenser. The mixture was filtered to remove the solid, and the filtrate was reduced in volume by evaporation. A crop of yellow crystals of CH₃SnI₃ was obtained. The product was recrystallized from benzene and melted at 84–85.5° (86.5° in ref. 2).

Anal. Calcd. for CH₃SnI₃: C, 2.34; H, 0.59. Found: C, 2.86; H, 0.75.

Diethyltin Dichloride.—Molten tin was sprayed in a fine stream into a reaction chamber 60 cm. × 28 mm. heated to 350°, through which preheated C₂H₅Cl was passed. After 5 hr. a yield of 2 g. of (C₂H₅)₂SnCl₂ was obtained. The product was recrystallized from benzene and melted at 83–84° (84° in ref. 2).

Anal. Calcd. for C₄H₁₀SnCl₂: C, 19.41; H, 4.07. Found: C, 19.25; H, 4.19.

MALLINCKRODT LABORATORY OF HARVARD UNIVERSITY
CAMBRIDGE, MASS.

N-Substituted 2-Nitrocarbazoles¹

BY EUGENE SAWICKI

RECEIVED APRIL 25, 1953

In the investigation of chemical and physical properties of aromatic carcinogens and allied compounds, a series of N-substituted 2-nitrocarbazoles have been prepared. The analogous 2-nitrofluorene has been shown to be carcinogenic to rats.²

The physical properties and yields of the compounds are given in Table I. The chemical, physical and biological properties of these compounds are being further studied.

General Procedure.—Two ml. of 66% aqueous potassium hydroxide was added to a solution of 2.12 g. (0.01 mole) of 2-nitrocarbazole³ in 30 ml. of acetone. To this red-brown solution was added 0.015 mole of RX. The mixture was allowed to stand for 4 hours with occasional shaking. The change in color of the mixture from red-brown to yellow

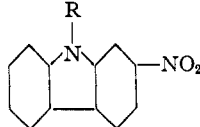
(1) This investigation was supported by research grant C-1308 from the National Cancer Institute of the National Institutes of Health, U. S. Public Health Service

(2) H. P. Morris, C. S. Dubnik, T. B. Dunn and J. M. Johnson, *Cancer Research*, **7**, 730 (1947).

(3) P. A. S. Smith and B. B. Brown, *This Journal*, **73**, 2435 (1951).

(6) E. G. Rochow and W. F. Gilliam, *This Journal*, **67**, 1772 (1945).

TABLE I



R	M.p., ^a °C.	Yield, %	Nitrogen, % Calcd.	Found
Methyl	166-166.5	98	12.4 ^b	12.4
Ethyl	148.5-149	85	11.7 ^c	11.6
Acetyl	229-230	85	11.0	10.8
Methanesulfonyl	202-204	80	9.66	9.97
C ₂ H ₅ OCO ^d	153-154.5	90	9.86	9.73
FC ₂ H ₄ OCO ^e	167-168	90	9.27	9.10
<i>p</i> -Methylbenzenesulfonyl	272	70	7.65	7.65
Propargyl ^f	188-189	95	11.2	10.9

^a All melting points are uncorrected. ^b Calcd. for C₁₃H₁₀N₂O₂: C, 69.03; H, 4.42. Found: C, 68.90; H, 4.65. ^c Calcd. for C₁₄H₁₂N₂O₂: C, 70.00; H, 5.00. Found: C, 70.01; H, 4.81. ^d Prepared using ethyl chlorocarbonate. ^e Prepared using β -fluoroethyl chlorocarbonate. ^f Propargyl bromide was generously supplied by General Aniline & Film Corporation.

denoted completion of the reaction. In some cases it was necessary to charge the mixture with a fresh batch of RX and alkali to complete the reaction. On completion of the reaction the yellow alkaline mixture was poured into excess water. Crystallization from heptane gave yellow needles and plates for the methyl and ethyl compounds, respectively. The remainder of the compounds were crystallized from heptane or benzene-heptane to give light yellow needles. Alcohol can also be used as a crystallizing solvent.

Acknowledgment.—The author is indebted to Dr. Francis E. Ray for his encouragement and interest in this work.

CANCER RESEARCH LABORATORY
UNIVERSITY OF FLORIDA
GAINESVILLE, FLORIDA

On the Formic Acid Rearrangement of 2-Phenyl-3-butyn-2-ol

BY TATSUO TAKEISHIMA

RECEIVED MARCH 14, 1953

Introduction and Discussion

It was reported by Rupe and Giesler¹ that 2-phenyl-3-butyn-2-ol (I) rearranged to β -methylcinnamaldehyde (II) in small yields. The semicarbazone obtained by them is described to give a melting point of 201° after the several crystallizations. However, the melting point of authentic semicarbazone of II has been reported as 205.5-206.5°, 206°.³

Hurd and Christ⁴ later tried the same reaction, but found no evidence to support Rupe and Giesler's statement. They obtained simply acetophenone (semicarbazone, m.p. 201°) in addition to tarry material.

Our work was undertaken to determine the exact nature of this reaction.

The reaction product obtained by treatment of I with formic acid was fractionated to yield principally two small fractions (b.p. 80-85° (12 mm.), *ca.*

(1) H. Rupe and L. Giesler, *Helv. Chim. Acta*, **11**, 656 (1928).

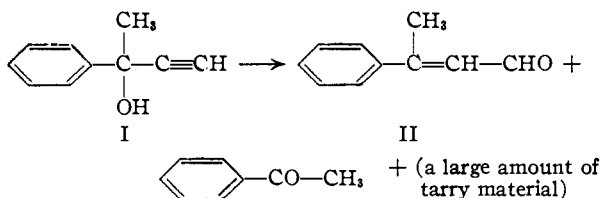
(2) J. F. Arens, D. A. van Dorp, G. van Dijk, B. J. Brandt, P. J. Hubers and H. Pieters, *Rec. trav. chim.*, **67**, 978 (1948).

(3) D. A. van Dorp and J. F. Arens, *ibid.*, **67**, 459 (1948).

(4) C. D. Hurd and R. E. Christ, *THIS JOURNAL*, **59**, 118 (1937).

109° (4 mm.)), the residue being a relatively large amount of tarry material. The lower-boiling fraction proved to be acetophenone. The higher-boiling fraction was reactive toward aldehyde reagents and was unsaturated. It gave a semicarbazone, the melting point of which was in good agreement with that of the semicarbazone of II, a 2,4-dinitrophenylhydrazone different from that of acetophenone, and on standing in air gave β -methylcinnamic acid. In addition a small amount of another semicarbazone corresponding to a C₁₀H₁₀O carbonyl compound was obtained from the same fraction and converted to the corresponding 2,4-dinitrophenylhydrazone which was different from that of II. These compounds were not investigated further owing to lack of material.

Thus, II and not the isomeric 3-phenyl-3-buten-2-one was isolated as the rearrangement product. Acetophenone formation may result from cleavage of II⁵ or I; its formation is consistent with the observation made by Hurd and Christ.⁴



Acknowledgment.—I wish to express my heartfelt thanks to Messrs. K. Furuhashi and K. Muto for the elementary analyses.

Experimental

2-Phenyl-3-butyn-2-ol (I).—The carbinol was prepared essentially according to the directions of Rupe and Giesler,¹ b.p. 101-104° (12 mm.).

Formic Acid Rearrangement of I.—13.5 g. of I was refluxed with 140 g. of *ca.* 80% formic acid for *ca.* 1.5 hr. and left overnight. The reaction product was then poured onto ice and potassium carbonate, extracted with ether, the ether extracts dried with calcium chloride, concentrated, and the residue was distilled under diminished pressure to yield the following fractions: (1) b.p. 80-85° (12 mm.), *ca.* 2 g., yield *ca.* 18%; (2) b.p. *ca.* 120° (12 mm.) or *ca.* 109° (4 mm.), 1.1 g., yield *ca.* 8%. In addition, a small amount of intermediate fraction boiling at 85-*ca.* 120° (12 mm.), and, as the residue, *ca.* 8 g. of brown-red tarry material were obtained.

Fraction (1) was only weakly reactive toward Schiff reagent.

Anal. Calcd. for C₈H₈O: C, 79.97; H, 6.71. Found: C, 79.71; H, 6.58.

Its semicarbazone was prepared in aqueous methanol and recrystallized from methanol to yield colorless needles, m.p. 198-200° (reported 201°,⁶ 198-200°,⁷ 207°,⁸ 206°⁸ for acetophenone semicarbazone⁸). (*Anal.* C, 61.29; H, 6.45; N, 23.26.) Its 2,4-dinitrophenylhydrazone was prepared from this semicarbazone in alcoholic sulfuric acid, and washed with ethanol to give orange crystals, m.p. 238-239.5°, which did not depress the melting point (240°) of authentic acetophenone 2,4-dinitrophenylhydrazone (reported 238-240°⁹).

Fraction (2) was a yellowish oil having a greater density than water. It was reactive toward Schiff reagent (light

(5) Cf. O. Wallach, *Ann.*, **289**, 338, 340 (1896); *Ber.*, **32**, 3338 (1899); L. Claisen, *Ann.*, **180**, 19 (1876).

(6) A. Klages, *Ber.*, **37**, 2306 (1904); F. Schlotterbeck, *ibid.*, **40**, 482 (1907).

(7) W. Borsche, *ibid.*, **34**, 4301 (1901).

(8) Beilstein, "Organische Chemie," Zweites Ergänzungs-Werk, Band 7, p. 217. The melting is described to range from 199° to 210° according to the rate of heating.

(9) W. Dirscherl and H. Nahm, *Ber.*, **73B**, 448 (1940).

greenish-yellow color was first produced, being accompanied by the formation of some dregs, then turning pink-purple), gently reduced ammoniacal silver nitrate on heating and decolorized bromine water.

Anal. Calcd. for $C_{10}H_{10}O$: C, 82.16; H, 6.90. Found: C, 81.57; H, 6.83.

Its semicarbazone was prepared in aqueous methanol and recrystallized from methanol to yield long faintly greenish-yellow plates, m.p. 206–206.5° (dec.) (reported 205.5–206.5°, 206°⁴ for semicarbazone of II).

Its 2,4-dinitrophenylhydrazone was prepared in alcoholic sulfuric acid, and recrystallized from pyridine containing some alcohol as dark red crystals, slightly soluble in alcohol, easily soluble in pyridine, m.p. 209–210°.

Anal. Calcd. for $C_{16}H_{14}O_4N_4$: C, 58.89; H, 4.32; N, 17.17. Found: C, 59.07; H, 4.26; N, 17.04.

The same 2,4-dinitrophenylhydrazone also was obtained directly from the above semicarbazone. A small amount of another semicarbazone, apparently isomeric, was obtained from the original mother liquor of the above semicarbazone and was recrystallized from methanol containing some water as colorless crystals, easily soluble in methanol, m.p. ca. 174°.

Anal. Calcd. for $C_{11}H_{13}ON_3$: N, 20.68. Found: N, 20.01.

This semicarbazone was converted to the corresponding 2,4-dinitrophenylhydrazone as mentioned above, and was washed with ethanol to give orange-red crystals, m.p. ca. 173° (*Anal.* C, 58.45; H, 4.10).

Autoxidation of Fraction (2).—The fraction was allowed to stand for a few days in the air, whereupon the greater part crystallized as colorless plates which were washed with ethanol and then had m.p. 98–99.5° (reported 98–99°, 97–98°, 97–98.5° for lower-melting β -methylcinnamic acid¹⁰).

(10) Beilstein, "Organische Chemie," Band 9, p. 614; Erstes Ergänzungswerk, Band 9, p. 254.

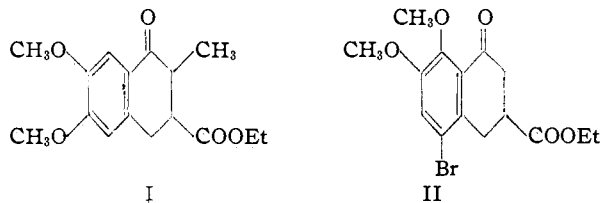
SCIENTIFIC RESEARCH INSTITUTE
TOKYO, JAPAN

Methoxy 3-Carboethoxy-1-tetralones

BY GORDON N. WALKER

RECEIVED APRIL 30, 1953

The carboethoxytetralones, I and II, are examples of a class of compounds which are difficult to synthesize by methods involving conventional cyclizations. These two compounds have now been prepared by polyphosphoric acid cyclization of the required acid esters, a method which has been applied successfully to other ketoesters of this type.^{1,2}



The precursor of I was obtained by Stobbe condensation of veratraldehyde with ethyl α -methylsuccinate, hydrolysis *in situ*, partial esterification, and hydrogenation of the resulting acid ester. Cyclization with polyphosphoric acid gave a mixture of I and the corresponding keto acid. Ketoester I was identified by the 2,4-dinitrophenylhydrazone. The synthesis of II involved Stobbe condensation of veratraldehyde with ethyl succinate, hydrogenation of the acid ester, and bromination. The latter reaction led primarily to nuclear monosubstitution

- (1) E. C. Horning and G. N. Walker, *THIS JOURNAL*, **74**, 5147 (1952).
(2) G. N. Walker, *ibid.*, **75**, 3387 (1953).

under the conditions described in the Experimental section. When the bromo acid ester so obtained was cyclized with polyphosphoric acid, II was formed in moderately good yield. The over-all yield of II from veratraldehyde was 14%. Although II could not be analyzed successfully, it was identified as the 2,4-dinitrophenylhydrazone.

It is possible that II will be of interest in connection with morphine synthetic studies. However, II appeared to be unstable, and attempts to alkylate it with halo-esters did not meet with success.

Experimental^{3,4,5}

α -Methyl-3,4-dimethoxyphenylitaconic Acid.—Veratraldehyde (87 g., 0.524 mole) and α -methylsuccinic ester (111 g., 0.591 mole) were added to a solution of 26.5 g. (1.15 g. atoms) of sodium in 500 ml. of absolute ethanol. The mixture was stirred and refluxed for three hours, and excess ethanol (270 ml.) was distilled. The residue was treated with 475 ml. of water. The solution was distilled until 430 ml. of solvents had been collected, and was refluxed for two hours. It was diluted with 1000 ml. of cold water and acidified with 75 ml. of concentrated hydrochloric acid. The solution at this point was decanted from the tar which separated, and was washed with ethyl acetate. Further acidification, refrigeration, and trituration of the crystals with ether afforded 11.2 g. (8%) of di-acid, m.p. 172–176° (dec.). Recrystallization from methanol gave colorless crystals, m.p. 178–180.5° (dec.).

Anal. Calcd. for $C_{14}H_{16}O_6$: C, 59.99; H, 5.76. Found: C, 59.99; H, 5.79.

Monoethyl Ester of α -Methyl-3,4-dimethoxyphenylitaconic Acid.—A solution of 9.4 g. (0.034 mole) of the itaconic acid in 115 ml. of absolute ethanol containing 6 ml. of concentrated sulfuric acid was refluxed for four hours. The neutral product, after isolation in the usual way, consisted of 5.4 g. of oil. This material, apparently the diester, gave the original acid upon hydrolysis with 20% sodium hydroxide solution for three hours. The acidic fraction of the product, isolated by acidification of a dilute alkaline solution, was 4.0 g. of yellow crystals and gum. Recrystallization of this material from aqueous methanol gave 2.8 g. of pale yellow crystals, m.p. 133–135°. Further recrystallization did not raise this melting point.

Anal. Calcd. for $C_{16}H_{20}O_6$: C, 62.32; H, 6.54. Found: C, 62.46; H, 6.98.

2-Methyl-3-carboethoxy-6,7-dimethoxy-1-tetralone and 2-Methyl-3-carboxy-6,7-dimethoxy-1-tetralone. (A) **Hydrogenation.**—A solution of 2.5 g. of the acid-ester from the preceding experiment in 100 ml. of glacial acetic acid containing 2.0 g. of 5% palladium-charcoal catalyst was shaken under hydrogen (40 lb.) at 75° for 1.5 hours. Filtration of the catalyst and evaporation of the solvent gave 2.5 g. of an oil.

(B) **Cyclization.**—The hydrogenated material was stirred with 14 g. of polyphosphoric acid, and the mixture was heated at 100° for 15 minutes. Hydrolysis of the cooled solution with cold water led to a gum, which was extracted with ethyl acetate. The organic solution was washed with dilute sodium hydroxide solution, dilute acetic acid, sodium bicarbonate solution and water, and was dried over magnesium sulfate. Evaporation of the solvent gave 1.7 g. of neutral product. Trituration with ether afforded 0.9 g. of crystals, m.p. 97–109°. Recrystallization from methanol gave pale yellow crystals, m.p. 120.5–121.5°.

Anal. Calcd. for $C_{16}H_{20}O_5$: C, 65.74; H, 6.90. Found: C, 65.70; H, 6.64.

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; red crystals, m.p. 241.5–243°.

Anal. Calcd. for $C_{22}H_{24}O_8N_4$: C, 55.93; H, 5.12. Found: C, 56.08; H, 5.22.

The basic solution, upon acidification with hydrochloric acid, deposited 0.4 g. of crystalline material, m.p. 194–201°.

- (3) Melting points are corrected.
(4) Analyses were carried out by Dr. William C. Alford and his staff.
(5) Infrared spectral measurements were carried out by Mrs. Iris Siewers and Miss Alice Bernardi of the Instrument Laboratory.

after trituration with methanol. Recrystallization from methanol gave golden crystals of 2-methyl-3-carboxy-6,7-dimethoxy-1-tetralone, m.p. 202–204.5°.

Anal. Calcd. for $C_{11}H_{10}O_5$: C, 63.62; H, 6.10. Found: C, 63.51; H, 6.32.

This compound was soluble in sodium bicarbonate solution, and gave a red precipitate with 2,4-dinitrophenylhydrazine.

Monoethyl Ester of 2-Bromo-4,5-dimethoxybenzylsuccinic Acid. (A) **Stobbe Condensation.**—A reaction of 89 g. (0.537 mole) of veratraldehyde with 110 g. (0.632 mole) of ethyl succinate in the presence of sodium ethoxide prepared from 13 g. (0.565 g. atom) of sodium was carried out as described previously.¹ The crude acid-ester was isolated (126 g.) and was not purified.

(B) **Hydrogenation.**—The acid-ester obtained as described in (A) was hydrogenated in glacial acetic acid in the presence of 10 g. of 5% palladium-charcoal catalyst at 80°, as described previously.¹ Ninety per cent. of the theoretical amount of hydrogen was absorbed during a period of 8 hours. The crude product was isolated by filtration of the catalyst and evaporation of the acetic acid, and weighed 128 g.

(C) **Bromination.**—A solution of the crude acid-ester from (B) (128 g., 0.43 mole) in 600 ml. of dry benzene was treated with 70 g. (0.44 mole) of bromine and 0.5 g. of magnesium. The solution was warmed on the steam-cone for two hours after the initial exothermic reaction subsided. It was cooled, diluted with ethyl acetate, washed with four portions of water, and dried over magnesium sulfate. Evaporation of the solvents and trituration of the dark residue with ether afforded 72 g. (36% from veratraldehyde) of crystalline product, m.p. 95–98°, which was sufficiently pure for further reactions. Recrystallization from ether gave colorless crystals, m.p. 110–112°.

Anal. Calcd. for $C_{15}H_{10}O_5Br$: C, 48.01; H, 5.10. Found: C, 48.19; H, 4.85.

3-Carboethoxy-5-bromo-7,8-dimethoxy-1-tetralone.—A mixture of 72 g. of the bromo-acid-ester from the preceding experiment and 400 g. of polyphosphoric acid was heated on the steam-cone with stirring for a half-hour. The cooled solution was hydrolyzed with ice and water, and the product was extracted with ethyl acetate. The organic solution was washed with dilute sodium hydroxide solution, dilute acetic acid and sodium bicarbonate solution, and was dried over magnesium sulfate. Evaporation of the solvent and distillation *in vacuo* of the dark, residual oil afforded 33.5 g. of bright-yellow oil, b.p. 218–227° (2.3 mm.), which crystallized very slowly, and which darkened gradually upon exposure to air. Recrystallization of the distilled material from the ether gave 26.3 g. (39%) of colorless crystals, m.p. 96.5–98.5°, which exploded when an attempt was made to burn a sample for carbon-hydrogen analysis. The infrared spectrum (chloroform) had peaks at 5.78 and 5.92 μ .

The 2,4-dinitrophenylhydrazone was recrystallized from ethyl acetate; orange crystals, m.p. 232–232.5°.

Anal. Calcd. for $C_{21}H_{21}O_8N_4Br$: C, 46.94; H, 3.94. Found: C, 46.41; H, 3.66.

Attempts to alkylate this keto-ester with γ -bromobutyronitrile and ethyl bromoacetate in the presence of sodium amide led to the formation of dark, tarry products and partial recovery of the starting material.

LABORATORY OF CHEMISTRY OF NATURAL PRODUCTS
NATIONAL HEART INSTITUTE
NATIONAL INSTITUTES OF HEALTH
BETHESDA 14, MARYLAND

Acetoacetylation of Aromatic Compounds by Boron Fluoride to Form β -Diketones. Failure with Boron and Aluminum Chlorides¹

By HOWARD G. WALKER, JR., JAMES J. SANDERSON² AND CHARLES R. HAUSER

RECEIVED APRIL 6, 1953

Meerwein and Vossen³ observed that the Friedel-Crafts type of acetylation of benzene or toluene with

(1) Paper I on Condensations.

(2) Carbons and Carbon Chemicals Company, Paton, 1946–1947.

(3) H. Meerwein and D. Vossen, *J. prakt. Chem.*, **141**, 149 (1934).

acetic anhydride by boron fluoride produced small amounts of the corresponding acetoacetophenones along with the acetophenones. The β -diketone was obtained in good yield by further treatment of acetophenone with the anhydride and the reagent.

We have obtained satisfactory yields of the corresponding β -diketones from toluene, anisole and mesitylene by employing a larger excess (four moles) of the anhydride (Table I). Some of the intermediate ketone was also usually isolated. The acetoacetylation is illustrated below with toluene. The procedure employed was unsatisfactory with benzene and acetic anhydride and with toluene and propionic anhydride even though the intermediate ketones were formed in fair yields (23–30%).

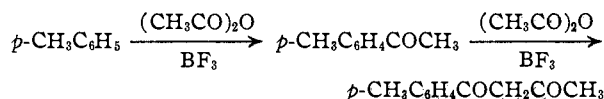


TABLE I

ACETOACETYLATION OF AROMATIC COMPOUNDS WITH ACETIC ANHYDRIDE BY BORON FLUORIDE

Aromatic cpd.	β -Diketone	B.p. or m.p., ^a °C.	Yield, %
Benzene	Benzoylacetone	2 ^b
Toluene	<i>p</i> -Methylbenzoylacetone	149–151 (13.5 mm.) ^c	43
Anisole	<i>p</i> -Methoxybenzoylacetone	M.p. 53–54.5 ^{d,e}	51
Mesitylene	Mesitylacetone	139–141 (8.5 mm.) M.p. 44.5–45.5 ^{f,g}	57

^a Melting points and boiling points are uncorrected. ^b Isolated as copper salt, m.p. 195–196° (W. Wislicenus and W. Stoeber, *Ber.*, **35**, 545 (1902)). ^c *Anal.* Calcd. for $C_{11}H_{12}O_2$: C, 74.96; H, 6.87. Found: C, 74.85; H, 7.12. The copper salt (light greenish blue) melted at 213–215°. Meerwein and Vossen (ref. 3) reported 155–156° (13 mm.) as the b.p. of the β -diketone and 129–130° as the m.p. of the copper salt. ^d E. Besthorn and G. Jaegle, *Ber.*, **27**, 910 (1894). ^e The copper salt (blue-green) melted at 210–211.5°. ^f R. C. Fuson and C. F. Woodward (*THIS JOURNAL*, **55**, 3474 (1933)) reported 45–46°. ^g The copper salt (dark grayish blue) melted at 193–194°.

That the products were β -diketones and not diketones having both of the acetyl groups attached to the aromatic rings was established by their characteristic enol test with ferric chloride, their complete solubility in alkali, and their conversion in high yield to copper salts with copper acetate. In these cases, exclusive acetylation at the α -hydrogen of the intermediate ketone evidently occurred even with acetomesitylene. However, in another connection, we have observed acetylation at the aromatic ring as well as at the α -hydrogen on treating mesitylacetone and acetic anhydride with boron fluoride, although no pure product was isolated.

In contrast to boron fluoride, boron chloride and aluminum chloride failed to effect the acetoacetylation of toluene in the presence of excess acetic anhydride, only the usual Friedel-Crafts acetylation to form the ketone being observed. Not even a trace of β -diketone could be detected by means of the sensitive ferric chloride enol test. Aluminum chloride has been observed to effect the diacetylation of mesitylene with excess acetyl chloride, but the second acetyl group as well as the first entered the aromatic ring.⁴

We further found that boron chloride fails to ef-

(4) C. A. Thomas, "Anhydrous Aluminum Chloride in Organic Chemistry," Reinhold Publ. Corp., New York, N. Y., 1941, pp. 320, 222.

fect the acetylation of the α -hydrogen of cyclohexanone or acetophenone with acetic anhydride to form the β -diketone; instead some of the ketone underwent self-condensation. Moreover, neither boron chloride nor aluminium chloride brought about acetylation of the α -hydrogen of even *p*-nitrophenylacetone, which is relatively reactive.

Similar observations were reported recently by Perfetti and Levine⁵ who showed that neither aluminium chloride nor stannic chloride can effect the acetylation of acetophenone to form benzoylacetone. However, these workers did realize this acetylation with zinc chloride and ferric chloride, although the temperature employed (110°) is much higher than that (0°) known to effect the reaction with boron fluoride.

Experimental

Acetoacetylations by Boron Fluoride.—A mixture of the aromatic compound (0.20 mole) and acetic anhydride (0.80 mole) was saturated with boron trifluoride at 0–10° in two to three hours and then stirred for an additional period to make a total reaction time of four hours. A solution of 100 g. of sodium acetate in 500 ml. of water was added and the reaction mixture refluxed 15–30 minutes. The mixture was cooled and extracted two or three times with 30–60° ligroin. The combined ligroin solution was washed three times with small portions of water and once with saturated sodium bicarbonate solution. The ligroin solution was then extracted several times with cold 2% sodium hydroxide solution until the ligroin phase no longer gave a positive

(5) B. M. Perfetti and R. Levine, *THIS JOURNAL*, **75**, 626 (1953).

enol test. The combined alkaline solution was acidified at 0° and the β -diketone taken up in ether, from which it was recovered by fractionation of the dried solution (Table I). The ligroin phase was dried and fractionated, yielding the monoketone and some high-boiling residue.

Experiments with Boron Chloride and Aluminum Chloride.—A mixture of toluene (0.20 mole) and acetic anhydride (0.8 mole) was saturated with boron chloride at 10° and the reaction mixture worked up as described above for boron fluoride. There was obtained a 27% yield of *p*-methylacetophenone, b.p. 101–102° at 13 mm.

A mixture of cyclohexanone (0.15 mole) and acetic anhydride (0.30 mole) was saturated with boron chloride in 40 minutes at 10°. After stirring 30 minutes longer, the reaction mixture was decomposed with excess sodium acetate in ice-water. The mixture was extracted with ligroin and, after drying, the ligroin solution was fractionated to give 2-cyclohexylidencyclohexanone⁶ (59%), b.p. 142–143° at 17 mm.⁶; semicarbazone, m.p. 178–179°.⁶

Mixtures of acetophenone and acetic anhydride and of *p*-nitrophenylacetone and this anhydride were treated similarly with boron chloride. There were obtained some dypnone and tarry material, respectively.

A mixture of *p*-nitrophenylacetone (0.02 mole), acetic anhydride (0.06 mole), aluminum chloride (0.14 mole) and 40 ml. of carbon disulfide was stirred 12 hours at room temperature. After distilling most of the solvent, the mixture was poured onto ice and hydrochloric acid to give the original ketone (colored).

In all of these experiments, the products gave negative enol tests with ferric chloride showing the absence of β -diketones.

(6) A. D. Petrov, *Bull. soc. chim.*, [1V] **43**, 1272 (1928).

DEPARTMENT OF CHEMISTRY
DUKE UNIVERSITY
DURHAM, N. C.

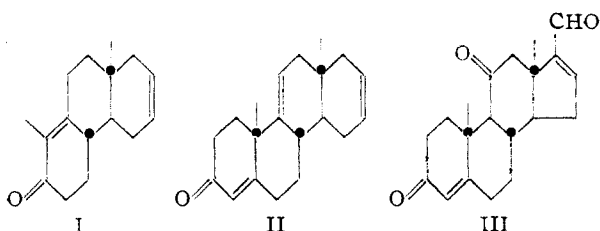
COMMUNICATIONS TO THE EDITOR

A SYNTHESIS OF *dl*-CORTISONE ACETATE

Sir:

We wish to report a direct synthesis of *dl*-cortisone acetate from the Woodward tricyclic ketone,¹ *dl*-1,14-dimethyl-2-keto- $\Delta^{1(11),6,9}$ -octahydrophenanthrene. A distinguishing feature of this synthesis is that the cortical side chain and the eleven oxygen function are introduced without protecting the α,β -unsaturated ketone in ring A.

Selective hydrogenation of the Woodward tricyclic ketone with palladium on strontium carbonate gave the oily dihydrotricyclic ketone I ($\lambda_{\text{max}}^{\text{alc}}$, 250 m μ , ϵ 15,300. Found: C, 83.5; H, 9.5). I was blocked in the 3 position by the methyl-



(1) Cf. R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, and W. M. McLamore, *THIS JOURNAL*, **74**, 4223 (1952).

anilinoethylene group¹ (m.p. 124–125°. Found: C, 82.8; H, 8.3.). The protected ketone was condensed with β -propiolactone² in the presence of potassium amide in ether. Removal of the blocking group yielded *dl*-1-(β -carboxyethyl)-1,14-dimethyl-2-keto- $\Delta^{6,10}$ -decahydrophenanthrene as a crystalline isomer³ (m.p. 171–173°. Found: C, 75.2; H, 8.7). This keto-acid was converted to the enol lactone (m.p. 100–102°) and thence by treatment with methylmagnesium bromide followed by cyclization¹ to the tetracyclic ketone II (m.p. 147–148°. Found: C, 84.9; H, 9.2). II was oxidized with iodine and silver acetate in wet acetic acid⁴ to give a β -*cis*-glycol. Reaction with acetone gave *dl*-3-keto-16 β ,17 β -dihydroxy- $\Delta^{4,9(11)}$ -D-homoandrostadiene acetonide⁵ (m.p. 174–175°). The structure of the acetonide was proved by conver-

(2) Cf. T. L. Gresham, J. S. Jansen, F. W. Shaver, M. R. Frederick and W. L. Beears, *ibid.*, **73**, 2345 (1951), and earlier papers.

(3) The mother liquor from the isolation of this material undoubtedly contained the epimeric compound.

(4) A reagent described in a private communication from R. B. Woodward; cf. S. Winstein and R. E. Buckles, *THIS JOURNAL*, **64**, 2787 (1942).

(5) It is to be noted that our acetonide differs from Woodward's¹ in that it was derived from a β -*cis*-glycol whereas his was from an α -*cis*-glycol, where α and β designate configuration corresponding to standard steroid convention.