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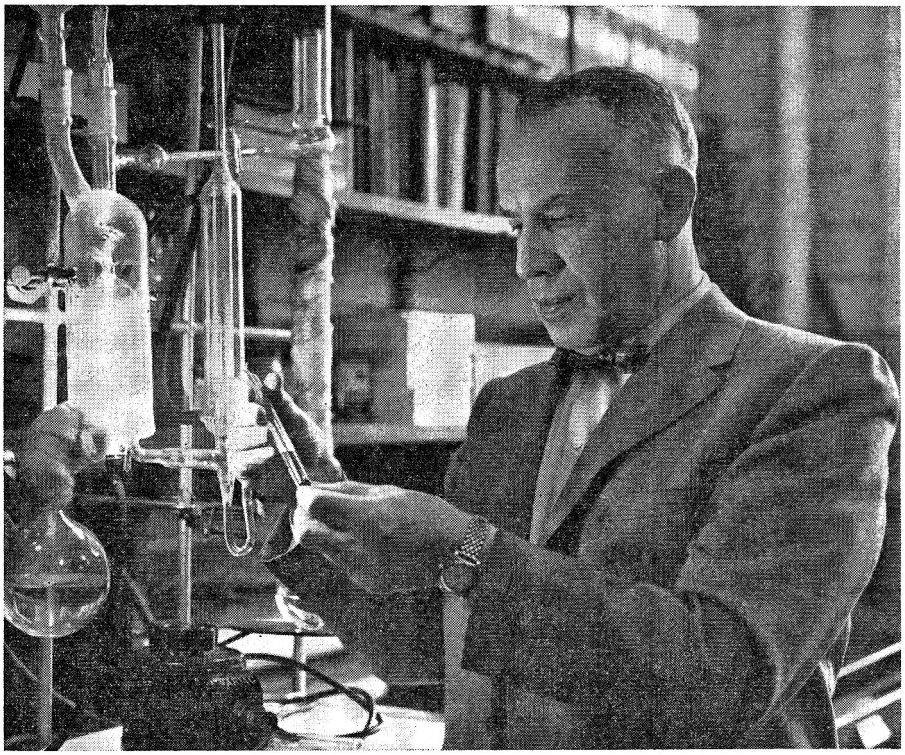
MORRIS S. KHARASCH

(1895–1957)

The services rendered to the Journal of Organic Chemistry by Dr. Morris S. Kharasch were very extensive and most significant. It was he, more than anyone else, who gave the necessary impetus to its founding. Then, in several capacities, he helped nurture its growth and development. He served for many years on the Board of Editors and on the Executive Committee, giving unsparingly of his time and energy. Over the years of his very active life he was a regular contributor to its pages.



The money which came to the Journal from the original publishers, the Williams and Wilkins Co., was used for the printing of extra pages. There were times when even this money was not adequate to publish additional worthy papers. Then it was that Dr. Kharasch, assisted by a small group, displayed an extra talent for obtaining supplementary financial assistance from various sources, particularly the chemical industries. Subsequently the Journal was put on a sounder fiscal basis by a finance committee, of which Dr. Kharasch was chairman. The equitable arrangement, devised by this committee,

involving two types of subscription was cordially supported and proved eminently satisfactory. Some time after this plan was inaugurated the Journal, which had always been associated with the Division of Organic Chemistry of the American Chemical Society, became one of the publications of the American Chemical Society. The important role played by Dr. Kharasch in the sound growth of the Journal cannot be over-emphasized.

Dr. Kharasch was born in the Ukraine on August 24, 1895. He was educated at the University of Chicago from which he received the Ph.D. degree in 1919. During both World Wars he made notable contributions to the Chemical Warfare Services. Actually, at the time of his death in Copenhagen on October 9, 1957, he was actively assisting the Chemical Corps. He made significant contributions to the Government Synthetic Rubber Project. In his work for the U. S. Government, whether as a contractor or as an adviser, he always brought a fresh point of view that was realistic, practical, and stimulating.

His numerous publications cover a broad range of researches with particular emphasis in recent years on free radicals in reaction mechanisms. His book with Dr. Otto Reinmuth on "Grignard Reactions of Nonmetallic Substances" is one of classical excellence. In his research publications and lectures he demonstrated a high measure of vigorous, critical insight that reflected his personal interest and dedication to his chosen profession.

After the completion of his formal training, Dr. Kharasch served on the chemistry staff at the University of Maryland until 1928 when he returned to the University of Chicago. At the time of his death he was Director of the Institute of Organic Chemistry at the University of Chicago.

The illustrious career of Dr. Morris S. Kharasch will long be remembered not only for his notable researches and writings in the field of organic chemistry, his teaching and training of many students, his professional services to the Government, but also for his effective work over a long period to set a sound course for the Journal of Organic Chemistry.

HENRY GILMAN

[CONTRIBUTION NO. 1485 FROM THE STERLING CHEMISTRY LABORATORY, AND THE BINGHAM OCEANOGRAPHIC LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. XLVI. Phospholipids of a Sea Anemone[1]

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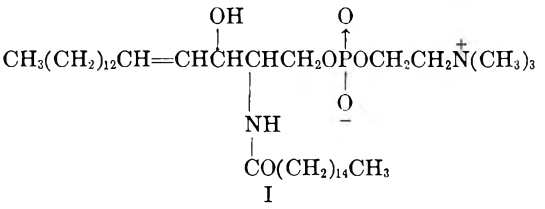
WERNER BERGMANN AND ROBERT A. LANDOWNE

The phospholipids of the sea anemone, *Anthopleura elegantissima*, have been isolated and analyzed. The principal, if not the only, representatives were *sphingomyelin* and *plasmalogen* in a ratio of twenty to one. The sphingomyelin consisted mainly of the *N-palmityl* type. The plasmalogen fraction was obtained in a high state of uniformity. Its rather small degree of unsaturation, its infrared spectrum, and the presence of only one chain of methylene groups showed the acetal attachment of the aldehyde moiety in agreement with Feulgen's original formulation.

In connection with our comparative studies on the composition and evolution of the lipids of marine invertebrates, we have investigated the phospholipids of the common sea anemone of the West Coast, *Anthopleura elegantissima*.[2] The composition of the phospholipid mixture was of an exceptional simplicity which made possible a relatively facile isolation in a pure state of its only representatives, sphingomyelin and plasmalogen. They occurred in a ratio of about twenty to one, and plasmalogen, the minor component, constituted about 0.1 per cent of the dry weight of the anemone.

The sphingomyelin, a colorless powder, m.p. 181.5–183° (dec.) appeared to be free of other phospholipids when subjected to paper strip chromatography. Its elementary analysis indicated that it was a sphingomyelin with an *N*-palmityl group (I). In accordance with this structure the



I

sphingomyelin upon hydrolysis afforded choline, sphingosine, and palmitic acid. The choline was isolated as its reineckate, and the sphingosine was characterized as its triacetyl derivative, m.p. 97°; $[\alpha]_D$ −18.2°. The palmitic acid was isolated as its methyl ester and determined by means of gas chromatography.[3] Besides methyl palmitate the ester mixture contained small amounts of esters of acids of the order C_{12} to C_{20}. The low iodine number of the ester mixture indicated unsaturation not exceeding 0.1 double bond per mole. Similar results were obtained by means of gas chromatography of the brominated esters, and catalytic hydrogenation of spingomyelin. In the latter only 0.1 mole of hydrogen was consumed in addition to the one mole required to saturate the double bond in the sphingosine moiety. The infrared spectrum of the dihydrosphingomyelin differed from the unsaturated material only in the diminution of the absorption band at 10.3 microns, which is attributable to the disappearance of the *trans*-substituted double bond.

The simplicity of the phospholipid mixture made possible the isolation of the plasmalogen fraction without taking recourse to hydrolyses. Only selective treatments with organic solvents at room temperature were required, ensuring the isolation of an unaltered plasmalogen fraction. The material thus obtained appeared to be of a uniformity rarely if ever equaled before. It was a white wax, which upon heating decomposed above 200°. Its optical activity, $[\alpha]_D$ −7.85°, agreed in direction and magnitude with that of Rapport's plasmalogen fraction,[4] but not with that of Thannhauser's sample; $[\alpha]_D$ +6.25°.[5] The plasmalogen rapidly gave a positive Schiff's aldehyde test. Its elementary analysis, and the quantitative determinations of choline and glycerol showed that the aldehyde group constituted the only long methylene chain in the molecule. Hydrolysis afforded a mixture of aldehydes in a yield of nearly ninety per cent. The aldehydes showed the well-known tendency to polymerize, and some crystalline polymeric product was obtained. The unpolymerized material was converted to the 2,4-dinitrophenylhydrazones, whose elementary

(1) This investigation was supported by a research grant, Nonr 253(00) from the Office of Naval Research.

(2) The authors express their gratitude to Dr. E. C. Dougherty of the University of California School of Medicine for a generous supply of this anemone.

(3) The authors are greatly indebted to Dr. S. R. Lipsky of the Yale University School of Medicine for his help in performing the gas chromatographic analyses.

(4) M. M. Rapport, B. Lerner, N. Alonzo, and R. E. Franzl, *J. Biol. Chem.*, 225, 859 (1957).

(5) S. J. Thannhauser, N. F. Boncoddo, and G. Schmidt, *J. Biol. Chem.*, 188, 417 (1951).

TABLE I

COMPARISON OF CEREBROSIDE AND PHOSPHOLIPID CONTENTS

Anemone	Cerebroside, %	Lecithin, %	Cephalin, %	Sphingomyelin, %	Plasmalogen, %
Anthopleura	<0.1	<0.1	<0.1	2.00	0.11
Gyrostoma	0.83	3.08	0.97	0.25	..

analysis corresponded best with the derivative of a C_{18}-aldehyde. It must be assumed, however, that this derivative represented mainly the lower homologs of the aldehyde mixture, and that the polymer was composed of the higher homologs which are particularly prone to polymerize. The iodine number of the hydrazone was equivalent to 0.23 double bond per molecule. Almost the same degree of unsaturation was observed for the plasmalogen itself. All unsaturation of the latter therefore appears to reside in the aldehyde moiety.

The infrared spectrum of the plasmalogen (Fig. 1] is notably void of a carbonyl band. Its absence

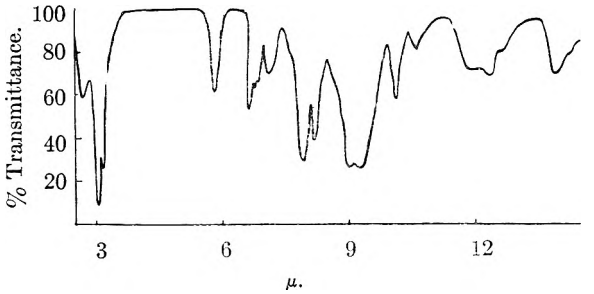


Fig. 1. Infrared absorption spectrum of sea anemone plasmalogen

not only excludes significant quantities of any of the common phosphatides with ester or amide groups, but also the presence of an ester group in the plasmalogen itself. This supports the chemical observation that the aldehydogenic unit is the only aliphatic chain in the molecule. The infrared spectrum also shows a broad hydroxyl band at 3.04 microns which is also shown by a typical lecithin such as has been prepared by Baer *et al.*[6] Since lecithin possesses no free C—OH group, this broad band is due either to the P-OH or the N-OH group, the same groups must be the cause for the analogous band in the plasmalogen spectrum. Absent in the latter is a sharp peak at lower wavelengths such as would be indicative of the presence of either an α or β-hydroxyl group in the glycerol fragment of the plasmalogen.

DISCUSSION

Last year, Rajagopal and Sohonie[7] reported the results of their titrimetric analyses of certain complex lipids of the sea anemone, *Gyrostoma sp.*, which is common along the shores of Bombay. By making standard assumptions and without isolating any of the lipid components they estimated by standard procedures that the dry animal contained various phospholipids in amounts listed in Table I, where they are compared with the present findings. The differences between the two findings are surprisingly large, the more so because both species are fairly closely related members of the *Actinaria*. While it is possible that seasonal and environmental differences may account for some variations in lipid content, they can hardly be held responsible for such extraordinary discrepancies. These point, however, to the dangers which are inherent in a casual transfer of methods of estimation from higher to lower animals. An *a priori* assumption of considerable chemical similarity among quite unrelated organisms may easily obscure the true purpose of a comparative study. One cannot always regard as a true measure of sphingomyelin the difference between total and acid-soluble phosphorus, nor estimate correctly the amount of phospholipids on the assumption that they contain four per cent of phosphorus. Equally unreliable is a procedure of separating phospholipids which is based on suspected differences in solubilities. Thus Baer *et al.*[6] have shown recently that contrary to expectations hydrolecithins are quite difficultly soluble in ether. Additional examples of the well-known influence of impurities on solubilities will be found in the experimental section of this report.

In our investigation we have attempted to work as quantitatively as possible, and to isolate and characterize all phospholipid fractions present in more than trace amounts. The success met by such measures is best illustrated by the fact that it was possible to isolate from two kilograms of anemones a 450-mg. sample of plasmalogen of remarkable uniformity. Had they been present in equal or even significantly smaller amounts, lecithins and cephalins, and also cerebrosides, would not have been overlooked. An explanation of the remarkable absence of such compounds must await further study. Whatever its outcome may be, it is doubtful that it will detract from the dominant position of the sphingosides among the phospholipids of sea anemones.

(6) E. Baer, D. Buchnea, and A. G. Newcombe, *J. Am. Chem. Soc.*, **78**, 232 (1956).

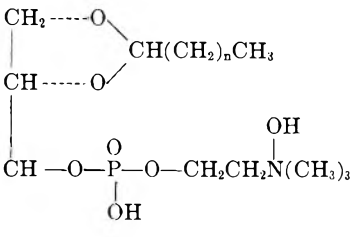
(7) M. V. Rajagopal and K. Sohonie, *Biochem. J.*, **65**, 34 (1957).

The plasmalogen which was isolated as the minor component belongs to the group of widely distributed phosphatides whose most characteristic property is the release of higher fatty aldehydes when treated with weak mineral acids. The adequacy of an acetal structure (II) for plasmalogens, first proposed by their discoverers, Feulgen and Bersin[8] and more recently supported by Thannhauser *et al.*[5] has been questioned repeatedly.[4,9–12] The alternate structures which have been proposed, III,[10,11] IV,[4,11] and V[12] are based on a disparity between the rates of aldehydogenesis of native plasmalogen and a synthetic glyceryl acetal,[4] the possible presence of a second aliphatic chain, unsaturation,[4,11] and hydrogenation to a compound believed to be the butyl alcohol phosphoric acid.[10,12] While these structures adequately express the behavior of previously reported plasmalogens, some admittedly impure, they do not agree with the physical and chemical properties of sea anemone plasmalogen which we hold to be pure.[13] Elementary aualyses, determinations of glycerol and choline, and the results of hydrolysis, coupled with the absence in the infrared spectrum of an ester carbonyl band (Fig. 1), exclude structures IIIb, IVb, Vb. The absence of a C—OH band in the infrared spectrum of the present plasmalogen, and the presence of less than one fourth of a double bond equivalent of unsaturation, exclude structures IIIa, IVa, and Va (lysoplasmalogens).[4] The only structural formula therefore which is in best agreement with our observations is Feulgen's original acetal structure II, in which choline is the base and the aldehyde chain represents a mixture of saturated and unsaturated units of an average length of twenty or twenty-two carbon atoms.[14]

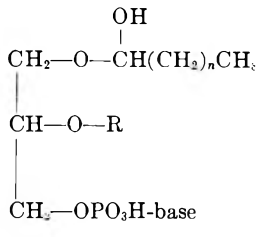
EXPERIMENTAL

Isolation of the phospholipids. The alcohol-preserved sea anemones, *Anthopleura elegantissima* (2 kg.), were ground in 200-g. lots in a Waring blender for 2–3 min. with 150 ml. of a mixture of two volumes of chloroform and one of methanol. The homogenate was filtered by suction, the fleshy parts treated as before and finally washed with 200 ml. of chloroform. After air-drying the residual material weighed 351 g.

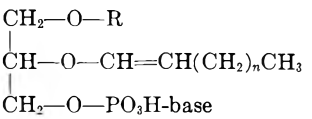
All extracts were combined and washed according to the procedure recommended by Folch *et al.*[15] The extract was placed in a beaker at the bottom of a cylindrical tank which was carefully filled with water of a volume ten times that of the extract. After standing overnight, the water was siphoned off except for a thin layer containing a small amount of fluffy material which adhered to the surface of the chloro-



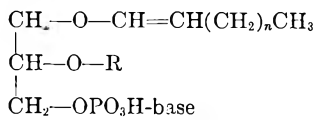
II



III



IV



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a) R = H; b) R = $CO(CH_2)_mCH_3$;

base = $-CH_2CH_2\overset{+}{N}(CH_3)_3$ or $-CH_2CH_2NH_2$

(8) R. Feulgen and Th. Bersin, *Z. physiol. Chem.*, 260, 217 (1939).

(9) M. Anchel and H. Waelsch, *J. Biol. Chem.*, 152, 50 (1944).

(10) E. Klenk and H. Debuch, *Z. physiol. Chem.*, 296, 179 (1954); 299, 66 (1955).

(11) M. M. Rapport and R. E. Franzl, *J. Neurochem.*, 1, 303 (1957).

(12) G. V. Marinetti and J. Erbland, *Biochim. Biophys. Acta* 26, 429 (1957); G. V. Marinetti, J. Erbland and E. Stotz, *J. Am. Chem. Soc.*, 80, 1624 (1958).

(13) We have recently isolated from the sponge, *Spheciospongia vesparia*, an aldehydogenic lecithin whose properties are best expressed by the plasmalogen structure first proposed by Rapport *et al.*,[14,11] and supported by Marinetti.[12] This compound contains an aldehyde in an enol ether linkage and one fatty acid attached to the glycerylphosphorylcholine moiety. It appears therefore that there are at least two types of plasmalogens occurring in nature. If the term plasmalogen is to be retained it should be used to designate the aldehydogenic phospholids in general rather than a special type.

(14) A related compound, derived from palmital and ethanolamine has been synthesized by M. J. Egerton and T. Malkin, *J. Chem. Soc.*, 2800 (1953).

(15) J. Folch, I. Ascoli, M. Lees, J. A. Meath, and F. N. LeBaron, *J. Biol. Chem.*, 191, 833 (1951).

form solution remaining in the beaker. The final separation was carried out in a separatory funnel, and the water and fluffy material were extracted twice with 25 ml. of chloroform which was then combined with the main extract.

The combined extracts were added to 3.5 times their volume of acetone which brought about precipitation of the bulk of the phospholipids. The mixture was kept at 5° overnight and the precipitate was collected by centrifugation; *Fraction A;* 8.3 g. The solvent of the supernatant liquid was removed at 25° in a rotary evaporator. There remained 49.5 g. (12.5% of the dry weight) of a yellow-brown oil. It was digested with 200 ml. of alcohol-free acetone, and the precipitate which separated was collected by centrifugation; *Fraction B;* 1.3 g. The dried remains of the anemones were extracted further in Soxhlet apparatus, first with ether for 40 hr., and then with ethanol for 90 hr. Evaporation of the ether extract gave only a small amount of oil, which upon treatment with acetone afforded less than 100 mg. of an untractable gum, which was discarded. Evaporation of the ethanol-extract left a more significant amount of residue which was dissolved in chloroform. The chloroform solution was washed with water, concentrated to 50 ml. and then mixed with 175 ml. of acetone. A dark, waxy precipitate formed, which was collected by centrifugation; *Fraction C;* 0.35 g.

Sphingomyelin. Fraction A, 8.3 g., was a light tan colored material, rather stable in the presence of air and moisture. Its infrared spectrum showed an amide carbonyl band. The fraction contained nitrogen, phosphorus and choline in a ratio of 2:1:1. It gave a negative carbohydrate test. The material was dissolved in 35 ml. of chloroform and precipitated by addition of 3.5 volumes of acetone, and this purification was repeated once more. It did not entail a noticeable loss of phosphorus-containing material. The final product was a nearly white powder, 8.16 g., m.p. 181.5–183° (dec.). The properties of *Fraction C* were quite similar to those of Fraction A. Its purification afforded an additional amount of sphingomyelin.

The sphingomyelin was subjected to paper strip chromatography[16] on a Whatman No. 1 paper and with a solvent mixture of chloroform and ethanol, 4:1, saturated with water. Upon development with phosphomolybdic acid and acidic stannous chloride only one spot was obtained. In a separate test no spots were developed with ninhydrin. All but less than 1 mg. of a 100-mg. sample of sphingomyelin was soluble in 10 ml. of cold glacial acetic acid, indicating that the material was essentially free of cerebrosides.

Anal. Calcd. for $C_{39}H_{81}N_2O_7P$(*N*-palmityl derivative): P, 4.30; N, 3.89; choline, 16.81. Found:[17] P, 4.51; N, 3.95; choline, 17.1. N/P, 1.94; choline/P, 0.97.

Hydrolysis of sphingomyelin[18] *and identification of choline.* One g. of sphingomyelin was refluxed for 4 hr. with 90 ml. of 2*N* sulfuric acid in methanol. The methyl esters were then extracted with four 50-ml. portions of petroleum ether. The methanolic layer was made alkaline (*p*H 8) with 30% KOH in methanol, filtered, acidified to *p*H 6 with glacial acetic acid, and then concentrated *in vacuo* to a volume of 25 ml. About 15 ml. of water was added to dissolve the salts, the solution was made alkaline and was then extracted with three portions of 50 ml. of ether to remove the sphingosine. The remaining methanolic solution was acidified to *p*H 4 with glacial acetic acid, and was mixed with an excess of a 2% aqueous solution of ammonium reineckate. The mixture was cooled for 1 hr. to 4°, and the precipitate was then collected on a glass filter. The choline reineckate thus obtained was washed with cold water, cold ethanol, dried, and then recrystallized from acetone; λ_{max}: 327 (ϵ = 5.88 × 10^3); 527. Reported[19] λ_{max}: 327 (ϵ 5.81 × 10^3); 526. The ether extract containing the sphingosine was washed with two 25-ml. portions of water and dried over anhydrous sodium sulfate. The solvent was then removed *in vacuo*, and the pale yellow, waxy residue, 0.30 g. (71%) was triturated twice with petroleum ether to give the crude sphingosine in the form of a white powder, m.p. 60–61°. It was at once converted into the triacetate by heating with pyridine and acetic anhydride.[18] The triacetate was recrystallized three times from hexane when a further recrystallization did not raise the melting point, m.p. 96–97°, soft needles; $[\alpha]_D^{23°} = -18.2°$.

Anal. Calcd. for $C_{24}H_{43}NO_5$: C, 67.73; H, 10.18; N, 3.29. Found: C, 67.67; H, 10.0, N, 3.46.

Hydrogenation of sphingomyelin. The sphingomyelin was reduced with an Adam's catalyst in acetic acid in Ogg and Cooper's micro-hydrogenation apparatus.[20] On the basis of the molecular weight of sphingomyelin (721), the hydrogen uptake was 1.09 moles, which included 0.08 mole for the fatty acid moiety. The recovery of dihydrosphingomyelin was nearly quantitative; m.p. 186–186.5°.

Anal. Calcd. for $C_{39}H_{83}N_2O_7P$: N, 3.88; P, 4.28. Found: N, 4.02; P, 4.20.

Isolation of the acidic fragment. The petroleum ether solution containing the methyl esters formed during the acid hydrolysis of the sphingomyelin was washed quickly with 50 ml. of sodium bicarbonate solution and 50 ml. of water, and was then dried over anhydrous sodium sulfate. Removal of the solvent *in vacuo* afforded 0.35 g. (95+%) of nearly colorless esters. Analysis of the esters by gas chromatography[3,21] showed methyl palmitate to be the only major component and the methyl esters of other acids from C_{12} to C_{20} to be rather minor constituents; m.p. 30–34°, $n_D^{45°}$ 1.4315. (Methyl palmitate, m.p. 30°, $n_D^{45°}$ 1.4318.)

Anal. Calcd. for $C_{17}H_{34}O_2$: C, 75.56; H, 12.59. Found: C, 75.77; H, 12.29.

The iodine number of the ester mixture, as determined by Yasuda's method,[22] was only seven, corresponding to not more than 0.08 double bond per mole of methyl palmitate. A sample of the ester mixture, 113 mg., was dissolved in 25 ml. of ether and brominated with Yasuda's reagent. After standing for 15 min., the mixture was washed with water, twice with 5% sodium bicarbonate solution, and twice more with water. After drying the solution over anhydrous sodium sulfate, the ether was removed and the residue of saturated and brominated esters, 116 mg. (95+%), was submitted to chromatographic analysis under the same conditions as before. The only observable changes in the chromatogram were the disappearance of the small peaks at C_{12} and C_{20}.

Plasmalogen. The infrared spectrum of Fraction B, 1.3 g., and a positive reaction with digitonin indicated the presence of significant amounts of sterols and esters. The fraction was therefore washed twice with 100 ml. each of acetone, and when this did not bring about complete removal of the sterols twice more with 100 ml. each of anhydrous ether. The product thus obtained was free of sterols. It was dissolved in 10 ml. of chloroform and precipitated by addition of 35 ml. of acetone. After an additional reprecipitation, the plasmalogen was obtained as a white, semi-crystalline, waxy material; 0.45 g. (0.11% of total dry weight of anemone). Depending on the rate of heating the plasmalogen softened around 100° and decomposed above 200°. With Schiff's reagent, fuchsin and sulfurous acid, plasmalogen

(16) T. H. Bevan, G. I. Gregory, T. Malkin, and A. G. Poole, *J. Chem. Soc.*, 841 (1951).

(17) P and N analyses by Schwarzkopf Microanalytical Laboratory, Woodside 77, N. Y. Choline was determined gravimetrically as the reineckate.

(18) H. E. Carter, W. P. Norris, F. J. Glick, G. E. Phillips, and R. Harris, *J. Biol. Chem.*, **170**, 269 (1947).

(19) R. W. Engel, W. D. Salmon, and C. J. Ackerman, *Methods of Biochemical Analysis*, **1**, 274 (1954).

(20) C. L. Ogg and F. J. Cooper, *Anal. Chem.*, **21**, 1400 (1949).

(21) S. R. Lipsky and R. A. Landowne, *Biochim. et Biophys. Acta*, **27**, 666 (1958).

(22) M. Yasuda, *J. Biol. Chem.*, **94**, 401 (1931).

gives a fairly rapid positive test; $[\alpha]_D^{27.5} = -7.85°$ (1.905% in absolute ethanol, $\alpha = -0.15°$).

Anal. Calcd. for $C_{30}H_{64}NO_7P$: P, 5.32; N, 2.41; glycerol, 15.8; choline, 20.62. Found:[17] P, 5.30; N, 2.42; glycerol, 15.5, choline, 20.6. N/P, 1.01; choline/P, 0.99.

Hydrolysis of plasmalogen. A 0.1-g. sample was heated to boiling on a steam bath with 10 ml. of ethanol and 5 ml. of concentrated hydrochloric acid. Fifteen ml. of water and an additional 2 ml. of hydrochloric acid were added and the heating continued for a few minutes. The mixture was left standing at room temperature overnight when a flocculent precipitate was formed. This was collected by centrifugation and dissolved in low-boiling petroleum ether. The acid solution remaining from the plasmalogen hydrolysis was extracted three times with 25 ml. each of low-boiling petroleum ether. All extracts were combined, dried over anhydrous sodium sulfate, and the solvent was evaporated *in vacuo*. The residue consisted of a mixture of aldehydes in form of a soft wax, 50 mg. (89%). Its infrared spectrum showed a strong carbonyl band at 5.84 microns.

A significant part of the aldehyde mixture rather rapidly polymerized to form a product quite difficultly soluble in ethanol. Recrystallization of the polymer from ethanol gave needle-shaped crystals, m.p. 74–77°. The polymers of hexadecanal and octadecanal melt near 73°.

The soluble, unpolymerized part of the aldehyde fraction was treated with Brady's reagent in the standard manner. The 2,4-dinitrophenylhydrazones were purified by chromatography over alumina in a benzene solution and by two recrystallizations from 80% ethanol; m.p. 90–105°. The dinitrophenylhydrazone of hexadecanal has been reported to melt at 105–107°, and its higher homologs somewhat higher.

Anal. Calcd. for $C_{24}H_{40}N_4O_4$: C, 64.29; H, 8.93. Found: C, 64.81; H, 8.82.

Unsaturation. The unsaturation of the unhydrolyzed plasmalogen and the 2,4-dinitrophenylhydrazones of the aldehyde mixture was determined according to Yasuda's method[22] with 0.02*N* pyridine sulfate dibromide as the brominating agent. The average of two closely agreeing determinations were as follows: plasmalogen: iodine number, 10; double bonds per mole, 0.24; aldehyde-2,4-dinitrophenylhydrazones: iodine number, 13; double bonds per mole, 0.23.

NEW HAVEN, CONN.

[CONTRIBUTION NO. 1490 FROM THE STERLING CHEMISTRY LABORATORY, YALE UNIVERSITY]

Contributions to the Study of Marine Products. XLVII 22-Dehydrocholesterol[1]

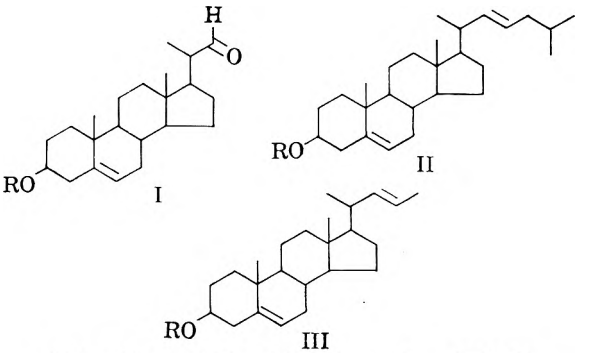
WERNER BERGMANN AND JOHN P. DUSZA

Received February 24, 1958

22-Dehydrocholesterol and 3β-hydroxy-$\Delta^{5,22}$-choladiene have been prepared by means of the Wittig reaction.

Among naturally occurring sterols with a methyl or ethyl group at the 24 position of their side chain those with a Δ^{22}-*trans*-oriented double bond are relatively common. The best known examples are ergosterol and stigmasterol. One might expect on biogenetic grounds that the corresponding derivative of cholesterol is also present in natural sterol mixtures. As yet, however, the natural occurrence of 22-dehydrocholesterol (II), while often suspected, has not been convincingly established. In connection with the synthesis of other sterols now in progress in this laboratory this unknown sterol has now been prepared, not only in order to obtain a reference sample to guide isolation studies but also to obtain starting material for the preparation of the ergosterol analog of cholesterol and its irradiation products.

The sterol was prepared from 3β-acetoxy-5-cholen-22-al (1) by means of the Wittig reaction which had previously been used with conspicuous success in the synthesis of 24-methylenecholesterol,[2,3] 24-[4,5] and 25-dehydrocholesterol.[3,5] Although the Wittig reaction is known to be nonstereospecific,[6] in the present synthesis the interaction between the aldehyde and the ylide generated



a) R = H; b) R = $COCH_3$ c) R = COC_6H_5

(1) This investigation was supported by a research grant, Nonr 253(00) from the Office of Naval Research.

(2) W. Bergmann and J. P. Dusza, *Ann.*, **603**, 36 (1957).

(3) D. R. Idler and U. H. M. Fagerlund, *J. Am. Chem. Soc.*, **79**, 1988 (1957).

(4) U. H. M. Fagerlund and D. R. Idler, *J. Am. Chem. Soc.*, **79**, 6473 (1957).

(5) W. Bergmann and J. P. Dusza, *J. Org. Chem.*, **23**, 459 (1958).

(6) G. Wittig and U. Schöllkopf, *Ber.*, **87**, 1318 (1954).

from triphenylphosphonium iodide[7] afforded mainly if not exclusively the *trans*-isomer (III). Its infrared spectrum showed the strong peak at 10.30μ which is associated with *trans*-oriented double bonds and which has been used to assign the *trans*-configuration to the Δ^{22}-double bond in the side chain of such naturally occurring sterols as ergosterol and stigmasterol.[8-10] In contrast, the spectrum showed no absorption in the 14-μ region which might have pointed to the presence of a *cis-oriented* double bond in the side chain.[11]

Upon treatment with bromine, the steryl acetate rapidly formed a nicely crystalline tetrabromide which afforded unchanged starting material upon debromination. Catalytic hydrogenation of the acetate gave cholestanyl acetate. This reaction proves that no significant inversion has taken place at C-20 either during the preparation of the aldehyde or its reaction with the Wittig reagent. As shown in Table I the melting points of 22-dehydrocholesterol and its derivatives are quite similar to those reported for β-sitosterol and derivatives. The melting points also fall within the range of those reported for many ill-defined sterol mixtures and their respective derivatives.[12] The possible occurrence of 22-dehydrocholesterol may therefore have easily been overlooked. As expected the 22-dehydrocholesterol is somewhat more levorotatory than cholesterol. The average difference between the molecular rotations of the two sterols and their respective derivatives is -70, a figure which is in good agreement with the Δ^{22}-value of 61 $\pm$ 20 reported for the C-24 methyl and ethyl homologs.[14]

TABLE I

COMPARISON OF MELTING POINTS

	22-Dehydrocholesterol	β-Sitosterol
Sterol	133.5–134	137[12]
Acetate	126–126.5	127[12]
Benzoate	146–147	146[13]

In another application of the Wittig reaction the previously unknown 3β-hydroxy$\Delta^{5,22}$-choladiene (III) has also been prepared. Reaction of the aldehyde (I) and the ethyl-ylide afforded a mixture of *cis* and *trans* isomers, and treatment with iodine was necessary to afford the pure trans isomer (III).

(7) A. Michaelis and H. von Soden, *Ann.*, 229, 295 (1885).

(8) J. H. Turnbull, D. A. Whiffen, and W. Wilson, *Chem. & Ind. (London)* **33**, 626 (1950).

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(11) D. Barnard, L. Bateman, A. J. Harding, H. P. Koch, N. Sheppard, G. B. B. M. Sutherland, *J. Chem. Soc.*, 915 (1950).

(12) W. Bergmann, *Ann. Rev., Plant Physiol.*, 4, 383 (1953).

(13) S. Bernstein and E. S. Wallis, *J. Org. Chem.*, 2, 341 (1937).

(14) D. H. R. Barton, *J. Chem. Soc.*, 512 (1946).

EXPERIMENTAL

Triphenylisoamyl phosphonium iodide. A solution of 10 g. of triphenylphosphine in 50 ml. of anhydrous toluene was heated in a pressure flask with 11.3 g. of pure isoamyl iodide at 115° for 24 hr. The precipitate was filtered, recrystallized several times from aqueous ethanol, and finally thoroughly dried *in vacuo;* 11.92 g., m.p. 174–176° (rep.[7] 174°); λ_{max} 6.97 and 10.02μ.

22-Dehydrocholesteryl acetate (IIb). A solution of 3.16 g. of 3-β-acetoxybis-nor-5-cholen-22-al (1)[15] in 25 ml. of absolute ether was added to the ylide generated from 11.75 g. of triphenylisoamyl phosphonium iodide, 23.0 ml. of 1.11*N* butyllithium solution,[16] and 35 ml. of anhydrous ether in a pressure flask. The contents were stirred magnetically for about 1 hr. at room temperature, after which the flask was capped and heated to 65° for 15 hr. After cooling, the excess reagent was decomposed with moist ether, the solution evaporated to dryness, and the residue heated to 95° for one hr. with 20 ml. of acetic anhydride and 20 ml. of pyridine. The mixture was diluted with water and the crude acetate thus obtained was chromatographed in hexane on silicic acid–Celite (2:1). The acetate (1.5 g.) was eluted by hexane-benzene (1:1). A 1.23 g. sample of the acetate m.p. 126° was dissolved in 5 ml. of ether, and the solution mixed with 9 ml. of a 10% solution of bromine in glacial acetic acid. A precipitate formed readily (1.42 g.), a part of which was recrystallized from ethyl acetate. The 22-dehydrocholesteryl acetate tetrabromide thus obtained melted with decomposition at 188–189°; λ_{max} 5.76 and 8.08μ in KBr.

Anal. Calcd. for $C_{29}H_{46}Br_4O_2$: C, 46.67; H, 6.21. Found: C, 46.62; H, 6.54.

The acetate tetrabromide was suspended in 25 ml. of ether and 1 ml. of glacial acetic acid. Zinc dust (400 mg.) was added, and the mixture stirred for 10 min. The ether was then decanted from the zinc which was washed several times with ether. The combined extracts were washed with water and dried over anhydrous sodium carbonate. The solution was evaporated to dryness and the residue chromatographed in hexane on neutral alumina (Brockmann II). Elution with hexane-benzene (1:1) gave the acetate (IIb) which was recrystallized several times from methanol; 0.55 g.; m.p. 126–126.5°; $(\alpha)_D^{23}$ $-63.2°$; (C = 1.15 in $CHCl_3$); λ_{max} 5.76, 7.95, 10.30, and 12.52μ in KBr.

Anal. Calcd. for $C_{29}H_{46}O_2$: C, 81.63; H, 10.87. Found: C, 81.88; H, 10.80.

22-Dehydrocholesterol (IIa). The free sterol was obtained by hydrolysis of the acetate with potassium hydroxide in ethanol. It was recrystallized several times from methanol; m.p. 133.5–134°; $(\alpha)_D^{27}$ $-57.3°$; (C = 1.22 in $CHCl_3$); λ_{max} 2.97, 7.29, 7.34, 10.29, and 12.51μ in KBr.

Anal. Calcd. for $C_{27}H_{44}O$: C, 84.31; H, 11.53. Found: C, 84.21; H, 11.35.

Benzoylation of the sterol with benzoyl chloride in pyridine gave the benzoate (IIc). It was recrystallized from acetone; m.p. 146–147° with a play of colors which clears at 172°; $(\alpha)_D^{26}$ $-29.2°$; (C = 0.65 in $CHCl_3$) λ_{max} 5.82, 7.89, 8.00, 10.30, and 14.05μ in KBr.

Anal. Calcd. for $C_{34}H_{48}O_2$: C, 83.55; H, 9.90. Found: C, 83.66; H, 9.68.

Hydrogenation of 22-dehydrocholesteryl acetate. A 100-mg. sample of the acetate dissolved in 40 ml. of glacial acetic acid was shaken with 50 mg. of platinum oxide in a hydrogen atmosphere of 14-lb. pressure. After 2 hr. the catalyst was removed by filtration and the solvent evaporated under re-

(15) The authors are very much indebted to Dr. M. E. Herr, of the Upjohn Co., Kalamazoo, Mich., for the gift of a generous amount of stigmasterol and for explicit directions to convert it to the aldehyde. The aldehyde obtained showed m.p. 113–115°; $(\alpha)_D$ $-60.3°$; λ_{max} 3.68, 5.75, 5.77, 7.90, and 8.03 μ.

(16) H. Gilman and A. H. Haubein, *J. Am. Chem. Soc.*, 66, 1515 (1944).

duced pressure. After two recrystallizations from methanol, the residue gave cholestanyl acetate, m.p. 108–109°, which gave no depression of the melting point when mixed with an authentic sample. Its infrared spectrum was undistinguishable from that of the reference material.

3β-Acetoxy-5,22-choladiene (IIIb). A solution of 5.0 g. of triphenylphosphine in 50 ml. of anhydrous toluene was heated in a pressure flask with 10.2 g. of freshly distilled ethylbromide at 105° for 24 hr. The precipitate was filtered and dried; 6.35 g., m.p. 202–205°, reported 202–205°[17]; λ_{max} 6.90, 6.99, and 10.03μ.

A solution of 1.68 g. of 3β-acetoxybisnor-5-cholen-22-al (I)[15] in 25 ml. of anhydrous ether was added to the ylide generated from 3.35 g. of the triphenylethylphosphonium bromide and 7.0 ml. of 1.3*N* butyllithium in 25 ml. of absolute ether in a pressure flask. The mixture was then treated as described above, and the crude acetate was chromatographed on silicic acid: Celite and recrystallized from methanol; 0.74 g. m.p. 117–122°. The infrared spectrum showed a strong band at 10.27μ indicative of a *trans*-oriented double bond,[8-10] and a weak band at 10.02μ indicative of a *cis* double bond.[11]

The mixed acetates were refluxed with 100 ml. of benzene and 0.35 g. of iodine for 6 hr. The solution was cooled, washed with a solution of sodium thiosulfate, dried, and evaporated to dryness. The residue was dissolved in hexane, and the solution chromatographed over neutral alumina (Brockmann II). Hexane eluted a small fraction containing halogen. The main fraction was eluted with hexane-benzene (9:1). It was recrystallized three times from methanol; m.p. 127–129°, $(\alpha)_D^{26}$ −72.2° (C = 0.64 in $CHCl_3$); λ_{max} 5.76, 8.02, and 10.27 μ in KBr.

Anal. Calcd. for $C_{26}H_{40}O_2$: C, 81.20; H, 10.46. Found: C, 80.85; H, 10.56.

Δ5,22-Choladien-3β-ol (IIIa). Hydrolysis of the acetate with potassium hydroxide in ethanol gave the sterol which was recrystallized from methanol; m.p. 117–117.5°; $(\alpha)_D^{25}$ −65.8°; (C = 0.59 in $CHCl_3$); λ_{max} 2.96, 10.28, and 12.50μ in KBr.

Anal. Calcd. for $C_{24}H_{38}O$: C, 84.15: H, 11.18. Found: C, 83.94; H, 11.25.

(17) G. Wittig and D. Wiggenberg, *Ann.*, 606, 1 (1957).

NEW HAVEN, CONN.

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Hydroxylated Codeine Derivatives

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The application of osmium tetroxide to the introduction of hydroxyl groups in the codeine and neopine series is described. Lithium aluminum hydride or sodium borohydride reduction of 8,14-dihydroxydihydrocodeinone leads to epimeric dihydroxydihydrocodeines. Analogous treatment of 14-hydroxycodeinone yields *true* 14-hydroxycodeine.

The observation that 3,4 dimethoxy-Δ6,7-13-ethylhexahydrophenanthrene (a degradation product of dihydrothebaine)[3] reacted smoothly with osmium tetroxide to yield, after hydrolysis of the osmate ester, the corresponding 6,7-glycol, led to the present study of the action of this reagent on the following morphine derivatives containing an alicyclic unsaturated center in ring C: desoxycodeine-C, codeine methyl ether, acetyl codeine, acetyl isocodeine, and acetyl neopine. It was of interest to pursue this investigation for several reasons: (1) the possibility of arriving at pharmacologically interesting substances was apparent; (2) conceivably this approach could improve upon earlier hydroxylation attempts (of codeine) where low yields were reported[4]; and (3) a route to the unknown 8,14-dihydroxylated neopine[5] (VI) might be afforded.

The considerable number of codeine and codeinone derivatives (containing one or more new hydroxyl groups in ring C) together with their ED_{50} values, relative to codeine, are shown in Table I. It will be noted that enhanced activity is elicited principally by those substances derived from 14-hydroxycodeinone VII. None of the presently reported derivatives showed significant analgesic activity; with the exception of 7-hydroxydihydroco-

TABLE I

Compound	ED_{50} (Mice)[a]
10-Hydroxycodeine	50.4
14-Hydroxycodeine	17.2
10-Hydroxydihydrocodeine	22.5
14-Hydroxymorphinone	42.2
14-Hydroxydihydromorphinone	0.17
14-Hydroxydihydromorphine	1.05
14-Hydroxydihydrocodeinone	1.4
8-Hydroxydihydrocodeinone	>150
14-Hydroxycodeinone	6.1
8,14-Dihydroxydihydromorphinone	6.3
8,14-Dihydroxydihydrocodeinone	16.7
7-Hydroxydihydrocodeine	None[b]
7,8-Dihydroxydihydrocodeine	>400
7,8-Dihydroxydihydrocodeine methyl ether	>100
8,14-Dihydroxydihydrocodeine	>200

[a] We are indebted to Dr. Nathan B. Eddy, of this Laboratory, for permission to use these unpublished data. Codeine ED_{50} = 14.2. (ED_{50} is the dose which is effective for 50% of the test subjects.) [b] Fatal dose (LD_{50} = 50).

(1) Koppers Co., Verona, Pa.

(2) Deceased, June 1957.

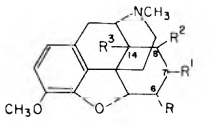
(3) L. J. Sargent and L. F. Small, *J. Org. Chem.*, 16, 1031 (1951).

(4) R. S. Cahn and R. Robinson, *J. Chem. Soc.*, 908 (1926).

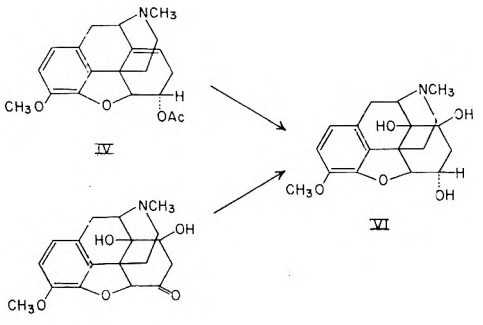
(5) K. W. Bentley, *The Chemistry of the Morphine Alkaloids*, Oxford University Press, London, ref. 5, p. 124 (1954).

deine which was relatively toxic (LD_{50} = 50 mg./kg.), their ED_{50} values were above 100 mg./kg.

The first hydroxycodeine to be described, now known[6] to be 10-hydroxycodeine, was prepared by Knorr[7] through the action of cold chromic acid on codeine. Subsequently Freund[8] and Wieland[9] synthesized 1- or 2-hydroxycodeine from nitrocodeine, and Cahn[4] obtained 7,8-dihydroxydihydrocodeine (III) in low yield from the permanganate oxidation of codeine. 14-Hydroxycodeinone (VII), from the reaction of thebaine with hydrogen peroxide,[10] should also be mentioned, whose reduction product, 14-hydroxydihydrocodeinone (Oxycodone[11a]) and its demethylated derivative, 14-hydroxydihydromorphinone (Oxymorphone[11a, b]) show extraordinary analgesic powers. The oxidation of thebaine by manganic acetate, first studied by Vieböck,[12] yields 8-(or 14-)acetyl-8,14-dihydroxydihydrothebaine which, upon brief treament with hot dilute HCl, gives 8,14-dihydroxyhydrocodeinone (V). In a careful study of the catalytic hydrogenation of 14-hydroxycodeinone (VII), Lutz[13] found that two isomers were formed, *viz:* 14-hydroxydihydrocodeine-B (IX) along with a lesser amount of 14-hydroxydihydrocodeine-C (the two being epimeric about C^6). Both differed, however, from 14-hydroxydihydrocodeine-A which resulted from catalytic hydrogenation of the zinc-acetic acid[14] reduction product of 14-hydroxycodeinone (VII). It was suggested[13] that the singularity of isomer-A was possibly due to a structural alteration that occurred during the metal-acid treatment, a view which is supported by pharmacological studies. Thus, isomers B and C differ in their analgesic activity to about the extent anticipated for an epimeric pair, whereas isomer-A deviates widely, in its effect, from the other two.



I - R = R' = OH; $R^2 = R^3 = H$
II - R = OCH_3; R' = R^2 = OH; R^3 = H
III - R = R' = R^2 = OH; R^3 = H

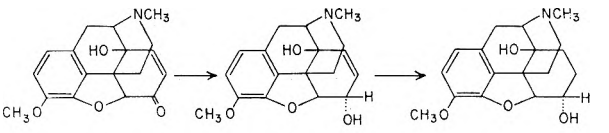


IV V VI

(6) H. Rapoport and G. W. Stevenson, *J. Am. Chem. Soc.*, **76**, 1796 (1954).

(7) F. Ach and L. Knorr, *Ber.*, **36**, 3067 (1903).

(8) M. Freund and E. Speyer, *Ber.*, **44**, 2339 (1911).



VII VIII IX

More recently Findlay[15] discovered that codeinone (in *acid* solution) is capable of adding the elements of water across its 7,8-unsaturated center to form 8-hydroxydihydrocodeinone which upon reduction gave rise to 8-hydroxydihydrocodeine. A remarkable and related observation is that due to Weiss[16] who found that 14-hydroxymorphinone (in *alkaline* medium) readily added the elements of water to yield 8,14-dihydroxydihydromorphinone. Rapoport[17] has latterly reported the use of osmium tetroxide in a series of hydroxylation experiments with codeine derivatives having $\Delta^{7,8}$ unsaturation and in the one instance, 7,8-dihydroxydihydrocodeine (III), where his and our experiments overlap, good agreement in physical properties is evident.

The hydroxylation of the various morphine derivatives outlined below was carried out as described by us previously.[3] However, in cleaving the osmate esters, we found it advantageous, from the standpoint of product work-up, to substitute sodium sulfite[18] for the alkaline mannitol procedure utilized earlier.[3]

Apart from the straightforward osmic acid oxidations referred to, this investigation also afforded the opportunity of verifying the purported *cis* hydroxyl arrangement in Vieböck's[12] 8,14-dihydroxydihydrocodeinone (V). Reduction of the carbonyl function in the latter either with lithium aluminum hydride or sodium borohydride resulted in a mixture of crystalline, epimeric 8,14-dihydroxydihydrocodeines (VI) one of which was identical with the osmic acid oxidation product of acetylneopine (IV) in which only a *cis* (8,14-)glycol arrangement is tenable. The hydroxyl group in the other epimer presumably has the *iso* configuration at C.[6] Of the two reduction techniques tested, lithium aluminum hydride proved superior on two counts: (1) workup

(9) H. Wieland and P. Kappelmeier, *Ann.*, **382**, 306 (1911).

(10) M. Freund and E. Speyer, *J. prakt. Chem.*, **94**, 135 (1916).

(11) (*a*) International non-proprietary name; (*b*) U. Weiss, *J. Am. Chem. Soc.*, **77**, 5891 (1955).

(12) F. Vieböck, *Ber.*, **67**, 197 (1934).

(13) R. E. Lutz and L. F. Small, *J. Org. Chem.*, **4**, 220 (1939).

(14) E. Speyer and K. Sarre, *Ber.*, **57**, 1404 (1924).

(15) S. P. Findlay and L. F. Small, *J. Am. Chem. Soc.*, **72**, 3247 (1950); **73**, 4001 (1951).

(16) U. Weiss, *J. Org. Chem.*, **22**, 1505 (1957).

(17) H. Rapoport, M. S. Chada, and C. H. Lovell, *J. Am. Chem. Soc.*, **79**, 4694 (1957); *cf.* ref. 11a in latter. (*Note:* With the exception of the neopine glycols, all of the substances presently reported were prepared prior to 1951).

(18) (*a*) A. Butenandt, J. Schmidt-Thomé, and H. Paul, *Ber.*, **72**, 1112 (1939); (*b*) L. H. Sarett, *J. Am. Chem. Soc.*, **71**, 1171 (1949).

was less cumbersome and (2) better over-all yields were obtained.

Evidence in support of the *normal* configuration of the C^{14}-hydroxyl in 8,14-dihydroxydihydrocodeinone (V) was forthcoming from an examination of the optical rotation of the phenylhydrazone of this substance. The observed value, $[\alpha]_D^{20}$ $-604.8°$ is in accord with Gates's[19] consistent findings of abnormally high rotations by dinitrophenylhydrazones in the *normal* (*cis*) series of the morphine alkaloids. The phenylhydrazones of 14-hydroxycodeinone and of 14-hydroxydihydrocodeinone were prepared for comparison and these showed $[\alpha]_D^{20}$ values of $-1416°$ and $-649°$, respectively.

That 14-hydroxydihydrocodeine-A differs from the epimers 14-hydroxydihydrocodeine-B and -C has already been alluded to. Because of the dubiety of the A-isomer and its precursor "14-hydroxycodeine,"[20] *true* 14-hydroxycodeine (VIII) was prepared, for the first time, by sodium borohydride reduction of 14-hydroxycodeinone (VII). Since Gates[21] has recently shown that this reagent reduces codeinone practically quantitatively and stereospecifically to codeine, it is reasonable to infer that *true* 14-hydroxycodeine has the C^6 codeine configuration. Catalytic reduction of *true* 14-hydroxycodeine yielded a substance which was identical with 14-hydroxycodeine-B; this must therefore have the C^6 codeine configuration too.[22] Since 14-hydroxydihydrocodeine-B and -C were shown[13] to be epimeric about C^6, it follows that the C-isomer must have the isocodeine configuration at this center.

EXPERIMENTAL[23]

7-Hydroxydihydrocodeine (I).[24] To a cold (0°) solution of 0.292 g. of osmium tetroxide (1 equiv.) and 0.195 ml. (2 equiv.) of dry pyridine in 15 ml. of dry ether, a cold solution of 0.325 g. of desoxycodeine-C in 15 ml. of dry ether was added at one time. After keeping at 0° for 5 hr., the brown adduct was collected, washed with ether, and dried; yield 0.68 g. (85%).

A mixture of the adduct with 2.4 g. of sodium sulfite, 16 ml. of 95% ethanol, and 10 ml. of water was heated (reflux) for 3.5 hr. During this interval a black precipitate gradually separated. The latter was centrifuged and washed with two 10-ml. portions of boiling methanol. Concentration (vacuum) of the combined supernate and washings afforded a crystalline residue which was washed with a little ice-cold water and dried; yield 0.19 g. (55%), m.p. 227–229°. After three crystallizations from methanol, there were obtained rectangular plates, m.p. 230–232°. The analytical sample was dried for 2.5 hr. at 78°/0.4 mm.

Anal. Calcd. for $C_{18}H_{23}NO_4$: C, 68.1; H, 7.30; N, 4.41. Found: C, 68.2; H, 7.45; N, 4.56. $[\alpha]_D^{20}$ $-138°$ (c = 0.333, methanol).

7,8-Dihydroxydihydrocodeine methyl ether (II). Codeine methyl ether (5.14 g.) in 100 ml. of cold anhydrous ether was added to a cold solution of 5 g. of osmium tetroxide in 200 ml. of anhydrous ether. The system was refrigerated for 6 hr. and then kept at room temperature for 72 hr. After removal of the solvent (vacuum), the brown residue was heated (reflux) for 3.5 hr. with 50 g. of sodium sulfite in 200 ml. of water and 125 ml. of ethanol. Centrifugation was carried out as above and the combined supernate and ethanol washings were removed (vacuum) to yield 5 g. of a colorless, crystalline product. The latter was recrystallized three times from dilute ethanol (Norit) to give 4 g. (60%) of glycol, m.p. 216–218°.

Anal. Calcd. for $C_{19}H_{25}NO_5$: C, 65.69; H, 7.25. Found: C, 65.67; H, 6.97. $[\alpha]_D^{20}$ $-74.8°$ (c = 1.01, 95% ethanol).

7,8-Diacetoxydihydrocodeine methyl ether. A solution of 0.3 g. of II in a mixture of 6 ml. of acetic anhydride and 10 ml. of anhydrous pyridine was kept at 5° for 96 hr. Removal of the solvent (vacuum) afforded a quantitative yield of the diacetoxy derivative which proved to be quite soluble in ether, ethanol, or acetone. After three sublimations at 125°/0.2 mm., 0.25 g. of pure derivative, m.p. 133–135°, was obtained.

Anal. Calcd. for $C_{23}H_{29}NO_7$: C, 64.02; H, 6.78. Found: C, 64.09; H, 6.75.

7,8-Dihydroxydihydrocodeine (III).[25] A solution of 6.68 g. of acetylcodeine in 100 ml. of cold, anhydrous ether was added to one of 5 g. of osmium tetroxide in 150 ml. of the same solvent, and the mixture was kept at room temperature for 72 hr. After the usual work-up, the aqueous solution (following removal of ethanol) was extracted with 4 × 25 ml. portions of chloroform from which 5.6 g. of crude III was obtained. Two crystallizations from ethanol (Norit) yielded 3.9 g. (60%) of III, m.p. 207–208° (lit.[4,17] m.p. 208–209°; 210–211°).

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.9; H, 6.9. Found: C, 65.0; H, 7.0.

The *triacetoxy* derivative prepared as above (acetic anhydride–pyridine) was crystallized twice from ether and sublimed at 186°/0.1 mm.; m.p. 198–199° (lit.[4,17] m.p. 200°; 200–202°).

Anal. Calcd. for $C_{24}H_{29}NO_8$: C, 62.7; H, 6.36. Found: C, 62.7; H, 6.35.

Acetyl neopine (IV).[26] Five g. of neopine was added to a cooled mixture of 20 ml. of dry pyridine and 10 ml. of acetic anhydride. After keeping at 25° for 48 hr. and the usual work-up, the product was evaporatively distilled (cold finger) at 125–130°/0.3 mm.; yield 4.9 g. colorless crystals. A sample was resublimed; m.p. 117°.

Anal. Calcd. for $C_{20}H_{23}NO_4$: CH_3CO, 12.6. Found: CH_3CO, 12.5. $[\alpha]_D^{20}$ + 15.2° (c = 0.972, 95% ethanol).

8,14-Dihydroxydihydrocodeine (VI). The interaction of IV (2.7 g.) in 50 ml. of dry ether with 2 g. of osmium tetroxide in 50 ml. of the same solvent gave, after 48 hr., 1.6 g. of slightly tacky crystals. Two crystallizations from ethyl acetate yielded 1.3 g. (50%) of colorless prisms which sublimed unchanged at 150°/0.2 mm., m.p. 186–186.5° (evac. tube).

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.8; H, 7.0. Found: C, 65.1; H, 6.84. $[\alpha]_D^{20}$ $-147°$ (c = 1.07, 95% ethanol).

Acetylisocodeine. The acetylation of isocodeine (10 g.) was carried out, as above, with a mixture of 10 ml. of dry

(19) M. Gates and G. Tschudi, *J. Am. Chem. Soc.*, **78**, 1380 (1956); especially ref. 23 therein.

(20) *Cf.* ref. (14). An attempt to elucidate this structure is in progress.

(21) M. Gates, *J. Am. Chem. Soc.*, **75**, 4340 (1953).

(22) *Cf.* ref. (13). These authors intimated that their pharmacological data suggested C^6-dihydrocodeine and dihydroisocodeine configurations, respectively, for the B and C isomers.

(23) Analyses are by the Analytical Service Laboratory of this Institute, under the supervision of Dr. W. C. Alford. Melting points are uncorrected.

(24) K. Goto and T. Arai, *Bull. Chem. Soc. Japan*, **17**, 113 (1942), obtained this substance (30% yield) through permanganate oxidation of desoxycodeine-C and reported the empirical formula $C_{18}H_{23}NO_4$–0.5 H_2O, which possibly accounts for their lower $[\alpha]_D$ $-128°$.

(25) *Cf.* refs. (4) and (17).

(26) C. F. van Duin, R. Robinson, and J. C. Smith, *J. Chem. Soc.*, 903 (1926) first reported this substance as an oil.

pyridine and 10 ml. of acetic anhydride. The colorless crystals were purified from absolute ethanol (Norit) at −5° (to minimize losses); yield 8 g. of small prisms, m.p. 88–89°.

Anal. Calcd. for $C_{20}H_{23}NO_4$: CH_3CO, 12.6; Found: CH_3CO, 12.4. $[\alpha]_D^{20}$ −270° (c = 1.02, 95% ethanol).

7,8-Dihydroxydihydroisocodeine. In the manner outlined above, acetylisocodeine (2.5 g.) in 50 ml. of dry ether was oxidized (during 24 hr.) with 2 g. of osmium tetroxide in 75 ml. of the same solvent. After concentration, hydrolysis and the customary manipulation, 1.9 g. of an amber oil (that crystallized overnight) was obtained. This was recrystallized from absolute ethanol (Norit); yield 1.1 g. (42%) of nearly colorless crystals. A sample was recrystallized again and dried 1 hr. at 70°/0.1 mm., m.p. 241–242° (evac. tube); it was not completely anhydrous.

Anal. Calcd. for $C_{18}H_{23}NO_5 \cdot 0.5\ H_2O$: C, 63.2; H, 7.07; H_2O, 2.63. Found: C, 63.8; H, 6.86; H_2O, 2.30. $[\alpha]_D^{20}$ −78.7° (c = 0.502, 95% ethanol).

8,14-Dihydroxydihydrocodeinone (V). The hydroxylation of thebaine (40 g.) with freshly prepared manganic acetate according to the procedure outlined by Vieböck[12] yielded 7 g. of dihydroxydihydrocodeinone. After recrystallization from ether 5.7 g. of colorless prisms were obtained; m.p. 169–170° (lit. m.p. 170°). The substance sublimes unchanged at 165–170°/0.05 mm.

Anal. Calcd. for $C_{18}H_{21}NO_5$: C, 65.2; H, 6.39; active H, 2.0. Found: C, 65.3; H, 6.32; active H, 2.2. $[\alpha]_D^{20}$ −191° (c = 1.0, 95% alcohol).

The *phenylhydrazone.* A mixture of 0.25 g. of V in 4.5 ml. of absolute ethanol with 0.25 g. of redistilled phenylhydrazine and 4 drops of glacial acetic acid was heated on the steam bath for 10 mins. Basification of the cooled solution (NH_4OH) precipitated a yellow gum which solidified after 48 hr. The powdered product was collected, washed with water, and dried; yield 0.25 g. This was dissolved in 1 ml. of hot methanol and seeded; the practically colorless plates were rinsed with a few drops of cold methanol. After a second recrystallization, the derivative showed the m.p. 162–164° dec. (evac. tube), with previous softening at 112°.

Anal. Calcd. for $C_{24}H_{27}N_3O_4$: N, 9.97. Found: N, 10.2. $[\alpha]_D^{20}$ −605° (c = 1.03, $CHCl_3$).

14-Hydroxycodeinone phenylhydrazone. From 0.5 g. of VII (as above) a gum was obtained which crystallized in glassy prisms (0.35 g.) from absolute ethanol, m.p. 193–194° (evac. tube).

Anal. Calcd. for $C_{24}H_{25}N_3O_3$: N, 10.4. Found: N, 10.2. $[\alpha]_D^{20}$ −1216° (c = 0.998, $CHCl_3$).

14-Hydroxydihydrocodeinone phenylhydrazone. This derivative, prepared as above, was recrystallized twice from absolute ethanol; faintly tan needles, m.p. 176° (gas evolution, evac. tube). $[\alpha]_D^{20}$ −649° (c = 1.0, $CHCl_3$).

Epimeric cis-8,14-dihydroxydihydrocodeines (VI). (*a*) *Via lithium aluminum hydride.* To a magnetically stirred mixture of 8.5 ml. (excess) of 1.65*N* lithium aluminum hydride and 35 ml. of dry ether was added, during 1.75 hr., a solution of 1 g. of V in 150 ml. of dry ether. The system was gently refluxed for 7 hr., then stirred (at 25°) for 15 hr. longer. After decomposing the excess reagent with water, 2*N* hydrochloric acid was added (to Congo acidity) and the suspension stirred into solution. The cooled aqueous phase was basified with a slight excess of 10*N* sodium hydroxide, nearly saturated with sodium chloride, and extracted three times with chloroform. Concentration (vacuum) of the dried extracts yielded a clear gum (0.9 g.) which crystallized when moistened with ethyl acetate and seeded with authentic *cis*-8,14-dihydroxydihydrocodeine (obtained from osmium tetroxide oxidation of o-acetylneopine).

The product was dissolved in boiling ethyl acetate, filtered, and concentrated to small volume; seeding induced the separation of colorless prisms (A). After 1.5 hr. the supernatant liquor was removed and the crystals rinsed with a little cold ethyl acetate (which was added to the mother liquor—see below). A second crystallization from ethyl acetate gave 0.46 g. of prisms, m.p. 177–179°. The analytical sample was recrystallized once again, m.p. unchanged.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95. Found: C, 64.68; H, 6.84. $[\alpha]_D^{20}$ −144° (c = 1.0, 95% ethanol).

The infrared spectrum of this substance was indistinguishable from that of the osmium tetroxide–acetylneopine product; moreover no depression was observed in a mixture m.p.

Concentration (steam-bath) of the ethyl acetate mother liquors yielded a yellow gum which crystallized when rubbed with ether. Recrystallization from the latter solvent afforded 0.19 g. of flat, colorless prisms (B), m.p. 171–173°. A second recrystallization raised the m.p. to 174–176°. A mixture of this with epimer (A) showed the m.p. 158–160°; in addition, the respective infrared spectra differed significantly.

Anal. Calcd. for $C_{18}H_{23}NO_5$: C, 64.85; H, 6.95. Found: C, 64.80; H, 7.05. $[\alpha]_D^{20}$ −133° (c = 1.0, 95% ethanol).

The combined yield of epimers was 65%.

(*b*) *Via sodium borohydride.* A solution of 1.7 g. V in 17 ml. of absolute methanol was added dropwise (during 15 min.) to a suspension of 0.7 g. of sodium borohydride in 10 ml. of the same solvent. After stirring for 2.25 hr. longer, the system was acidified with 2*N* HCl and heated on the steam bath (reflux) for 10 min. Methanol was removed (*vacuum*). Water (10 ml.) and methanol (15 ml.) were added and the system concentrated (*vacuum*). The process was repeated once again. The aqueous residue was basified with saturated potassium carbonate and extracted six times with chloroform which yielded 0.8 g. of a foamy glass. This was triturated four times with 30 ml. portions of boiling ether; the combined extracts yielded 0.4 g. of colorless crystals, m.p. 160–168°. Soxhlet (ether) extraction of the residue (0.23 g.) during 60 hr. afforded 70 mg. of crystals, m.p. 160–164°, and 0.13 g. of insoluble material.

The aqueous solution from the chloroform extractions (above) was concentrated to dryness (steam bath) and the residue Soxhlet (chloroform) extracted during 15 hr. This yielded 0.8 g. of a yellow powder which was heated for 20 min. with a mixture of 20 ml. of methanol and 3 ml. of 2*N* HCl. After another methanol-acid treatment and the usual work-up (as above) the aqueous residue was basified with saturated potassium carbonate. The oily suspension crystallized when seeded with the above crystals (m.p. 160–168°). The air-dried product (0.7 g.) was recrystallized from ether (0.12 g. insoluble) and yielded 0.44 g. of faintly yellow prisms, m.p. 179–181°.

The combined ether-insoluble fractions (0.25 g.) were again treated with methanol and 2*N* HCl. This afforded an additional 95 mg. of crystals, m.p. 176–178°. The combined crystalline material (1.05 g.) represents a 60% yield of mixed epimers.

Separation of epimers by fractional recrystallization. The crystalline material was dissolved in boiling ethyl acetate, filtered, concentrated to small volume and seeded. After 36 hr. at 25°, the nearly colorless material was collected, 0.61 g. (crop I), m.p. 174–176°. Recrystallization from ether gave 0.58 g. of colorless prisms, m.p. 179–180.5°. A mixture of this substance with its counterpart (m.p. 177–179°) obtained *via* lithium aluminum hydride reduction (above) showed no m.p. depression.

From the further concentrated ethyl acetate mother liquor (after 24 hr. at 25°) there was obtained 0.19 g. (crop II) of crystals, m.p. 168–170°. Recrystallization from ether yielded 0.17 g. of flat prisms, m.p. 171–173°; not depressed when mixed with the corresponding lithium aluminum hydride fraction. A mixture of crops I and II showed the m.p. 161–163°.

The combined yield of recrystallized epimers was 48%.

True 14-Hydroxycodeine (VIII). A stirred suspension of 5 g. of VII[13] in 75 ml. of absolute methanol was gradually treated with 2 g. of sodium borohydride in 25 ml. of the same solvent. Stirring was maintained for 2 hr. and the solution was concentrated (vacuum) to one-half the original volume. After adding 50 ml. of 10% NaOH the solution was

boiled vigorously for a few moments and the remainder of the methanol removed (vacuum) whereupon the product crystallized. The latter was recrystallized from 50% ethanol; yield 4.3 g., m.p. 155–156°. A sample was sublimed at 150°/0.1 mm., m.p. 156–157°.

Anal. Calcd. for $C_{18}H_{21}NO_4$: C, 68.6; H, 6.71. Found: C, 68.5; H, 6.64. $[\alpha]_D^{20}$ −81.1° (c = 1, 10% HOAc).

14-Hydroxydihydrocodeine-B. A solution of 1 g. of *true* 14-hydroxycodeine in 30 ml. of 95% ethanol was shaken under hydrogen with 75 mg. of PtO_2. After the uptake of 1.2 moles of hydrogen (35 mins.), the usual manipulation yielded 0.84 g. of colorless crystals, m.p. 145–146°; the melting point was not depressed when mixed with 14-hydroxydihydrocodeine-B[13] (of m.p. 145–145.5°).

A small sample of the above product was acetylated (acetic anhydride–pyridine) and the product worked up as usual. Recrystallized from ethanol, the substance had the m.p. 181° alone or admixed with diacetyldihydrocodeine-B[13] (of m.p. 181–181.5°).

6,14-Diacetoxycodeine. A solution of 1.4 g. of *true* 14-hydroxycodeine in a mixture of 3 ml. of acetic anhydride and 1.5 ml. of dry pyridine was kept at 25° for 24 hr. The resulting crystalline magma was poured onto ice and treated slowly with 6*N* NH_4OH producing a colorless, crystalline precipitate which was collected and recrystallized from 95% ethanol; yield .2 g. colorless prisms. After a second recrystallization, m.p. 199° (evac. tube).

Anal. Calcd. for $C_{22}H_{25}NO_6$: C, 66.2; H, 6.31; CH_3CO, 21.5. Found: C, 66.1; H, 6.38; CH_3CO, 21.3. $[\alpha]_D^{20}$ −46.2° (c = 1.02, 10% HOAc).

BETHESDA, MD.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents. V. Some Sulfur-Substituted Derivatives of Cysteine[1]

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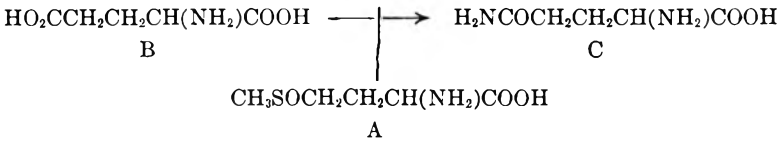
A number of *S*-alkyl and *S*-aryl derivatives of DL- and L-cystine, as well as some of their sulfoxides and sulfones, have been prepared for testing as possible anticancer agents.

In a search for compounds with anticancer activity, a number of derivatives of DL- and L-cysteine have been prepared. These compounds can be considered as potential amino acid antimetabolites; they could affect certain metabolic systems in a way similar to that in which methionine sulfoxide (A) acts as a glutamic acid (B) antagonist in the conversion of glutamic acid (B) to glutamine (C).[2]



The *S*-alkyl- and *S*-arylcysteines in Table I were prepared by a variety of methods. Direct alkylation of L-cysteine with reactive halogen compounds in the presence of dilute aqueous alkali and at room temperature gave good yields of compounds I–IV. The preparation of *S*-methyl-L-cysteine (V) was carried out with dimethyl sulfate and required a long reaction time in order to achieve a good yield. The *N*-benzoyl and *N*-acetyl derivatives of *S*-methyl-L-cysteine (V) were prepared by conventional procedures. The preparation of *S*-isopropyl-L-cysteine (VI) by direct alkylation of L-cysteine with isopropyl bromide or isopropyl iodide gave low yields of VI. The procedure of Gawron and Lieb[3] utilizing the alkylation with isopropyl bromide of the sodium salt of L-cysteine prepared from L-cystine in liquid ammonia gave a high yield of *S*-isopropyl-L-cysteine (VI).

The preparation of *S*-trimethylsilylmethyl-L-cysteine (VII) from L-cysteine and (chloromethyl)-trimethylsilane required a long reaction time in refluxing aqueous dioxane, an indication of the low order of activity of the halogen of the silane. An effort was made to prepare a phosphorylated compound by reaction of L-cysteine in alkali with (chloromethyl)phosphonic acid or dialkyl (chloromethyl)phosphonates. New ninhydrin-positive material was formed in these reactions as shown by paper chromatography, but efforts to purify the products were unsuccessful. Although many of the compounds in Table I are designated as derivative of L-cysteine, it is recognized that the conditions used in methods A, B, and D might lead to various degrees of racemization.

(1) This work was carried out under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper of this series, *cf.* Elmer J. Reist, Leon Goodman, Roland R. Spencer, and B. R. Baker, *J. Am. Chem. Soc.*, **80**, 3962 (1958).

(2) E. Borek, P. Sheiness, and H. Waelsch, *Federation Proc.*, **5**, 123 (1946).

(3) O. Gawron and J. A. Lieb, *J. Am. Chem. Soc.*, **74**, 834 (1952).

TABLE I

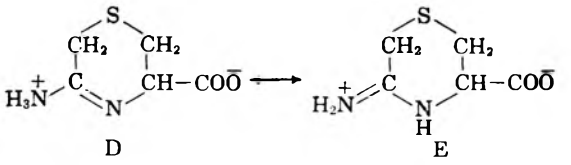
S-ALKYLATED AND *S*-ARYLATED L- AND DL-CYSTEINES

$RSCH_2CH(\overset{+}{N}H_3)\overset{-}{C}OO$

Compound No.[d]	R	Method[c]	Yield, %	M.P., °C. (Dec.)	$[\alpha]_D$ (°C.)[f]	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
I	HO_2CCH_2[a]	A	72	197–203[h]	0.0 (25)[u]						
II	$C_6H_5COCH_2$[a,e]	A	68	90–95	−0.6 (28)	53.2	5.68	5.64	53.6	5.54	5.62
III	$NCCH_2$[a,f]	A	49	>300	−14.6 (25)	37.5	5.03	17.5	37.1	4.83	16.9
IV	NH_2COCH_2[a]	A	77	188–190[i]	−6.6 (26)[v]						
V	CH_3[a]	B[g]	88	230[j]	0.0 (27)[w]						
VI	$(CH_3)_2CH$[a]	C[g]	33	237–239[k]	+3.0 (27)[x]						
VII	$(CH_3)_3SiCH_2$[a]	D	99	165–198	0.0 (28)[y]	40.5	8.27	6.76	40.5	8.28	6.45
VIII	C_6H_5[b]	E	72	190[l]							
IX	2-$CH_3C_6H_4$[b]	E	84	193[m]		56.8	6.21	6.63	57.2	6.30	6.64
X	3-$CH_3C_6H_4$[b]	E	84	190–191[n]		56.8	6.21	6.63	56.7	6.32	6.57
XI	4-$CH_3C_6H_4$[b]	E	54	195–197[o]		56.8	6.21	6.63	56.4	6.06	6.61
XII	4-ClC_6H_4[b]	E	77	195–196[p]							
XIII	4-$NO_2C_6H_4$[b]	E	94	175[q]		44.6	4.17	11.6	44.6	4.17	11.4
XIV	2-$NH_2C_6H_4$[b]	E	94	240		50.9	5.70	13.2	50.9	5.95	13.4
XV	3-$CF_3C_6H_4$[a]	F	17	183–185	+68.2 (28)	45.3	3.77	5.28	45.0	4.00	5.30
XVI	4-FC_6H_4[a]	F	12	185–186[r]	+82.7 (28)[z]	50.2	4.68	6.51	50.4	4.83	6.50

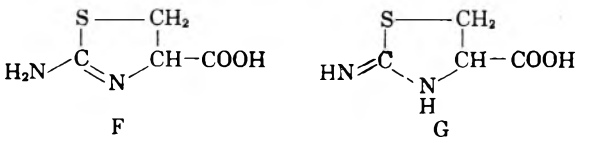
[a] Derivative of L-cysteine. [b] Derivative of DL-cysteine. [c] See Experimental. [d] All compounds were determined to be homogeneous by paper chromatography. [e] Calculated analytical figures are for the hemihydrate. Compound II could be recrystallized from water but only with very poor recovery; the analytical figures are for the crude, washed product. [f] The compound actually exists in the cyclic form (see Discussion). The analytical figures are for the crude, washed product. [g] Method of Gawron and Lieb.[3] [h] Lit. m.p. 204–207°,[4] 175–176°,[5] 193–194°.[6] [i] Lit. m.p. 188–190°.[4] [j] Lit. m.p. 247–248°,[4] 238°.[7a] [k] Lit. m.p. 237–239°,[8] 223–224°.[3] [l] Decomposed without melting; lit. reports compound to decompose without melting above 160°.[9] [m] Lit. m.p. for L-isomer, 166–167°.[10] [n] Lit. m.p. for L-isomer, 175–176°.[10] [o] Lit. m.p. for L-isomer, 200–202°.[10] [p] Lit. m.p. 202°.[11] [q] Lit. m.p. 151°.[11] [r] Lit. m.p. 180–183°.[12] [s] Method of du Vigneaud, Loring, and Craft.[7b] [t] 1% solutions in 1*N* HCl unless otherwise noted. [u] Lit.[4] $[\alpha]_D^{24}$ +0.5° (1% in 1*N* HCl); this compound is not racemic since compounds XXIV and XXX were prepared from I and are optically active. [v] Lit.[4] $[\alpha]_D^{24}$ −6.0° (1% in 1*N* HCl). [w] Lit.[4] $[\alpha]_D^{24}$ −9.6° (1% in 1*N* HCl); product V is evidently racemic. [x] Lit.[5] $[\alpha]_D^{21}$ −19.0° (1% in H_2O). [y] Probably racemic. [z] 0.56% in 1*N* HCl.

Compound III is designated as *S*-cyanomethyl-L-cysteine in Table I. It seems clear, however, that the actual form of the compound is the cyclic structure (D) [or possibly its tautomer (E)]. The infrared spectrum of III showed a typical amino



D E

acid zwitterion spectrum but showed no nitrile absorption near 4.5μ. The ninhydrin color of III was a faint yellow, in contrast with the distinct blue color noted with I, IV, V, VI, and VIII, another indication that the compound probably has the cyclic structure. Alkylation of *N*-benzoyl-L-cysteine with chloroacetonitrile[13] led to *N*-benzoyl-*S*-cyanomethyl-L-cysteine, whose infrared spectrum showed strong nitrile absorption at 4.44μ, a strong suggestion that III, lacking this infrared band, does not possess the open-chain structure but has the cyclic amidine structure (D or E). These results find analogy in the work of Schöberl,[14] who showed that the compound thought to be *S*-cyano-L-cysteine is in reality the cyclic thiazoline (F or G, presumably as the zwitterion).



F G

Compound II was prepared in good yield from either phenacyl chloride or phenacyl bromide. The product gave a yellow color with ninhydrin and it was suspected that the true structure was the cyclized formula (H). The infrared spectrum of

(4) M. D. Armstrong and J. D. Lewis, *J. Org. Chem.*, **16**, 749 (1951).

(5) L. Michaelis and M. P. Schubert, *J. Biol. Chem.*, **106**, 331 (1934).

(6) S. A. Harris, N. R. Easton, D. Heyl, A. N. Wilson, and K. Folkers, *J. Am. Chem. Soc.*, **66**, 1757 (1944).

(7) (a) S. Yurugai, *J. Pharm. Soc. Japan*, **74**, 519 (1954). (b) V. du Vigneaud, H. S. Loring, and H. A. Craft, *J. Biol. Chem.*, **105**, 481 (1934).

(8) A. Stoll and E. Seebeck, *Helv. Chim. Acta*, **32**, 866 (1949).

(9) E. Baumann and C. Preusse, *Z. Physiol. Chem.*, **5**, 336 (1881).

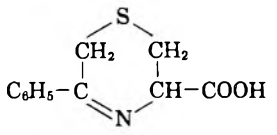
(10) H. D. West and G. R. Mathura, *J. Biol. Chem.*, 208, 315 (1954).

(11) H. Behringer and E. Fackler, *Ann.*, **564**, 73 (1949).

(12) S. J. Zbarsky and L. Young, *J. Biol. Chem.*, **152**, 599 (1944).

(13) Leon Goodman, Leonard O. Ross, and B. R. Baker, Paper XII of this series, *J. Org. Chem.*, in press.

(14) A. Schöberl, M. Kawohl, and R. Hamm, *Ber.*, **84**, 571 (1951).

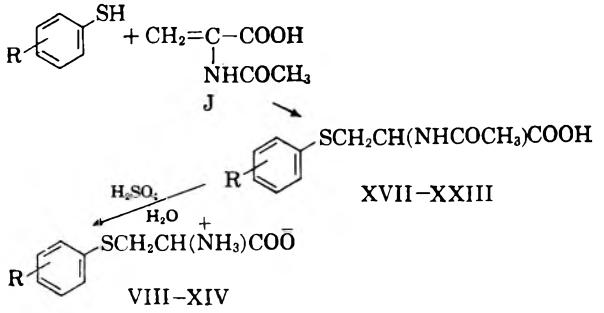


H

compound II, however, showed a strong aromatic ketone carbonyl band at 6.01μ and ammonium ion absorption at 3.30 and 6.12μ, which is typical of α-amino acids. Further, the ultraviolet spectrum of II was very similar to that of acetophenone in water and was essentially the same in 0.1N hydrochloric acid, a strong indication that II exists as the open-chain, α-amino acid. Compound II decomposed upon warming in water and it was necessary to crystallize the compound rapidly from hot water in order to obtain even low recoveries. It is interesting that Dittmer[15] prepared a related compound, aspartophenone [$C_6H_5COCH_2$-$CH(NH_2)COOH$] and reported it to be more effective biologically after heating, possibly an indication of cyclization upon heating.

Attempts to *S*-alkylate L-cysteine with chloroacetone were completely unsuccessful; the products were highly colored, nonhomogeneous solids.

Two methods were used to prepare the *S*-aryl cysteines (VIII–XVI). The method of Behringer and Fackler,[11] involving the base-catalyzed addition of a thiophenol to α-acetamidoacrylic acid (J), gave the corresponding mercapturic acids (XVII–XXIII) (*cf.* Table II) which, in turn, were subjected to acidic hydrolysis, to give the *S*-aryl-DL-cysteines



(VIII–XIV). Both the preparation of the mercapturic acid and the acid hydrolysis gave generally good yields, although the use of *ortho*-substituted thiophenols seemed to result in somewhat lower yields.

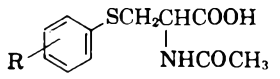
The second method used to prepare *S*-arylcysteines involved the reaction between a diazotized substituted aniline and the cuprous salt of L-cysteine. This method has been described by du Vigneaud[16] and by West and Mathura[10] and, although it gives generally low yields, it is convenient when the appropriate substituted aniline is available, and has the additional advantage of giving the L-form of the substituted cysteine. It was found,

(15) K. Dittmer, *Ann. N. Y. Acad. Sci.*, **52**, 1292 (1950).

(16) V. du Vigneaud, J. L. Wood, and F. Binkley, *J. Biol. Chem.*, **138**, 369 (1941).

TABLE II

DL-MERCAPTURIC ACIDS



Compound No.	R	Yield, %	M.P., °C.	Lit. M.P., °C.
XVII	H	61	150–151	151[11]
XVIII[a]	2-CH_3	30	134–136	For L-isomer, 144.5–145[10]
XIX[b]	3-CH_3	61	128–130	For L-isomer, 141[10]
XX	4-CH_3	51	155–156	154[11]
XXI	4-Cl	65	148–150	148[11]
XXII	4-NO_2	56	168–170	167–168[11]
XXIII[c]	2-NH_2	34	145	

[a] Calcd. for $C_{12}H_{15}NO_3S$: C, 56.9; H, 5.96; N, 5.53. Found: C, 56.8; H, 5.71; N, 5.66, 5.77. [b] Calcd. for $C_{12}H_{15}NO_3S$: C, 56.9; H, 5.96; N, 5.53. Found: C, 56.7; H, 5.97; N, 5.62. [c] Calcd. for $C_{11}H_{14}N_2O_3S$: C, 52.0; H, 5.55; N, 11.0. Found: C, 52.0, 52.2; H, 5.69, 5.77; N, 10.6.

in the present work, that the use of a catalytic quantity of the cuprous salt of L-cysteine with the remainder of the L-cysteine present as the free amino acid represented a distinct inprovement over the procedure which utilized a stoichiometric amount of the preformed cuprous salt of L-cysteine. A disadvantage of the diazonium salt procedure for the preparation of *S*-aryl-L-cysteines resulted from the contamination of the products with appreciable amounts of L-cystine, which was difficult to remove by recrystallization from water. However, it was found that the contaminating L-cystine could be readily removed by recrystallizing the product from water containing sodium sulfite; the L-cysteine was thereby converted to soluble amino acids without affecting the desired *S*-aryl-L-cysteines.[17] Compounds XV and XVI were prepared using both of the described modifications of the diazonium salt synthesis.

Most of the compounds listed in Table I were subjected to oxidation with 30% hydrogen peroxide with the use of a variety of conditions. The alkylated L-cysteines (I, III, and IV) were converted to their sulfoxides (XXIV, XXV, and XXVI, respectively) in excellent yield by heating the compounds in aqueous solution for a short time with a large excess of 30% hydrogen peroxide. Such a procedure gave complete degradation of *S*-methyl- and *S*-isopropyl-L-cysteine. Only a low yield of the sulfoxide XXVII of *S*-isopropyl-L-cysteine (VI) could be obtained by the reaction of VI with a stoichiometric amount of hydrogen peroxide in acetic acid as solvent, the procedure employed by Stoll and Seebeck.[8] The material yielded poor analytical figures (comparable to those obtained by Stoll and Seebeck[8]) but was homogeneous ac-

(17) This method of purification of compounds XV and XVI was suggested by O. P. Crews, Jr.

TABLE III

ALKYLATED AND ARYLATED L- AND DL-CYSTEINE SULFOXIDES

$RSOCH_2CH(\overset{+}{N}H_3)C\overset{-}{O}O$

Compound No.	R	Method[f]	Yield, %	M.P., °C. (Dec.)	$[\alpha]_D$ (°C.)	Analyses					
						Calcd.			Found		
						C	H	N	C	H	N
XXIV	HO_2CCH_2[a]	G	73	190–191	+27.3 (29)[h]	30.8	4.65	7.18	31.0	4.87	7.07
XXV	$NCCH_2$[a,g]	G	80	>300	−30.3 (28)[i]	34.1	4.54	15.9	34.2	4.67	14.9, 14.1
XXVI	NH_2COCH_2[a]	G	84	157–160	+14.1 (29)[j]	30.9	5.19	14.4	30.8	5.33	14.44
XXVII	$(CH_3)_2CH$[a,d]	H[e]	18	154–156[c]		38.3	7.50		38.0	6.98	
XXVIII	C_6H_5[b]	J	46	186–187		50.7	5.20	6.57	50.4	5.47	6.46
XXIX	3-$CH_3C_6H_4$[b]	K	37	137–138		52.8	5.76	6.16	53.0	5.75	6.01

[a] Derivative of L-cysteine. [b] Derivative of DL-cysteine. [c] Lit. m.p. 155–156°.[8] [d] The calculated analytical values are for the hemihydrate; Stoll and Seebeck[8] reported similar analytical results. [e] Method of Stoll and Seebeck.[8] [f] See Experimental. [g] Compound XXV exists in the cyclic form as shown by the absence of nitrile infrared absorption near 4.5μ. [h] 1% in 1*N* HCl. [i] 0.86% in 1*N* HCl. [j] 0.55% in 1*N* HCl.

cording to paper chromatography and possessed an infrared spectrum in accord with structure XXVII. A number of attempts were made to convert *S*-methyl-L-cysteine (V) to its sulfoxide in a worthwhile yield, but these were uniformly unsuccessful. It is evident that the simple *S*-alkyl-L-cysteines are rapidly degraded under mild oxidizing conditions. Conditions were found that permitted the isolation of *S*-aryl-L-cysteine sulfoxides XXVIII and XXIX by hydrogen peroxide oxidation of VIII and X, respectively. Generally, the oxidation of the *S*-arylcysteines listed in Table I could not be stopped at the sulfoxide stage, so that separation of the mixture of parent amino acid, sulfoxide, and sulfone was impractical. Even carrying out the oxidations in strong acid as suggested by Bordwell and Bouton[18] did not favor the formation of sulfoxides. The data concerning the sulfoxides are summarized in Table III.

The use of infrared spectra and of paper chromatography was especially helpful in determining the composition of the products of the oxidations. The sulfoxide absorpton band near 9.75μ and the two sulfone bands near 7.70 and 8.80μ were completely reliable for the identification of both the pure oxidation products and mixtures of them. The solvent system *n*-butyl alcohol/methyl ethyl ketone/17*N* ammonia/water (5/3/1/1)[19] was generally capable of resolving mixtures of the parent amino acids, sulfoxides, and sulfones, all of which could be detected with ninhydrin. In the above solvent system, the parent acid moved faster than the sulfone, which, in turn, moved faster than the sulfoxide.[20] In the acidic solvent system *t*-butyl alcohol/formic acid/water (6.95/0.10/2.95)[21] the order of movement was also parent acid>sulfone>sulfoxide. An exception was the case of compounds III and XXV, where the sulfoxide XXV moved faster than the parent acid III, a further indication that both III and XXV exist in the cyclic form.

Only one of the alkylated cysteines, namely, *S*-carboxymethyl-L-cysteine (I), could be converted to its sulfone (XXX) by direct oxidation. The conversion was effected by use of a large excess of 30% hydrogen peroxide and a long reaction time.[22] The yield of sulfone (XXX) was low and was accompanied by large amounts of inorganic solids formed by degradation reactions. The oxidation of the *S*-arylcysteines (VIII–XIII and XV–XVI) to the corresponding sulfones (XXI–XXX–VIII) was carried out in aqueous acetic acid or aqueous hydrochloric acid with excess hydrogen peroxide and proceeded in generally good yield (*cf.* Table IV). It was not possible to convert *S*-2-aminophenyl-DL-cysteine (XIV) to a sulfoxide or sulfone with either 30% hydrogen peroxide or alkaline potassium permanganate; only tars resulted. Possibly the (aminophenyl)cysteine sulfones are inherently unstable, since the addition of 4-acetamidobenzenesulfinic acid to α-acetamidoacrylic acid followed by acid hydrolysis yielded a solid which appeared to be the desired sulfone as determined by infrared spectrum and paper chromatography but which decomposed during recrystallization.

In the isolation of water-soluble sulfoxides and sulfones prepared with a large excess of hydrogen peroxide, it was found convenient to destroy the excess peroxide before isolation of the product by addition of small amounts of a commercial 5% platinum-on-charcoal catalyst.

(18) F. G. Bordwell and P. J. Bouton, *J. Am. Chem. Soc.*, 79, 717 (1957).

(19) M. Wolfe, *Biochim. et Biophys. Acta*, 23, 186 (1957).

(20) In the present work circular paper chromatograms were used to establish homogeneity. These were rapid and reliable with proper controls but did not give accurate R_f values.

(21) L. B. Rockland and J. C. Underwood, *Anal. Chem.*, 26, 1557 (1954).

(22) While this paper was being refereed the preparation, by another method, of XXX, m.p. 185.5–186° dec., was reported by B. J. Finkle and E. L. Smith, *J. Biol. Chem.*, 230, 679 (1958).

TABLE IV

ALKYLATED AND ARYLATED L- AND DL-CYSTEINE SULFONES

$RSO_2CH_2CH(\overset{+}{N}H_3)\overset{-}{C}OO$

Compound No.	R	Method[d]	Yield, %	M.P., °C. (Dec.)	$[\alpha]_D^{28}$	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
XXX	HO_2CCH_2[a]	L	25	193–194[22]	+10.2[e]	28.4	4.30	6.63	28.8	4.67	6.63
XXXI	C_6H_5[b]	M	61	155–156		47.2	4.83	6.11	47.3	5.21	6.08
XXXII	2-$CH_3C_6H_4$[b]	N	27	160–162		49.4	5.39	5.76	49.4	5.60	5.83
XXXIII	3-$CH_3C_6H_4$[b]	N	17	135–137		49.4	5.39	5.76	49.7	5.44	5.84
XXXIV	4-$CH_3C_6H_4$[b]	N	44	155–157		49.4	5.39	5.76	49.1	5.30	5.39
XXXV	4-ClC_6H_4[b]	M	97	171–172		41.1	3.80	5.31	41.2	3.96	5.36
XXXVI	4-$NO_2C_6H_4$[b]	M	70	156–157		39.4	3.68	10.2	39.7	3.54	10.2
XXXVII	3-$CF_3C_6H_4$[a,c]	N	68	148–150	+12.7[f]	39.2	3.62	4.57	39.3	3.76	4.41
XXXVIII	4-FC_6H_4[a]	N	52	172–174	+18.6[g]	43.8	4.07	5.67	43.6	4.28	5.74

[a] Derivative of L-cysteine. [b] Derivative of DL-cysteine. [c] The calculated values are for the hemihydrate. [d] See Experimental. [e] 1% in 1*N* HCl. [f] 0.57% in 1*N* HCl. [g] 0.84% in 1*N* HCl.

Although a number of the compounds listed in the tables showed considerable toxicity, none of them showed selective activity against the mouse tumors, Sarcoma 180, Carcinoma 755, or Leukemia 1210.[23]

EXPERIMENTAL[24]

S-Phenacyl-L-cysteine (II). *Method A.* A suspension of 1.0 g. (6.35 mmoles) of L-cysteine hydrochloride and 0.97 g. (6.35 mmoles) of α-chloroacetophenone in a mixture of 4 ml. of water and 2 ml. of 95% ethanol was prepared. To the well-stirred mixture was added, dropwise, a solution of 0.84 g. (12.7 mmoles) of potassium hydroxide in 5 ml. of water. Upon complete addition of the base, 1.07 g. (68% yield) of compound II precipitated as a crystalline, slightly yellow compound. It could be recrystallized in poor yield from water on a small scale but decomposed rapidly on prolonged heating in water. Purification of the material was carried out by washing thoroughly with cold water and acetone. The material melted at 90–95° (dec.) and was homogeneous on paper using the *t*-butyl alcohol/formic acid/water system.[21] Compound II gave a faint yellow color with ninhydrin.

Anal. Calcd. for $C_{11}H_{13}NO_3S \cdot {}^1/_2H_2O$: C, 53.2; H, 5.68; N, 5.64. Found (washed material): C, 53.6; H, 5.54; N, 5.62. Found (recrystallized material): C, 52.90; H, 5.79; N, 5.74.

Compound II had the following ultraviolet absorption: $\lambda_{max}^{H_2O}$ 247 mμ (ε 14,000), $\lambda_{max}^{0.1NHCl}$ 244 mμ (ε 13,200).

Infrared spectrum: λ_{max}^{KBr} 3.30, 6.12, and 6.55 ($\overset{+}{N}H_3$); 6.01 (aromatic ketone C = O); 6.33 and 7.17 (CO_2^-); 13.75 and 14.59 μ (mono-substituted phenyl).

Attempts to oxidize compound II with hydrogen peroxide in either water or ethanol led to rapid darkening of the solution and isolation and dark-colored, nonhomogeneous solids.

N-Benzoyl-S-methyl-L-cysteine. Method B. Benzoylation of 0.50 g. (3.7 mmoles) of *S*-methyl-L-cysteine (V) under conventional Schotten-Baumann conditions gave 0.77 g. (87%) of yellow solid, m.p. 40–50°. A portion of it was crystallized from water (1 g./10 ml.) and melted at 50–59°. (Izumiya *et al.*[7] reported m.p. 59–61° for the compound, prepared by an unstated method. It seems probable that the material described above is partially racemized.)

Anal. Calcd. for $C_{11}H_{13}NO_3S$: C, 55.2; H, 5.48. Found: C, 55.3; H, 5.64.

Infrared spectrum: λ_{max}^{KBr} 2.98 (NH); 5.77 (carboxyl C = O); 6.09 (amide C = O); 6.53 (amide NH); 13.95μ (mono-substituted phenyl).

N-Acetyl-S-methyl-L-cysteine. Method C. A solution of 1.0 g. (7.4 mmoles) of *S*-methyl-L-cysteine (V) in 10 ml. of acetic anhydride was allowed to stand at room temperature for 18 hr. The excess acetic anhydride was evaporated *in vacuo*, leaving a sirupy residue which solidified after standing a few days at 0°. The residue was recrystallized from 5 ml. of 95% ethanol to yield 0.40 g. (33%), m.p. 147–149°.

Anal. Calcd. for $C_6H_{11}NO_3S$: C, 40.7; H, 6.26. Found: C, 40.7; H, 6.05.

Infrared spectrum: λ_{max}^{KBr} 2.99 (NH); 3.85 (carboxyl OH); 5.88 (carboxyl C = O); 6.21 (amide C = O); 6.45μ (amide NH).

S-Trimethylsilylmethyl-L-cysteine (VII). *Method D.* A mixture of 0.79 g. (5.0 mmoles) of L-cysteine hydrochloride, 0.61 g. (5.0 mmoles) of (chloromethyl)trimethylsilane (Peninsular ChemResearch, Inc.), 10 ml. of dioxane, and 3 ml. of water was cooled to 0° and to it was added a cold solution of 0.66 g. (10.0 mmoles) of potassium hydroxide in 3 ml. of water. The two-phase mixture was heated, under nitrogen and with stirring, at 80–90° for 24 hr., at the end of which time the *p*H of the mixture was 8. The mixture was adjusted to *p*H 6. with 6 drops of 6*N* hydrochloric acid and was filtered from inorganic salts. The filtrate was evaporated to dryness *in vacuo* and the residue was extracted with 60 ml. of boiling absolute ethanol. The extract was filtered hot and the alcoholic filtrate was evaporated to dryness *in vacuo*, leaving 1.15 g. of residue. Paper chromatography[24] in system D showed the presence of a trace of cystine along with the desired product. Partition chromatography[25] of

(23) The anticancer assays were performed by the Biology Department, Stanford Research Institute, under a contract with the Cancer Chemotherapy National Service Center.

(24) Microanalyses were by the Microanalytical Laboratory of Stanford Research Institute, Menlo Park, Calif., and Berkeley Analytical Laboratory, Albany, Calif. Melting points were taken on the Fisher-Johns apparatus and are uncorrected. The paper chromatograms were run by the circular technique on Whatman No. 1 paper, using ninhydrin spray to detect the spots and using the following solvent systems:

A[21] *t*-butyl alcohol/formic acid/water (6.95/0.10/2.95)

B[25] *n*-butanol/acetic acid/water (5/2/3)

C[19] *n*-butanol/methyl ethyl ketone/water/17*N* ammonia (5/3/1/1)

D[26] water-saturated *n*-butanol.

Optical rotations were obtained using a Standard Polarimeter Model D attachment to the Beckman DU spectrophotometer, calibrated with standard sucrose solutions [A. S. Keston, Abstracts of the 127th meeting, American Chemical Society, 18C (1955)].

(25) D. M. Brown, A. Todd, and S. Varadarajan, *J. Chem. Soc.*, 2388 (1956).

572 mg. of the residue on Celite using *n*-butanol/water removed cystine and inorganic salts and gave an 89% recovery of VII. On this basis the yield was 98.7%. The purified material decomposed gradually over the range 165–198°, the decomposition being vigorous at 195–198°. The compound could also be recrystallized from water (about 1 g./10 ml.) but the recovery was poor. The analytical data are given in Table I.

Infrared spectrum: λ_{max}^{KBr} 3.25–3.40, 6.14, and 6.65 (NH_3^+); 6.25 (shoulder) and 7.17 (CO_2^-); 8.01 and 11.75μ ($SiCH_3$).

A picrate was prepared from 0.20 g. of VII and 0.42 g. of picric acid in a total volume of 50 ml. of water. The picrate, 0.25 g., m.p. 145.5–147.5°, was recrystallized from 25 ml. of hot water and had m.p. 146–148.5°.

Anal. Calcd. for $C_7H_{17}NO_3Si.^1/_2C_6H_3N_3O_7.^1/_2H_2O$: C, 36.3; H, 5.94. Found: C, 36.6; H, 6.14.

Infrared spectrum: λ_{max}^{KBr} 3.25–3.40 and 6.10 (NH_3^+); 5.77–5.90 (carboxyl C = O); 6.43 and 7.55 (NO_2); 7.85 (phenolate ion); 8.01 and 11.75 ($SiCH_3$); 12.66 μ (picrate ion).

*N-Acetyl-S-2-aminophenyl-*DL*-cysteine* (XXIII). *Method E.* A solution of 1.50 g. (10 mmoles) of α-acetamidoacrylic acid[29] and 1.62 g. (13 mmoles) of 2-aminobenzenethiol in 10 ml. of dioxane (Eastman White Label) and 15 drops of piperidine was heated under reflux for 1.5 hr. Dioxane was removed by evaporation *in vacuo* to leave a brown, sirupy residue. The residue was extracted with 5 ml. of methylene chloride and the nonextractable material was dissolved in 5 ml. of water and brought to *p*H 8 with concentrated ammonium hydroxide. The *p*H was adjusted to 4 with 6*N* hydrochloric acid and the product slowly crystallized to yield 1.0 g. (34%) of XXIII, m.p. 145°. The analytical data are given in Table II.

Infrared spectrum: λ_{max}^{KBr} 3.00 and 3.07 (NH and NH_2); 5.83 (carboxyl C = O); 6.20 (amide C = O); 6.55 (amide NH); 13.20 μ (*o*-disubstituted phenyl).

Absolute ethanol was used as the solvent in many of the mercapturic acid preparations summarized in Table II.

*S-2-Aminophenyl-*DL*-cysteine* (XIV). *Method F.* A mixture of 1.0 g. (39 mmoles) of *N*-acetyl-*S*-2-aminophenyl-DL-cysteine (XXIII), 4 ml. of concentrated sulfuric acid, and 16 ml. of water was heated under reflux for 30 min. The hot solution was brought to *p*H 7 with concentrated ammonium hydroxide. The product (0.78 g., 94%) precipitated and was crystallized from hot water, m.p. 240° (dec.). On paper chromatography in system B, it gave a single red-brown spot. The analytical data are given in Table I.

Infrared spectrum: λ_{max}^{KBr} 2.91, 2.99, and 6.1–6.2 (NH_2); 3.25, 6.1–6.2, and 6.75 (NH_3^+); 6.30 and 7.15 (CO_2^-); 13.32 μ (*o*-disubstituted phenyl).

*S-3-(Trifluoromethyl)phenyl-*L*-cysteine* (XV). *Method G.* A solution of 5.50 g. (31.4 mmoles) of L-cysteine hydrochloride (monohydrate) in 100 ml. of 1.5*N* sulfuric acid was heated to 70–80° and, with stirring, 7.0 g. (49 mmoles) of cuprous oxide suspended in 100 ml. of water was added in 3 portions. After the solution had been stirred for 30 min., 5.50 g. (31.4 mmoles) of L-cysteine hydrochloride (monohydrate) was added, and the mixture was cooled to 0° with an ice-salt bath.

A solution of 9.0 g. (56 mmoles) of 3-(trifluoromethyl)-aniline, 100 ml. of water, and 10 ml. of concentrated sulfuric acid was cooled to −5° with an ice-salt bath and to it was added, with stirring, over a period of 2 hr., a solution of 5.0 g. (73 mmoles) of sodium nitrite in 50 ml. of water.

The cold diazonium salt solution was added dropwise, with stirring, to the cuprous cysteinate solution while the temperature was maintained at −5 to 0°. The stirred reaction mixture was allowed to rise to room temperature during a 12-hr. period and was then heated to 95°, at which temperature it was saturated with hydrogen sulfide. The resulting mixture was filtered, using Celite, and the filtrate was extracted with two 50-ml. portions of ether to remove phenols. The aqueous phase was adjusted to *p*H 6 with ammonium hydroxide, whereupon 3.5 g. (24%) of a crystalline product precipitated. This was recrystallized from water (1 g./60 ml.) to yield 2.55 g. (17%) of product, m.p. 183–185° (dec.). The product gave a single lavender-grey spot when chromatographed on paper using solvent system C. The analytical data are given in Table I.

Infrared spectrum: λ_{max}^{KBr} 3.25, 6.13, and 6.60 (NH_3^+); 6.33 and 7.00 (CO_2^-); 8.46 and 8.85 (CF_3); 12.65μ (*m*-disubstituted phenyl).

When the reaction was carried out with 5.0 g. (29 mmoles) of L-cysteine hydrochloride (monohydrate), 1.0 g. (7.0 mmoles) of cuprous oxide, and 6.2 g. (39 mmoles) of diazotized 3-(trifluoromethyl)aniline, the yield of XV was 33.1% (before recrystallization).

The product from several large-scale preparations of XV was seriously contaminated with L-cystine and it was very wasteful to remove the impurity by a number of recrystallizations from water. It was found that recrystallization of 0.50 g. of crude XV from 60 ml. of hot water which contained 0.50 g. of sodium sulfite gave a recovery of 0.40 g. of XV which was chromatographically homogeneous.

*S-Carboxymethyl-*L*-cysteine sulfoxide* (XXIV). *Method H.* A suspension of 1.0 g. (5.6 mmoles) of recrystallized *S*-carboxymethyl-L-cysteine (I) in a mixture of 20 ml. of water and 8 ml. (78 mmoles) of 30% hydrogen peroxide was heated on the steam bath for 15 min. To the hot solution was added 250 ml. of 95% ethanol and the resulting mixture was allowed to stand at room temperature for 2 days. During this period 0.80 g. (73%) of analytically pure product precipitated, m.p. 190–191° (dec.). The product gave a single red-brown spot when chromatographed on paper, using system A. It could be recrystallized from water but it appeared to decompose partially during the operation.

Anal. Calcd. for $C_5H_9NO_5S$: C, 30.8 H, 4.65. Found (for directly isolated product): C, 30.8; H, 4.72. Found (for the recrystallized product): C, 29.8; H, 4.74.

Infrared spectrum: λ_{max}^{KBr} 3.17 and 6.74 (NH_3^+); 5.90–6.00 (carboxyl C = O); 6.20 and 6.93 (CO_2^-); 9.70μ (S → O).

*S-Phenyl-*DL*-cysteine sulfoxide* (XXVIII). *Method J.* A mixture of 1.0 g. (5.1 mmoles) of *S*-phenyl-DL-cysteine (VIII), 20 ml. of water, and 10.0 ml. (98 mmoles) of 30% hydrogen peroxide was heated on the steam bath for 30 min., during which time complete solution was obtained. The solution was rapidly chilled to 15° with an ice bath, whereupon 0.50 g. (46%) of the sulfoxide XXVIII precipitated. The product gave a single gray-brown spot in solvent system C which moved slower than *S*-phenyl-DL-cysteine (VIII) or *S*-phenyl-DL-cysteine sulfone (XXXI). The analytical data are given in Table III.

Infrared spectrum: λ_{max}^{KBr} 3.4, 6.10, and 6.65–6.75 (NH_3^+); 6.31 and 7.25 (CO_2^-); 9.69 (S → O); 13.38 and 14.55μ (mono-substituted phenyl).

*S-m-Tolyl-*DL*-cysteine sulfoxide* (XXIX). *Method K.* To a solution of 1.0 g. (4.7 mmoles) of *S*-*m*-tolyl-DL-cysteine (X) in a mixture of 20 ml. of water and 5 ml. of glacial acetic acid was added 0.52 ml. (5.1 mmoles) of 30% hydrogen peroxide. The solution was heated on the steam bath for 1 hr. and was then evaporated *in vacuo*, yielding a sirup which solidified after standing at 0° for several days. The solid was recrystallized from 75% aqueous ethanol (1 g./25 ml.) to yield 0.4 g. (37%), m.p. 137–138° (dec.). The product gave a single gray-green spot in solvent system C which

(26) J. G. Buchanan, C. A. Dekkar, and A. G. Long, *J. Chem. Soc.*, 3162 (1950).

(27) N. Izumiya, A. Nagamatsu, and S. Ota, *Kyushu Mem. Med Sci.*, **4**, 1 (1953).

(28) This separation was performed according to the procedure of H. M. Kissman, C. Pidacks, and B. R. Baker, *J. Am. Chem. Soc.*, **77**, 18 (1955), and the elution pattern was followed by the relative intensity of an equal aliquot of each fraction spotted on paper and detected by ninhydrin.

(29) H. W. Coover and J. B. Dickey, U. S. Patent **2,622,-074** [*Chem. Abstr.*, **47**, 9998d (1953)].

moved slower than the parent compound (X). The analytical data are given in Table III.

Infrared spectrum: λ_{max}^{KBr} 3.3–3.4, 6.12, and 6.80 (NH_3^+); 6.27 (shoulder) and 7.25 (CO_2^-); 9.82 (S → O); 13.25μ (*m*-disubstituted phenyl).

*S-Carboxymethyl-*L*-cysteine sulfone* (XXX). *Method L.* A mixture of 1.0 g. (5.6 mmoles) of recrystallized *S*-carboxymethyl-L-cysteine (I), 5 ml. of water, and 5 ml. (48 mmoles) of 30% hydrogen peroxide was heated at 45–60°, with occasional stirring, for 10 hr. A small amount of material remained in suspension at the end of this time and was removed by filtration. To the filtrate was added about 0.2 g. of 5% platinum-on-charcoal catalyst (Baker and Co.) in small portions; the vigorous reaction required cooling. A copious, white precipitate formed during this treatment. The precipitate was brought into solution with 100 ml. of hot (80°) water and the resulting mixture was filtered to remove the platinum catalyst. The filtrate was evaporated *in vacuo*, leaving a yellow solid. This was crystallized from 40 ml. of water, using decolorizing carbon, to give 0.3 g. of white material that crystallized very slowly. This amounted to a 25% yield but no effort was made to recover the product which remained in the mother liquors. The material was crystallized a second time from 25 ml. of hot water. It melted at 193–194° (dec.)[22] and gave a single red-brown spot on paper chromatography in solvent system A which moved faster than the sulfoxide XXIV and slower than the parent compound (I). The analytical data are given in Table IV.

Infrared spectrum: λ_{max}^{KBr} 3.35, 6.04, and 6.57 (NH_3^+); 5.79 (carboxyl C = O); 6.35 and 7.08 (CO_2^-), 7.70 and 8.83μ (SO_2).

*S-4-Nitrophenyl-*DL*-cysteine sulfone* (XXXVI). *Method M.* A solution of 0.50 g. (2.1 mmoles) of *S*-4-nitrophenyl-DL-cysteine (XIII) in 10 ml. of water, 2.5 ml. of 6*N* hydrochloric acid, and 1.50 ml. (14.7 mmoles) of 30% hydrogen peroxide was heated on the steam bath for 10 min. A small amount of an unidentified precipitate was filtered and the filtrate was heated for an additional 80 min. The solution was chilled and adjusted to *p*H 6–7 with concentrated ammonium hydroxide. A precipitate, 0.40 g. (70%) slowly formed and was recrystallized from water (1 g./20 ml.), m.p. 156–157° dec. The product gave a single light yellow spot on paper chromatography in solvent system C which moved slower than the parent compound (XIII). The analytical data are given in Table IV.

Infrared spectrum: $\lambda_{max\mu}^{KBr}$ 3.23–3.45, 6.08, and 6.76 (shoulder) (NH_3^+); 6.35 and 7.15 (shoulder) (CO_2^-); 6.52 and 7.40 (NO_2); 7.68 and 8.70 (SO_2); 12.05 (*p*-disubstituted phenyl).

*S-4-Fluorophenyl-*L*-cysteine sulfone* (XXXVIII). *Method N.* To a solution of 1.0 g. (4.64 mmoles) of S-4-fluorophenyl-L-cysteine (XVI) in 20 ml. of glacial acetic acid was added 5.0 ml. (49 mmoles) of 30% hydrogen peroxide. The resulting solution was allowed to stand at room temperature for 49 hr. after which the excess hydrogen peroxide was decomposed by the addition of about 0.2 g. of 5% platinum-on-charcoal catalyst, added in small portions. The charcoal was removed by filtration and the filtrate was evaporated to dryness *in vacuo*. The residue was dissolved in 5 ml. of water and the resulting solution was neutralized to *p*H 7 with concentrated ammonium hydroxide yielding 0.80 g. (70%) of crystalline solid. This was recrystallized from hot water (0.2 g./25 ml.) to yield 0.60 g. (52%) of product, m.p. 172–174° (dec.). The product gave a single yellow spot on paper chromatography in solvent system C which moved slower than the parent amino acid (XVI). The analytical data are given in Table IV.

Infrared spectrum: $\lambda_{max\mu}^{KBr}$ 3.37–3.45, 6.05–6.10, and 6.60 (NH_3^+); 6.30 and 7.15 (CO_2^-); 7.60 and 8.72 (SO_2); 8.06 (C—F); 11.87 (*p*-disubstituted phenyl).

Acknowledgements. The authors wish to thank Dr. Peter Lim for infrared interpretations, Dr. L. K. Moss and group for column and paper chromatography, and Mr. O. P. Crews, Jr., and group for the large-scale preparation of intermediates.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE DEPARTMENT OF BIOLOGICAL SCIENCES, STANFORD RESEARCH INSTITUTE]

Potential Anticancer Agents.[1] VI. Synthesis of α-Amino-γ-sulfamoylbutyric Acids with Substituents on the Sulfonamide Nitrogen

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Chlorinolysis of L-cystine hydantoin and DL-homocystine hydantoin in 42% aqueous acetic acid gave 71% and 81% yields, respectively, of the corresponding 5-(chlorosulfonylalkyl)hydantoins. Procedures were devised for reaction of DL-5-(β-chlorosulfonylethyl)hydantoin with ammonia, alkylamines, arylamines, and glycinamide to form the respective sulfonamides, which, in turn, were base-hydrolyzed to the desired DL-α-amino-γ-sulfamoylbutyric acids. In contrast, L-5-(chlorosulfonylmethyl)hydantoin reacted satisfactorily only with the arylamines, and the resultant sulfonamides decomposed on attempted alkaline hydrolysis.

Interest in antagonists of L-glutamine as possible anticancer agents has been given considerable impetus by the observed anticancer activity of L-azaserine[2] and 6-diazo-5-oxo-L-norleucine.[3] These two compounds have been established to be antimetabolites of L-glutamine.[4] Reisner[5] has recently described the synthesis of α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$) along with two

(1) This program is under the auspices of the Cancer Chemotherapy National Service Center, National Cancer Institute, and is in collaboration with the Sloan-Kettering Institute for Cancer Research. For the preceding paper in this series, *cf.* L. Goodman, L. O. Ross, and B. R. Baker, *J. Org. Chem.*, **23**, 1251 (1958).

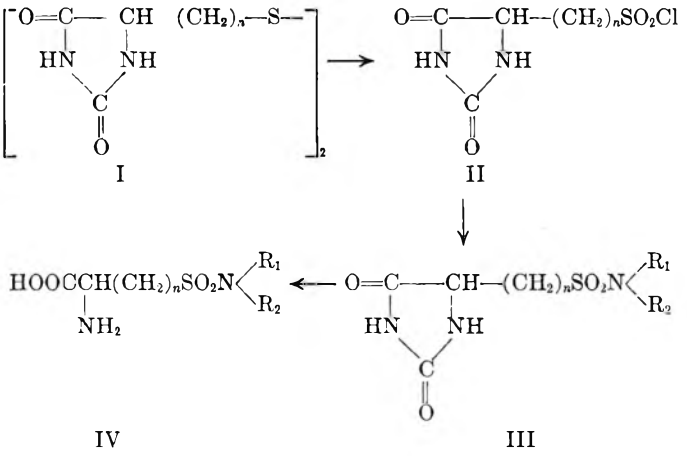
(2) C. C. Stock, H. C. Reilly, S. M. Buckley, D. A. Clarke, and C. P. Rhoads, *Nature*, **173**, 71 (1954).

(3) H. A. DeWald and A. M. Moore, Abstracts, American Chemical Society, 129th Meeting, 13 M (1956).

(4) B. Levenberg, I. Melnick, and J. M. Buchanan, *J. Biol. Chem.*, **225**, 163 (1957).

(5) D. B. Reisner, *J. Am. Chem. Soc.*, **78**, 5102 (1956).

related compounds, α-amino-γ-(ethylsulfamoyl)-butyric acid (IVb, $R_1 = C_2H_5$, $R_2 = H$) and α-amino-γ-[2-(benzylthio)ethylsulfamoyl)-butyric acid (IVb, $R_1 = C_6H_5CH_2SCH_2CH_2$, $R_2 = H$). Since he showed that α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$) had activity against T_2 coliphage of *E. coli* that was reversible by either glutamic acid or glutamine and since this amino acid had presumably not been tested as an anticancer agent,[6] the synthesis was repeated to obtain material for antitumor evaluation; several improvements in the procedures have given higher yields. In addition, a wider spectrum of substituents on the sulfonamide nitrogen has been investigated.



Chlorinolysis of DL-homocystine hydantoin (Ib) in aqueous suspension as described by Reisner[5] gave low and variable yields of pure DL-5-(β-chlorosulfonylethyl)hydantoin (IIb), particularly on a large scale. The main difficulty was that an insoluble, gummy mixture of product and starting material formed frequently and did not react further. It has now been found that 42% aqueous acetic acid is an excellent solvent for this reaction; since the product, but not the starting material, is soluble, total solution indicates completion of reaction. Consistent yields of better than 80% of nearly analytically pure material were obtained by this modification.

Treatment of an ether suspension of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) with ammonia as previously described[5] gave only a 20% yield of DL-5-(β-sulfamoylethyl)hydantoin (IIIb, $R_1 = R_2 = H$). Reisner recorded[5] a yield of 40% under these conditions. Again, since neither the starting acid chloride nor the products were soluble in ether, incomplete reaction resulted. In contrast, the use of the excellent solvent *N*,*N*-dimethylformamide gave a 62% yield of pure sulfonamide (IIIb, $R_1 = R_2 = H$). Hydrolysis[5] of the hydantoin moiety by aqueous barium hydroxide at 160° gave a 73% yield of pure DL-α-amino-γ-sulfamoylbutyric acid (IVb, $R_1 = R_2 = H$). Thus, with the above improvements the over-all yield from DL-homocystine hydantoin (Ib)[7] was increased more than one-and-a-half-fold from the previously described[5] yield of 21%.

Similarly, morpholine and diethylamine reacted with DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in *N*,*N*-dimethylformamide to give the corresponding new sulfonamides (IIIb) in 76% and 55% yield, respectively (Procedure A, Table I.) Hydrolysis[5] with barium hydroxide at 160° afforded good yields of the corresponding amino acids (IVb) (Table II).

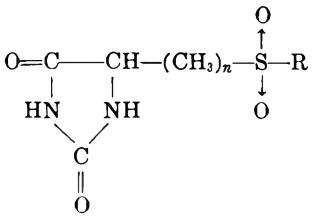
Attempts to react DL-5-(β-chlorosulfonylethyl)-hydantoin (IIb) with glycine ethyl ester hydrochloride in *N*,*N*-dimethylformamide containing triethylamine failed to give any of the desired *N*-(carbethoxymethyl)sulfonamide (IIIb, $R_1 = CH_2CO_2C_2H_5$, $R_2 = H$). With the more stable glycinamide hydrochloride under these conditions, a 50% yield of the desired sulfonamide (IIIb, $R_1 = CH_2CONH_2$, $R_2 = H$) was obtained. Hydrolysis with barium hydroxide at 160° followed by crystallization from water at *p*H 3 gave the peptide analog of γ-glutamylglycine, namely, DL-α-amino-γ-(*N*-carboxymethylsulfamoyl)butyric acid (IVb, $R_1 = CH_2COOH$, $R_2 = H$). A hydantoinsulfonamide (IIIb) could be obtained from phenylhydrazine in good yield, but the hydrolysis with barium hydroxide gave deep-seated decomposition, as indicated by the absence of sulfonamido S→O bands in the infrared absorption spectrum of the corresponding amino acid fraction; this reaction was not investigated further.

Although *N*,*N*-dimethylformamide was satisfactory for the preparation of the sulfonamides (IIIb) derived from aliphatic amines, the procedure worked poorly with arylamines. However, the use of pyridine as a solvent (Procedure B) gave sulfonamides (IIIb) derived from aniline in 35%

(6) We wish to thank Dr. Howard W. Bond of the Cancer Chemotherapy National Service Center and Dr. Ralph K. Barclay of the Sloan-Kettering Institute for Cancer Research for this information.

(7) J. V. Karabinos and J. L. Szabo, *J. Am. Chem. Soc.*, 66, 649 (1944).

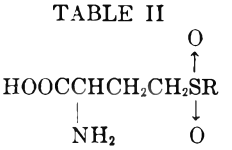
TABLE I



R[a]	n	Yield, %	Procedure	M.P., °C.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
Et_2N—	2	55	A	111–113 d.[b]	41.1	6.50	16.0	41.4	6.46	15.7
Morpholino	2	76	A	162–165[c]	39.0	5.45	15.2[d]	39.2	5.25	14.7
C_6H_5NH—	2	86	C[j]	207–209[c]	46.6	4.63	14.8[e]	46.5	4.73	14.8
C_6H_5NHNH—	2	84	C[m]	168–172 d.[f]	44.3	4.73	18.8	43.9	4.67	18.5
p-Cl-C_6H_4NH—	2	80	C[g]	196–198[h]	41.6	3.81	13.2[i]	41.7	3.74	13.3
m-CF_3-C_6H_4NH—	2	74	C[k]	188–189[f]	41.0	3.44	12.0[l]	41.0	3.36	11.9
3,4-Me_2-C_6H_3NH—	2	69	C	194–197[c]	50.2	5.47	13.5	50.2	5.68	13.8
p-F-C_6H_4NH[n]	2	69	C	211–213 d.[o]	43.9	4.01	14.0	43.9	4.10	13.7
p-F-C_6H_4NH[n]	2	75	C	170–173 d.[c]	43.9	4.01	14.0	44.1	4.40	14.0
m-Cl-C_6H_4NH—	2	84	C	206–207[c]	41.6	3.81	13.2	41.6	4.02	12.9
3,4-Cl_2-C_6H_4NH—	2	77	C	218–220[h]	37.5	3.15	11.9	37.6	3.27	11.5
p-Cl-C_6H_4NH—	1	68	C	203–207 d.[h]	39.5	3.32	13.8	39.6	3.46	13.6
m-CF_3-C_6H_4NH—	1	50	C	143–152 d.[c]	39.2	2.99	12.5	39.1	3.11	12.5

[a] All compounds had characteristic infrared absorption bands for the two hydantoin carbonyls and for the S → O vibration of the sulfonamide group. Compounds with $n = 2$ were DL-isomers and with $n = 1$ were L-isomers. [b] Recrystallized from methylene chloride–petroleum ether (b.p. 30–60°). [c] Recrystallized from H_2O. [d] Calcd. for S, 11.6. Found: S, 11.4. [e] Calcd. for S, 11.3. Found: S, 11.3. [f] Recrystallized from absolute ethanol. [g] Procedure B gave a 57% yield. No product could be isolated by Procedure A. [h] Recrystallized from 50% ethanol. [i] Calcd. for S, 10.1; Cl, 11.2. Found: S, 9.96; Cl, 11.1. [j] Procedures A and B gave 35% yields. [k] Procedure B gave a 48% yield. [l] Calcd. for S, 9.13. Found: S, 8.98, 9.02. [m] Procedure A gave a 76% yield. [n] Two crystal forms were obtained which were interconvertible by proper seeding. [o] Recrystallized from 70% ethanol.

TABLE II



R[a]	Yield, %	M.P. °C., dec.	Analyses Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
NH_2—	73[b]	232[c,d]			15.4			15.6
Et_2N—	87	205–210[e]	40.3	7.61	11.8	40.0	7.62	11.6
Morpholino	70	235–237[d]	38.1	6.39	11.1	38.5	6.30	11.4
C_6H_5NH—	58	238–240[d]	46.5	5.46	10.9[h]	46.3	5.47	10.7
p-Cl-C_6H_4NH—	37	235–243[d]	41.0	4.48	9.57	41.1	4.62	9.66
m-CF_3-C_6H_4NH—	56	228–234[d]	40.5	4.02	8.59	40.7	4.21	8.52
$HOOCCH_2NH$—	60	214–220[f,g]	30.0	5.04	11.2	30.0	5.07	11.4
3,4-Me_2-C_6H_3NH—	69	226–228[d]	50.2	6.32	9.80	50.1	6.32	9.72

[a] All compounds were prepared by barium hydroxide hydrolysis of the corresponding hydantoin at 160° according to the method of Reisner.[5] All the compounds showed infrared bands typical of the zwitterion structure of an α-amino acid and also showed typical S → O bands of a sulfonamide. [b] Reisner[5] reported a yield of 53%, m.p. 247° dec. [c] This compound gave a single spot, detected by ninhydrin, on Whatman No. 1 paper with either t-BuOH/HCOOH/H_2O (70/10/30) or methyl Cellosolve/H_2O (9/1). [d] Recrystallized from water. [e] Recrystallized from water by addition of 12 volumes of ethanol. [f] Recrystallized from 80% ethanol. [g] In addition to showing the typical bands exhibited in the infrared by these amino acids, this compound showed carboxyl absorption at 5.81μ. The usual work-up[5] of this compound afforded the ammonium salt of the desired product. The free acid crystallized from water at pH 3. [h] Calcd. for S, 12.4. Found: S, 12.3.

yield, p-chloroaniline in 57% yield, and m-(trifluoromethyl)aniline in 48% yield. Much higher yields of the sulfonamides (IIIb) (74–80%) were obtained when the sulfonyl chloride was added portionwise to an ethanolic solution of two equivalents of aromatic amine (Procedure C). Hydrolysis with barium hydroxide to the corresponding amino acids containing an *N*-arylsulfonamide group proceeded satisfactorily (Table II).

Addition of aqueous sodium azide to the sulfonyl chloride (IIb) in alcohol gave a 56% yield of the corresponding sulfonyl azide. However, attempted hydrolysis of the hydantoin ring with barium hydroxide gave deep-seated decomposition as de-

tected by lack of S→O bands of the sulfonamide in the infrared spectrum of the amino acid fraction.

The lower homologous members of this series derived from L-cystine hydantoin (Ia)[8] were also investigated. Chlorinolysis of L-cystine hydantoin (Ia) in aqueous suspension was completely unsuccessful, possibly due to either the insolubility of the starting material or the instability of the product or both. In contrast, chlorinolysis in 42% aqueous acetic acid gave a 71% yield of L-5-(chlorosulfonylmethyl)hydantoin (IIa). This compound was somewhat unstable; after a few days the odor of sulfur dioxide was present and in a few weeks the compound had decomposed, presumably by β-elimination of the chlorosulfonyl group.

L-5-(Chlorosulfonylmethyl)hydantoin (IIa) failed to give any sulfonamide (IIIa) when its solution in *N,N*-dimethylformamide was treated with ammonia. The crude product showed the proper absorption bands in the infrared for the hydantoin ring, but no S→O bands of a sulfonamide. Similarly, the sulfonyl chloride IIa gave no detectable sulfonamide when added to ethanolic ammonia. The product isolated contained typical hydantoin carbonyl bands in the infrared, but no sulfonamide S→O bands.

When L-5-(chlorosulfonylmethyl)hydantoin (IIa) was added portionwise to a solution of two equivalents of *p*-chloroaniline or *m*-(trifluoromethyl)-aniline in ethanol (Procedure C), satisfactory conversion (68% and 50%, respectively) to the desired *N*-arylsulfonamides (IIIa) was obtained. Attempts to hydrolyze either of these L-5-(sulfamoylmethyl)hydantoins (IIIa) with barium hydroxide to the respective α-amino acids (IVa) led to complete breakdown of the molecule, presumably initiated by β-elimination of the sulfonamide residue.[9]

EXPERIMENTAL[10]

DL-5-(*β-Chlorosulfonylethyl*)*hydantoin* (IIb). Chlorine gas was bubbled through a stirred suspension of 73 g. (0.23 mole) of DL-homocystine hydantoin (Ib)[7] in 750 ml. of water and 560 ml. of glacial acetic acid until complete solution was effected (1–3 hr.). The temperature was maintained at 15–20° by adequate cooling. The solution was poured into 1.4 l. of cold water, then saturated with salt and extracted with ethyl acetate (4 × 350 ml.). The combined extracts were dried with magnesium sulfate,[11] then evaporated to dryness *in vacuo* (bath 50°). The residue was dissolved in 700 ml. of hot ethyl acetate and filtered from a little insoluble material. Dilution with 1200 ml. of petroleum ether (b.p. 30–60°) and chilling gave 85.7 g. (81%) of nearly pure material, m.p. 138–139° dec.; λ_{max}^{Nujol} 3.10μ (NH), 5.68μ (C_4=O of hydantoin), 5.82μ (C_2=O of hydantoin), 7.54, 8.67μ (S → O of SO_2Cl).

Reisner[5] has recorded a crude yield (m.p. 122–124°) of 88% by chlorinolysis in water; the yield of pure material, m.p. 141–142° dec., was not recorded.

The rate of chlorination is dependent upon the type of stirring. With very rapid stirring and high rate of passage of chlorine, solution can be completed in 15 min. The chlorination should be stopped as soon as solution is complete, since further reaction leads to 5-(β-chlorosulfonylethyl)-1,3-dichlorohydantoin, m.p. 134–135°. A mixture of the latter with 5-(β-chlorosulfonylethyl)hydantoin melted about 115–120°.

Anal. Calcd. for $C_5H_5Cl_3N_2O_4S$: C, 20.3; H, 1.70. Found: C, 20.7; H, 2.12.

This compound contains positive chlorine, as shown by a potassium iodide test, and can be reconverted to the desired product by treatment with sodium bisulfite in dilute acetic acid. The *N*-chloro derivative can also be differentiated from the desired product by the difference in NH absorption at about 3μ and the hypsochromic shift of the hydantoin carbonyls of about 0.1μ.

L-5-(*Chlorosulfonylmethyl*)*hydantoin* (IIa). Chlorinolysis of 10 g. (0.034 mole) of L-cystine hydantoin (Ia)[8] in 75 ml. of acetic acid and 100 ml. of water, as described in the preceding experiment, gave 13.8 g. of residue, m.p. 137–142° dec., on evaporation of the ethyl acetate extracts. Recrystallization from 130 ml. of ethyl acetate by the addition of petroleum ether (b.p. 30–60°) gave 9.17 g. (62%) of pure product, m.p. 149–151° dec.; λ_{max}^{Nujol} 3.10, 3.20, 3.30μ (NH), 5.62μ (C_4=O of hydantoin), 5.74μ (C_2=O of hydantoin), 7.27, 8.41, 8.67μ (S → O of —SO_2Cl).

Anal. Calcd. for $C_4H_5ClN_2O_4S$: Cl, 16.7. Found: Cl, 16.8.

In a larger run the yield of crude product was 60 g. (71%) in two crops, m.p. 143–146° dec. and 139–141° dec.

DL-5-(*β-Sulfamoylethyl*)*hydantoin* (IIIb, R_1 = R_2 = H). Ammonia was passed for 75 min. through a stirred solution of 4.52 g. (0.02 mole) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 15 ml. of dry *N,N*-dimethylformamide cooled in an ice bath. The solvent was evaporated *in vacuo*. Recrystallization from 12 ml. of water with the aid of Norit gave 2.46 g. of product, m.p. 183–185°. By concentration of the mother liquor *in vacuo*, an additional 0.18 g. (total 62%), m.p. 184–185°, was obtained. Recrystallization of a sample from water gave white crystals, m.p. 186.5–187°; λ_{max}^{KBr} 3.10μ (NH), 5.68μ (C_4=O of hydantoin), 5.85μ (C_2=O of hydantoin), 6.50μ (NH of SO_2NH), 7.62, 8.82μ (S → O of SO_2NH).

Anal. Calcd. for $C_5H_9N_3O_4S$: C, 29.0; H, 4.38. Found: C, 29.0, 29.1; H, 4.40, 4.50.

The use of ether for the solvent as recommended by Reisner[5] gave a 20% yield of impure product, m.p. 169–178°. He recorded[5] a yield of 40% and m.p. of 182–183°.

Attempts to prepare 5-(sulfamoylmethyl)hydantoin by this procedure or with ethanol as the solvent were unsuccessful.

DL-5-(*β-Diethylsulfamoylethyl*)*hydantoin* (IIIb, R_1 = R_2 = C_2H_5). *Procedure A.* To a stirred solution of 1.81 g. (8 mmoles) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 5 ml. of dry *N,N*-dimethylformamide cooled in an ice bath was added dropwise 2.19 g. (30 mmoles) of diethylamine. After being stirred in the cooling bath for an additional 75 min., the mixture was allowed to stand at 3° for about 16 hr. in a stoppered flask. The precipitate of diethylamine hydrochloride was removed by filtration and washed with 2 ml. of *N,N*-dimethylformamide. The combined filtrate and washings were evaporated to dryness *in vacuo*. The residue was crystallized from water. For further details, see Table I. Other compounds prepared by this method (Procedure A) are also listed in Table I.

DL-5-[*β*-(*p-Chlorophenylsulfamoyl*)*ethyl*]*hydantoin* (IIIb, R_1 = *p*-Cl-C_6H_4, R_2 = H). *Procedure B.* To a stirred solution of 1.13 g. (5 mmoles) of DL-5-(β-chlorosulfonylethyl)hydantoin (IIb) in 7 ml. of reagent pyridine was added a solution

(8) W. C. Hess, *J. Am. Chem. Soc.*, 56, 1421 (1934).

(9) The ability of sulfur functions β to a carboxyl to eliminate is well known. For example, cystine and cysteine and cysteic acid are unstable to base. *Cf.* also B. R. Baker, M. V. Querry, W. L. McEwen, S. Bernstein, S. R. Safir, L. Dorfman, and Y. SubbaRow, *J. Org. Chem.*, 12, 186 (1947).

(10) Melting points were taken on a Fisher-Johns apparatus and are uncorrected.

(11) The process must be carried to this point without interruption, otherwise a lowering of the yield occurs.

of 0.64 g. (5 mmoles) of *p*-chloroaniline in 5 ml. of pyridine. After 30 min., the solvent was removed *in vacuo* and the residue crystallized from 55 ml. of water with the aid of Norit; yield, 0.90 g. (57%), m.p. 190–191°. Recrystallization from 50% ethanol gave white crystals, m.p. 196–198°; λ_{max}^{KBr} 2.93, 3.10, 6.70μ (NH), 5.65μ (C_4=O of hydantoin), 5.82μ (C_2=O of hydantoin), 7.55, 8.75μ (S → O of —SO_2N—), 11.95μ (*p*-disubstituted phenyl). For additional details and for other compounds prepared in the manner (Procedure B), see Table I.

DL-5-(*β-Phenylsulfamoylethyl*)*hydantoin* (IIIb, R_1 = C_6H_5, R_2 = H). *Procedure C.* To a stirred solution of 15.8 g. (0.17 mole) of aniline in 120 ml. of 95% ethanol was added portionwise 20.0 g. (0.088 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) over a period of 5 min. The reaction mixture was stirred for 90 min., then was allowed to stand overnight. The product was collected on a filter and washed with 40 ml. of 95% ethanol; yield, 20.7 g. (86%), m.p. 205–207°. For additional details, see Table I. Other compounds prepared by this method (Procedure C) are described in Table I. In some cases it was necessary to evaporate the ethanol and crystallize the product from water.

DL-5-[(*β-Carbamoylmethylsulfamoyl*)*ethyl*]*hydantoin* (IIIb, R_1 = CH_2CONH_2, R_2 = H). To a warm (56°) mixture of 0.90 g. (8.1 mmoles) of glycinamide hydrochloride in 8 ml. of dry *N,N*-dimethylformamide and 5 ml. of dry triethylamine was added with stirring a solution of 1.81 g. (8 mmoles) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 5 ml. of *N,N*-dimethylformamide, the temperature rising to 71°. After being stirred for an additional 45 min., the heterogeneous mixture was allowed to stand for 20 hr. in a closed flask. The reaction mixture was processed as in Procedure A; yield, 1.05 g. (50%), m.p. 230–248° dec. Two recrystallizations from 95% ethanol gave white crystals with the same m.p.; λ_{max}^{KBr} 2.88, 2.99, 3.12μ (NH), 5.66μ (C_4=O of hydantoin), 5.80μ (C_2=O of hydantoin), 6.00μ (amide C=O), 7.55, 8.75μ (S → O of —SO_2N—).

Anal. Calcd. for $C_7H_{12}N_4O_5S$: C, 31.8; H, 4.57; N, 21.2. Found: C, 32.1; H, 4.50; N, 20.8.

DL-5-(*β-Azidosulfonylethyl*)*hydantoin.* To a stirred solution of 8.0 g. (0.035 mole) of DL-5-(*β*-chlorosulfonylethyl)hydantoin (IIb) in 125 ml. of 95% ethanol was added immediately a solution of 3.0 g. (0.046 mole) of sodium azide in 11 ml. of water. After the mixture was stirred for 1 hr., the precipitate was collected on a filter and washed with 75 ml. of 95% ethanol in portions, then with water; yield, 5.8 g., m.p. 123–128°. Recrystallization from 110 ml. of absolute ethanol gave 4.6 g. (56%) of white crystals, m.p. 131–133°; λ_{max}^{KBr} 4.59, 4.65μ (—N_3), 5.60μ (C_4=O of hydantoin), 5.75μ (C_2=O of hydantoin), 7.30, 8.57, 8.65μ (S → O of —SO_2N—).

Anal. Calcd. for $C_5H_7N_5O_4S$: C, 25.8; H, 3.02; N, 30.0; S, 13.8. Found: C, 26.2; H, 2.92; N, 29.8; S, 14.0.

Acknowledgments. The authors wish to thank Dr. Peter Lim for interpretation of the infrared spectra and Dr. Leon Goodman for numerous discussions.

MENLO PARK, CALIF.

[CONTRIBUTION FROM THE RADIUM INSTITUTE OF THE UNIVERSITY OF PARIS]

Bromination of Some 1,2,2-Triarylethylenes

N. P. BUU-HOÏ, ELIE LESCOT, JR., AND N. D. XUONG

Received January 6, 1958

The synthesis of a number of new diversely substituted 1,2,2-triarylethylenes is described, and their bromination reactions are investigated. It is shown that in addition to normal substitution on the ethylene chain, nuclear bromination also can occur when reactive aryl or thienyl groups are present.

In the framework of a general investigation on potential chemical inhibitors of the secretions of the anterior pituitary,[1] 1,2,2-triarylethylenes were found to constitute an attractive group for the study of relationships between chemical structure and biological activity of this type.[2] The known fact that the introduction of further oxygen-containing radicals into the molecule of estradiol results in compounds with reduced estrogenic activity (*e.g.* estriol and 6-ketoestradiol) and which can act as antagonists of the mother-substance,[3] now suggested the study of 1,2,2-triarylethylenes derived from veratrole (those derived from anisole are known to be strong estrogens).[4]

1,2-Diphenyl-2-(3,4-dimethoxyphenyl)ethylene (I) was prepared by the reaction of benzylmagnesium chloride on 3,4-dimethoxybenzophenone and dehydration of the resulting tertiary carbinol by means of formic acid.[5] Bromination of this ethylene with one mole of bromine gave 1-bromo-1,2-diphenyl-2-(3,4-dimethoxyphenyl)ethylene (II); with two moles of bromine, nuclear bromination also occurred, the reaction product probably being 1-bromo-1,2-diphenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (III). This abnormal behavior is most likely due to the fact that in the molecule of the olefin (I), the position 6 in the veratryl radical is activated both by a *p*-methoxy group and by the *o*-styryl group; the influence of this latter group is in accord with the results of the theoretical computation of π-electron densities in the molecule of

(1) N. P. Buu-Hoï, *Acta Unio Intern. contra Cancrum*, **13**, 442 (1957).

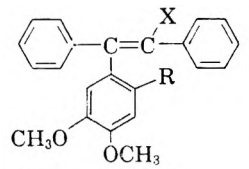
(2) N. P. Buu-Hoï, N. D. Xuong, and A. Beauvillain, *Experientia*, **13**, 20 (1957); *Bull. soc. chim. biol.*, **39**, 431 (1957); J. M. Gazave, N. P. Buu-Hoï, N. D. Xuong, and H. Clédière, *Bull. soc. chim. biol.*, **39**, 1343 (1957); N. P. Buu-Hoï, E. Lescot, and N. D. Xuong, *J. Org. Chem.*, **22**, 1057 (1957).

(3) *Cf.* C. Huggins and E. V. Jensen, *J. Exp. Med.*, **102**, 335, 347 (1955).

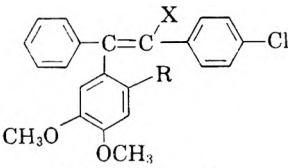
(4) *Cf.* J. M. Robson, A. Schönberg, and W. Tadros, *Nature*, **150**, 22 (1942); A. Lacassagne, N. P. Buu-Hoï, L. Corre, J. Lecocq, and R. Royer, *Experientia*, **2**, 70 (1946).

(5) N. P. Buu-Hoï, *Bull. soc. chim. France*, **13**, 117 (1946).

1,2,2-triphenylethylene.[6] The effect on halogenation of this double activation seems to be general, as



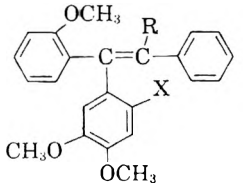
I; X = R = H
II; X = Br, R = H
III; X = R = Br



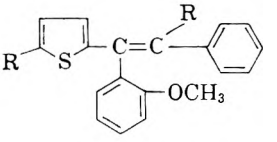
IV; X = R = H
V; X = Br, R = H
VI; X = R = Br

1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (IV), prepared from 3,4-dimethoxybenzophenone and *p*-chlorobenzylmagnesium chloride, behaved in the same way, one mole of bromine giving 1-bromo-1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (V), while with two moles, a dibromo compound (VI) was obtained.

In the case of 1-phenyl-2-(2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)ethylene (VII), prepared from benzylmagnesium chloride and 2′,3,4-trimethoxybenzophenone, the dibromination product (VIII) was already obtained with only one mole of bromine. The same observation was also made with 1-phenyl-2-(2-methoxyphenyl)-2-(2-thienyl)ethylene (IX), prepared from benzylmagnesium chloride and 2-(2-methoxybenzoyl)thiophene, which readily yielded 1-bromo-1-phenyl-2-(2-methoxyphenyl)-2-(5-bromo-2-thienyl)ethylene (X); the structure of this last compound was established by its formation in the monobromination of the ethylene prepared from 2-bromo-5-(2-methoxybenzoyl)thiophene. A similar instance of nuclear bromination of a thienyldiarylethylene had already been reported.[7]

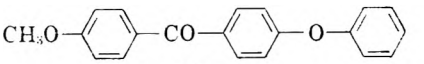


VII; R = X = H
VIII; R = X = Br

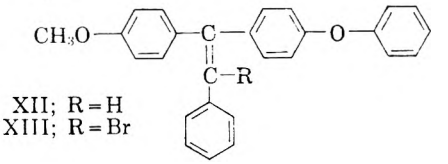


IX; R = H
X; R = Br

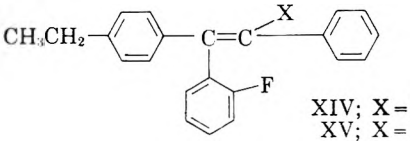
On the other hand, the presence of a phenoxyphenyl radical with a free *para*-position in the molecule of 1-phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XII) does not lead to dibromination; this ethylene, obtained from benzylmagnesium chloride and 4-methoxy-4′-phenoxybenzophenone (XI), gave the side-chain bromination product (XIII). Of course, when only unreactive aryl groups are present in the molecule of triarylethylene, only a monobromination product is to be expected, even when two moles of the halogen are used: thus, 1-phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene (XIV), prepared from 4-ethyl-2′-fluorobenzophenone, afforded the normal monobromination product (XV).



XI



XII; R = H
XIII; R = Br



XIV; X = H
XV; X = Br

In biological tests, the monobromo compounds II, V, VIII, and XII showed some Allen-Doisy activity; the other ethylenes were either barely estrogenic or inactive, and are therefore being examined for inhibitory effects on the secretions of the anterior pituitary.

EXPERIMENTAL

1,2-Diphenyl-2-(3,4-dimethoxyphenyl)ethylene (I). 3,4-Dimethoxybenzophenone (40 g., b.p. 235°/20 mm.) was prepared by Friedel-Crafts condensation of 39 g. of benzoyl chloride with 34 g. of veratrole in the presence of 34 g. of aluminum chloride in carbon disulfide. To an ice-cooled Grignard solution prepared from 7.8 g. of benzyl chloride and 2 g. of magnesium shavings in 150 ml. of ether, 10 g. of the above ketone was added portionwise with stirring, and the mixture refluxed for 10 min. to complete the reaction. After decomposition with dilute sulfuric acid, the organic layer was separated, washed with water, dried over sodium sulfate, and the solvent removed. The crude tertiary carbinol was treated with 80 ml. of formic acid, and the mixture refluxed for 5 min. to complete the dehydration. After cooling, water was added, the ethylene obtained taken up in benzene, the benzene solution washed with water and dried over sodium sulfate, the solvent removed, and the residue vacuum-fractionated. The yield was 8.5 g. of a product, b.p. 277–278°/28 mm., which crystallized from ethanol in fine colorless prisms, m.p. 102°.

Anal. Calcd. for $C_{22}H_{20}O_2$: C, 83.5; H, 6.4. Found: C, 83.2; H, 6.1.

1-Bromo-1,2-diphenyl-2-(3,4-dimethoxyphenyl)ethylene (II). A solution of 1 g. of the foregoing ethylene in 15 ml. of pure anhydrous chloroform was treated dropwise with a chloroform solution of 0.49 g. of bromine. After decoloration of the solution, the solvent was distilled off, and the residue crystallized several times from ethanol. The yield was 0.8 g. of fine colorless needles, m.p. 105°. The side-chain position of the bromine in this compound was ascertained by the formation of 3,4-dimethoxybenzophenone on chromic oxidation.

Anal. Calcd. for $C_{22}H_{19}BrO_2$: C, 66.8; H, 4.8. Found: C, 67.0; H, 4.9.

1-Bromo-1,2-diphenyl-2-(6-bromo-3,4-dimethoxyphenyl)-ethylene (III). A similar operation, effected with 1 g. of

(6) N. P. Buu-Hoï, C. A. Coulson, P. and R. Daudel, M. Martin, and A. and B. Pullman, *Rev. Sci.*, 85, 1041 (1947).

(7) N. P. Buu-Hoï, E. Lescot, and N. D. Xuong, *J. Org. Chem.*, 22, 1057 (1957).

ethylene I and 1 g. of bromine in chloroform, afforded a compound which crystallized from ethanol in shiny colorless prisms, m.p. 138°, yield: 1.2 g.

Anal. Calcd. for $C_{22}H_{18}Br_2O_2$: C, 55.7; H, 3.8. Found: C, 55.3; H, 3.9.

1-(4-Chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)-ethylene (IV). A Grignard solution, made from 9.5 g. of *p*-chlorobenzyl chloride and 2 g. of magnesium shavings in 150 ml. of ether, was treated with 10 g. of 3,4-dimethoxybenzophenone, and the reaction product worked up, as for ethylene III. The yield was 7.5 g. of a product, b.p. 285°/20 mm., crystallizing from ethanol in shiny colorless prisms, m.p. 119°.

Anal. Calcd. for $C_{22}H_{19}ClO_2$: C, 75.3; H, 5.5. Found: C, 75.5; H, 5.8.

1-Bromo-1-(4-chlorophenyl)-2-phenyl-2-(3,4-dimethoxyphenyl)ethylene (V). Monohalogenation of the foregoing ethylene (1 g.) in chloroform was best performed when a less than theoretical amount of bromine (0.3 g.) was used. The yield was 0.8 g. of a compound crystallizing from ethanol in fine colorless prisms, m.p. 124°. When the theoretical quantity of bromine was used, some of the dibrominated product was obtained.

Anal. Calcd. for $C_{22}H_{18}BrClO_2$: C, 61.5; H, 4.2. Found: C, 61.4; H, 4.2.

1-Bromo-1-(4-chlorophenyl)-2-phenyl-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (VI), prepared by treating either the previous ethylene with 1 mole of bromine, or ethylene IV with 2 moles of bromine, in chloroform, crystallized from ethanol in shiny colorless prisms, m.p. 168°.

Anal. Calcd. for $C_{22}H_{17}Br_2ClO_2$: C, 51.9; H, 3.3. Found: C, 52.2; H, 3.3.

2',3,4-Trimethoxybenzophenone was prepared by Friedel-Crafts condensation of 11.5 g. of 2-methoxybenzoyl chloride and 10 g. of veratrole with 10 g. of aluminum chloride in 75 ml. of carbon disulfide, in the cold. The yield was 10 g. of a pale yellow, viscous oil, b.p. 243°/18 mm.

Anal. Calcd. for $C_{16}H_{16}O_4$: C, 70.6; H, 5.9. Found: C, 70.7; H, 5.9.

1-Phenyl-2-(2-methoxyphenyl)-2-(3,4-dimethoxyphenyl)-ethylene (VII) was prepared from 10 g. of the foregoing ketone and a Grignard solution made from 6.8 g. of benzyl chloride and 1.3 g. of magnesium in 100 ml. of ether. The yield was 6 g. of a product, b.p. 268–270°/15 mm., crystallizing from methanol in fine colorless prisms, m.p. 136°.

Anal. Calcd. for $C_{23}H_{22}O_3$: C, 79.7; H, 6.4. Found: C, 79.8; H, 6.5.

1-Bromo-1-phenyl-2-(2-methoxyphenyl)-2-(6-bromo-3,4-dimethoxyphenyl)ethylene (VIII). This compound was the only product which could be isolated in the bromination of 1 g. of the foregoing ethylene and 0.46 g. (1 mole) of the halogen in chloroform. The yield was 0.6 g. of a compound crystallizing from acetic acid in fine colorless prisms, m.p. 155°.

Anal. Calcd. for $C_{23}H_{20}Br_2O_3$: C, 54.8; H, 4.0. Found: C, 54.9; H, 4.0.

2-(2-Methoxybenzoyl)thiophene, prepared in the usual way from 18.5 g. of 2-methoxybenzoyl chloride, 10 g. of thiophene, and 15.5 g. of aluminum chloride in 100 ml. of carbon disulfide, was a pale yellow, viscous oil, b.p. 208°/18 mm.; yield: 10 g.

Anal. Calcd. for $C_{12}H_{10}O_2S$: C, 66.1; H, 4.6. Found: C, 66.4; H, 4.7.

1-Phenyl-2-(2-methoxyphenyl)-2-(2-thienyl)ethylene (IX), prepared from 10 g. of the foregoing ketone and a Grignard solution made from 10 g. of benzyl chloride and 1.5 g. of magnesium in 100 ml. of ether, b.p. 258°/20 mm. (5 g.), crystallized from methanol in fine colorless prisms, m.p. 70–71°.

Anal. Calcd. for $C_{19}H_{16}OS$: C, 78.1; H, 5.5. Found: C, 78.1; H, 5.6.

Bromination of this ethylene with 2 moles of bromine in chloroform solution gave a 75% yield of the compound X, which crystallized from acetic acid in fine, yellowish prisms, m.p. 90°; the same compound was formed in 30% yield when one mole of the halogen was used. This derivative was identical with a product isolated in very poor yield from the reaction of 1 mole of bromine on the crude oily ethylene prepared from benzylmagnesium chloride and 5-bromo-2-(2-methoxybenzoyl)thiophene.

Anal. Calcd. for $C_{19}H_{14}Br_2SO$: C, 50.7; H, 3.1. Found: C, 50.5; H, 3.2.

4-Methoxy-4'-phenoxybenzophenone (XI). This ketone (27 g.), prepared by Friedel-Crafts condensation of 18 g. of anisoyl chloride with 18 g. of diphenyl oxide and 15 g. of aluminum chloride in carbon disulfide, crystallized from ethanol in fine colorless prisms, m.p. 120°.

Anal. Calcd. for $C_{20}H_{16}O_3$: C, 78.9; H, 5.3. Found: C, 79.2; H, 5.5.

1-Phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XII). Prepared from 10.8 g. of the foregoing ketone and a solution of 8 g. of benzylmagnesium chloride in 150 ml. of ether, this olefin (7 g.) was a pale yellow viscous oil, b.p. 309–311°/18 mm.

Anal. Calcd. for $C_{27}H_{22}O_2$: C, 85.7; H, 5.9. Found: C, 86.0; H, 5.9.

1-Bromo-1-phenyl-2-(4-methoxyphenyl)-2-(4-phenoxyphenyl)ethylene (XIII), prepared from 1 g. of the foregoing ethylene and 0.42 g. of bromine in chloroform, crystallized from ethanol in shiny colorless prisms, m.p. 96°; yield: 1 g.

Anal. Calcd. for $C_{27}H_{21}BrO_2$: C, 70.9; H, 4.6. Found: C, 71.2; H, 4.9.

4-Ethyl-2'-fluorobenzophenone. To a solution of 11 g. of ethylbenzene and 16 g. of *o*-fluorobenzoyl chloride in 50 ml. of carbon disulfide, 15 g. of aluminum chloride was added in small portions, and the mixture left overnight at room temperature, then refluxed for 30 min. on the water bath. After the usual treatment, the ketone was obtained as a pale yellow oil, b.p. 210°/25 mm., n_D^{20} 1.5711.

Anal. Calcd. for $C_{15}H_{13}FO$: C, 78.9; H, 5.7. Found: C, 79.2; H, 6.0.

1-Phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene (XIV). Prepared from 8 g. of the above ketone and a solution of 10 g. of benzylmagnesium chloride in 100 ml. of ether, this olefin (9 g.) crystallized from petroleum ether (b.p. 40–60°) in colorless prisms, m.p. 57°.

Anal. Calcd. for $C_{22}H_{19}F$: C, 87.4; H, 6.2. Found: C, 87.5; H, 6.2.

Bromination of this ethylene in chloroform, whether one or two moles of bromine were used, yielded *1-bromo-1-phenyl-2-(4-ethylphenyl)-2-(2-fluorophenyl)ethylene* (XV), crystallizing from acetic acid in fine colorless prisms, m.p. 107°.

Anal. Calcd. for $C_{22}H_{18}BrF$: C, 69.2; H, 4.7. Found: C, 69.0; H, 4.7.

PARIS VE, FRANCE

[CONTRIBUTION FROM THE FOREST PRODUCTS LABORATORY, UNIVERSITY OF CALIFORNIA]

Extractive Components from Incense Cedar Heartwood (*Heyderia decurrens* Torrey). VII. On the Occurrence of Heyderiol

EUGENE ZAVARIN

Received March 24, 1958

A new cryptophenolic compound, heyderiol, $C_{22}H_{30}O_4$, has been isolated from incense cedar heartwood in 0.14% yield (dry wood basis). It contains one phenolic hydroxyl, two methoxyls, and one ether oxygen. Oxidation with ferric chloride gave heyderioquinone, which, in turn, was oxidized with alkaline hydrogen peroxide to *p*-methoxycarvacrol. This elucidated the structure of the nonquinoidal part of the quinone. Demethylation of heyderiol, followed by oxidation with ferric chloride produced nonheyderioquinone, which upon pyrolysis gave 3-hydroxythymoquinone. This identified the quinoidal part of the heyderioquinone. Oxidation of the mixture of *p*-methoxythymol and *p*-methoxycarvacrol with alkaline ferricyanide produced heyderiol in addition to the expected libocedrol. Since coupling of this kind takes place normally in *o* or *p* positions to the hydroxyl, it would appear that heyderiol is 6-*p*-methoxycarvacroxy-*p*-methoxythymol.

The determination of the structure of heyderiol adds another member to the group of compounds with *p*-cymene carbon skeleton found in incense cedar heartwood, interrelated through enzymatic oxidation.

In continuing our investigation of the nature of the extractive components present in the heartwood of incense cedar (*Heyderia*[1] *decurrens* Torrey), the mother liquors from the separation of the libocedrol/*p*-methoxythymol addition complex[2] have been examined. Steam distillation removed the volatile portion leaving the nonvolatile residue amounting to 1.1% (dry wood basis), which was partially soluble in 10% sodium hydroxide solution. The insoluble portion amounted to 0.57% (dry wood basis) and represented a viscous, reddish liquid. *p*-Nitrobenzoylation and crystallization of the reaction product gave a sharply melting yellow *p*-nitrobenzoate in 0.14% yield (dry wood basis). Hydrolysis of this ester with alcoholic alkali gave a white, crystalline powder, m.p. 62.2–63.2°.

The isolated material, heyderiol (I), analyzed correctly for $C_{22}H_{30}O_4$, was optically inactive and contained two methoxyl groups. The C-CH_3 determination pointed out the presence of at least four methyls bonded to carbon. The elemental analysis of the *p*-nitrobenzoate ester substantiated the empirical formula and indicated that we are dealing with the monoester; determination of the molecular weight by the Rast camphor method also gave a value in agreement with this formula.

Heyderiol reacted with bromine in carbon tetrachloride solution with evolution of hydrogen bromide, slowly gave a red color with alcoholic ferric chloride, but was insoluble in sodium hydroxide solutions. This seems to point out its cryptophenolic nature.

The ultraviolet absorption spectrum of heyderiol was practically identical with the absorption spectrum of libocedrol[2] with the benzenoid B-band appearing at 287 mμ. In the infrared a sharp peak at 3520 cm.$^{-1}$ was present, stemming from the free OH stretching. No carbonyl band was detected. (Figs. 1 and 2.)

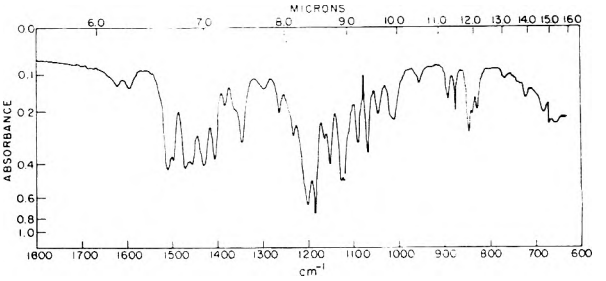


Fig. 1. Infrared absorption spectrum of heyderiol in the 1800–600 cm.$^{-1}$ region

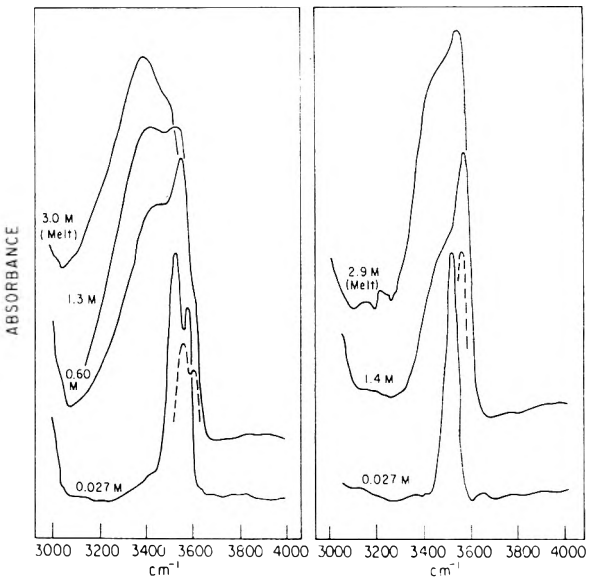


Fig. 2. Infrared absorption spectra in the 3000–4000 cm.$^{-1}$ region of hydroheyderioquinone (left) and heyderiol (right) in hexachlorobutadiene (———) and iso-octane (·····) solutions of various concentrations and in the melt form.

(1) According to the new classification by Li; *Libocedrus decurrens* Torrey according to the older classification. See H. L. Li, *J. Arnold Arboretum* (*Harvard Univ.*), **34**, 17 (1953).

(2) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **20**, 788 (1955).

Oxidation of heyderiol with alcoholic ferric chloride gave heyderioquinone (II), $C_{21}H_{26}O_4$, containing one methoxyl. The ultraviolet absorption spectrum of this quinone was very similar to that of libocedroquinone. It exhibited the quinoid bands with maxima at 260 mμ (A-band), 363 mμ (B-band), and 455 and 475 mμ (C-band) together with an inflection point at 284–285 mμ, resulting from the benzenoid B-band of the second, unoxidized aromatic nucleus. Applying Braude's rules[3] for the position of the absorption bands, it was possible to determine that the quinoid part of the molecule should be oxygen substituted in at least one position. The calculated positions were 262 mμ for A-band and 361 mμ for B-band. The infrared spectrum of the heyderioquinone was also very similar to that of libocedroquinone; it exhibited no bands in the OH region; possessed, however, strong bands corresponding to the conjugated carbonyl and conjugated double bond stretchings at 1660 and 1615 cm.$^{-1}$, respectivly. The NMR spectrum (40 mc.) was also reminiscent of that of libocedroquinone with three peaks in the aromatic region (−1.45, −1.30, −1.15 parts per million), corresponding to the three aromatic hydrogens, a peak at +1.3 parts per million corresponding to the methyl of the methoxy group, two peaks corresponding to the aromatic methyls (+2.70, +3.00 parts per million) and the isopropyl doublet (+3.80, +3.95 parts per million). The intensities of the peaks agreed with the above assignments.

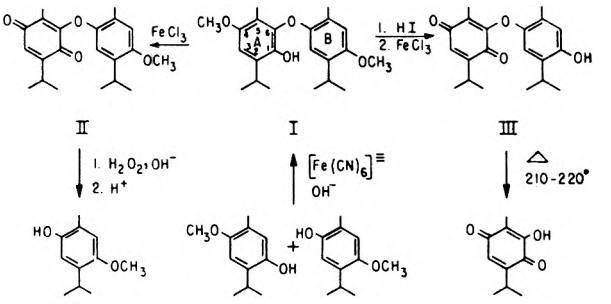
The results of the analyses, chemical and optical behavior, and the general nature of structure present in incense cedar heartwood seem to strongly suggest that we are dealing with a libocedrol-type compound formed through oxidative coupling of two *p*-methoxythymol or *p*-methoxycarvacrol units.

Oxidation of heyderioquinone with alkaline hydrogen peroxide and heating the reaction product with dilute sulfuric acid resulted in formation of *p*-methoxycarvacrol, identified by mixed melting point and infrared techniques. This establishes the structure of ring B of heyderioquinone.

Demethylation of heyderiol with hydriodic and acetic acid mixture and oxidation of the resulting product with ferric chloride produced norheyderioquinone, $C_{20}H_{24}O_4$ (III). Pyrolysis of the latter resulted in formation of 3-hydroxythymoquinone, identified with the synthetically prepared material by mixed melting point and comparison of the infrared spectra. This establishes the structure of the ring A of heyderioquinone.

The above degradative transformations do not determine which of the two ring A hydroxyls is methylated in heyderiol. As reported in one of the previous publications, the alkaline ferricyanide oxidation of *p*-methoxythymol produced libocedrol.[4]

When an analogous reaction was carried out using the mixture of *p*-methoxythymol and *p*-methoxycarvacrol, in addition to the expected libocedrol, heyderiol also could be isolated from the reaction mixture. The identity of the synthetic heyderiol with the naturally occurring compound was established by mixed melting point and infrared techniques. Since the ferricyanide coupling of the phenols takes place ortho or para to the hydroxyl, this synthesis seems to establish that in heyderiol the 4 hydroxyl is methylated, as the occurrence of the methoxyl in the 1 position would involve meta coupling of the two *p*-methoxycarvacrol units.



The occurrence of the methoxyl in ring A in 4 position has been substantiated also spectroscopically. It has been known that ortho substitution of the phenols exerts marked influence on the hydrogen bonding in solution. This effect can be studied best in the infrared where the shift from free hydroxyl stretching frequency (dilute solutions in nonpolar solvents) to the frequency of the hydroxyl engaged in hydrogen bonding (concentrated solutions or melts) is related to the strength of the hydrogen bonds. Sears and Kitchen[5] have defined hydrogen bonding indices to serve as a measure of this effect.

It is clear that a hydroxyl in position 1 should be susceptible to weaker hydrogen bonding than hydroxyl in position 4, due to the increased steric hindrance. The hydrogen bonding index for heyderiol has been determined from the infrared spectra, to be about 0.30; the same index for the free hydroxyl in position 4 could be estimated from the spectra of hydroheyderioquinone (prepared by the reduction of heyderioquinone with sodium hydrosulfite) and found to be at least 0.68; which agrees with the value of 0.73 calculated on the basis of Sears' and Kitchen's work. This suggests that the less hindered hydroxyl is methylated and is indicative of structure I for heyderiol.[6]

The determination of the structure of heyderiol is important from the biochemical standpoint. It

(3) E. A. Braude, *J. Chem. Soc.*, 490 (1945).

(4) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, **22**, 1122 (1957).

(5) W. C. Sears and L. J. Kitchen, *J. Am. Chem. Soc.*, 71, 4110 (1949).

(6) The ability of the demethylated hydroxyl to undergo stronger hydrogen bonding is also evident from the greater width of the OH absorption in case of hydroheyderioquinone as compared with heyderiol.[7]

(7) G. T. Bellamy, *The Infra-red Spectra of Complex Molecules*, London, Methuen & Co., Ltd., 1954, p. 92.

adds another member to the class of compounds with *p*-cymene carbon skeleton derived by oxidative coupling from the parent phenols, in the same way that lignanes are derived from the *n*-propylbenzene type phenols.

EXPERIMENTAL[8]

Isolation of heyderiol. The acetone extraction of a composite sample of sound incense cedar heartwood sawdust (8,640 g., dry wood basis) and the isolation of the libocedrol/*p*-methoxythymol complex from the petroleum ether soluble fraction of the extract was previously reported.[2] The mother liquors from the crystallization of the complex were evaporated to dryness, the residue steam distilled and the dark brown, semisolid nonvolatile portion recovered. It weighed 95 g. (1.1% dry wood basis).

A 23.5-g. portion of the material obtained was shaken with a mixture of 100 ml. of *n*-hexane and 100 ml. of 10% sodium hydroxide solution and filtered from an insoluble impurity. The aqueous phase was separated and the hexane solution extracted once more with 50 ml. of 10% sodium hydroxide. The aqueous phases were combined and extracted with 100 ml. of *n*-hexane in two portions. The combined organic extracts were dried with sodium sulfate, filtered, and evaporated to dryness to give 12.1 g. of a viscous, reddish liquid (0.57%).

This material was *p*-nitrobenzoylated in the usual way, using 15 g. of *p*-nitrobenzoyl chloride and 50 ml. of pyridine, then heating the resulting mixture for 1 hr. on a steam bath. To the cooled mixture, 500 ml. of 5% sodium carbonate solution was added and the whole extracted with 250 ml. of ethyl ether in three portions. The organic extracts were washed with 100 ml. of water, extracted with 500 ml. of 10% hydrochloric acid in two portions, dried with sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from acetone to give 8.5 g. of a pale yellow *p*-nitrobenzoate, m.p. 55–65° (unsharp). This ester was dissolved in 75 ml. of hot iso-octane, the solvent evaporated to about 25 ml. total volume to remove acetone of crystallization, the residue diluted with 50 ml. of iso-octane and the *p*-nitrobenzoate crystallized to give 6.55 g. of yellow crystals, m.p. 124–130°. Further purification was achieved by additional crystallizations from isooctane to give 4.38 g. of material, melting at 131–132° (0.14% yield, dry wood basis) and 1.65 g. of material melting at 128–155°, apparently consisting of a mixture of libocedrol and heyderiol *p*-nitrobenzoates.

An analytical sample of heyderiol *p*-nitrobenzoate was prepared by crystallization from iso-octane, m.p. 132.4–133.6°.

Anal. Calcd. for $C_{29}H_{33}NO_7$: C, 68.35; H, 6.92; N, 2.75; mol. wt 508. Found: C, 68.69; H, 6.76; N, 2.97; mol. weight (camphor) 480 ± 10%.

The *p*-nitrobenzoate of heyderiol represents a pale yellow, crystalline material when crystallized from acetone or acetone-alcohol mixtures, and intensive yellow crystals when crystallized from iso-octane or pure alcohol. The pale yellow form melts unsharply around 60° with some bubbles separating and probably contains acetone of crystallization. Upon standing, acetone is lost, the melting point becomes sharp, and rises to 124.4–124.7°. The *p*-nitrobenzoate in its intensive yellow form melts sharply and does not contain any solvent of crystallization. When treated with acetone it readily dissolves, but separates again in pale yellow form.

To obtain heyderiol from its ester, heyderiol/*p*-nitrobenzoate (2.987 g., m.p. 130–132°) was mixed with 10 ml. of ethanol to which 2 ml. of water and 1.0 g. of sodium hydroxide pellets was added. The resulting mixture was refluxed for 10 min., cooled, diluted to 30 ml. with cold water, and extracted with 40 ml. of chloroform in three portions. The extract was dried with sodium sulfate, filtered, and evaporated to dryness. The reaction product represented a viscous, oily liquid and weighed 2.1 g. (quantitative yield). After several months standing at room temperature, it solidified to a white, crystalline powder, m.p. 56–57°.

An analytical sample was prepared by crystallization from isooctane, m.p. 62.2–63.2°.

Anal. Calcd. for $C_{22}H_{30}O_4$: C, 73.71; H, 8.44; OCH_3 17.32. Found: C, 73.68; H, 8.32; OCH_3, 17.66. Anal. for $C.CH_3$: Calcd. for $4CH_3$, 16.8, for $3CH_3$, 12.6. Found: 14.4.

Ultraviolet absorption spectrum: λ_{max} 287 mμ, log ε 3.92 (iso-octane).

Infrared absorption spectrum: μ_{max} 3520 cm.$^{-1}$ (free hydroxyl) (hexachlorobutadiene) ν_{max} 1595, 1620 (benzenoid) (KBr pellet).

In isooctane the free hydroxyl stretching absorption shifts to μ_{max} 3560 cm.$^{-1}$

Heyderioquinone. A 120-mg. portion of heyderiol, m.p. 53.5–55° was dissolved in 5 ml. of ethanol and refluxed with 350 mg. of ferric chloride hexahydrate for 30 min. The resulting solution was diluted to 15 ml. with water and extracted with 15 ml. of chloroform in two portions. The organic extract was dried over magnesium sulfate, filtered, and evaporated to dryness. Crystallization of the residue from methanol gave dark red needles, 77.3 mg., m.p. 122–123° (67% yield).

An analytical sample was prepared by repeated crystallizations from methanol, m.p. 124.0–124.4°.

Anal. Calcd. for $C_{21}H_{26}O_4$: C, 73.66; H, 7.65; OCH_3, 9.06. Found: C, 73.55; H, 7.83; OCH_3, 9.34.

Ultraviolet absorption spectrum (methylcyclohexane): λ_{max} 235 mμ, log ε 4.15 (not very pronounced); 260 mμ, log ε 4.27 (quinoid A-band); infl. point at 284–285 mμ, log ε 3.57 (benzenoid B band); λ_{max} 363, log ε 2.98 (quinoid B band): 455 mμ, log ε 2.61; infl. point at 475 mμ, log ε 2.59 (quinoid C-band). Infrared absorption spectrum: ν_{max} 1660 cm.$^{-1}$ (conjugated carbonyl), 1615 cm.$^{-1}$ (conjugated double bond); also two bands at 1673 and 1640 cm.$^{-1}$ (KBr pellet). No OH band (carbon tetrachloride).

Nuclear magnetic resonance spectrum: (40-mc. frequency; carbon disulfide as a solvent; shifts in reference to ethanol hydroxyl band). A triplet with maxima at −1.45, −1.30, and −1.15 parts per million (rel. intensity 1.0: 1.0:1.1 units); a singlet at +1.3 parts per million (rel. intensity 3.0 units); a doublet with maxima at +2.70 and +3.00 parts per million (rel. intensity 3.0:3.1 units); and a doublet with maxima at +3.80 and +3.95 parts per million (rel. intensity 6.0:6.0 units).

Hydroheyderioquinone. A 501-mg. portion of heyderioquinone, m.p. 122–123°, was dissolved in 25 ml. of *n*-hexane to which a few ml. of chloroform was added to increase the solubility. The resulting liquid was shaken with a solution of 5.0 g. of sodium hydrosulfite in 25 ml. of water. The organic layer became gradually colorless; it was separated and the aqueous portion extracted with 15 ml. of chloroform. The organic extracts were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was dissolved in 10 ml. of *n*-hexane and allowed to crystallize at −5° to give 454 mg. of a white, crystalline material, m.p. 89–90° (90% yield).

An analytical sample was prepared by crystallizations from *n*-hexane, m.p. 91.2–92.4°.

Anal. Calcd. for $C_{21}H_{28}O_4$: C, 73.22; H, 8.20. Found: C, 73.19; H, 8.12.

Ultraviolet absorption spectrum (iso-octane): λ_{max} 288 mμ, log ε 3.93. Infrared absorption spectrum: ν_{max} 3520 and 3580 cm.$^{-1}$ (free OH stretching of the two hydroxyls) (carbon tetrachloride). In iso-octane the above maxima

(8) All melting points are corrected. Microanalysis by Microchemical Laboratory, University of California, Berkeley. Ultraviolet and infrared spectra were obtained on Beckman DK II and Perkin-Elmer Model 21 recording spectrophotometers, respectively, and the NMR spectra on Varian Associates high resolution NMR spectrometer.

shift to 3560 and 3600 cm.$^{-1}$, respectively. No carbonyl band (KBr pellet).

Oxidation of heyderioquinone. A 142-mg. portion of heyderioquinone, m.p. 122–123° was dissolved in 5 ml. of acetone to which 0.5 ml. of 30% hydrogen peroxide was added. The resulting mixture was heated to 50°, treated with 0.5 ml. of 10% sodium carbonate solution, and refluxed for 3 min. when it became yellow. One half ml. of 25% sodium solution was then added to the liquid which was refluxed for 5 min. when it became brown-red. Upon acidification with 15 ml. of 10% sulfuric acid the material was extracted with 30 ml. of *n*-hexane in two portions, the solvent evaporated, and the residue heated for 10 min. on a steam bath with 10 ml. of 10% sulfuric acid. The resulting liquid was cooled, diluted with 20 ml. of water, and extracted with 25 ml. of *n*-hexane in two portions. The combined *n*-hexane extracts were, in turn, extracted with 45 ml. of 10% sodium hydroxide solution in three portions, the aqueous solutions acidified with concentrated hydrochloric acid, and extracted with 25 ml. of chloroform in three portions. The chloroform solutions were combined, dried over sodium sulfate, filtered, and evaporated to dryness. The residue was crystallized from 3 ml. of *n*-hexane to give 39 mg. of *p*-methoxycarvacrol, m.p. 64–65° (52% yield).

Further purification was achieved through sublimation at 100° and 2-mm. pressure to give material melting at 66.2–66.6°. The melting point remained undepressed on admixture of the authentic sample. The infrared spectrum (KBr pellet technique) of the *p*-methoxycarvacrol isolated in this experiment was found to be identical to the one of an authentic sample.[9]

Norheyderioquinone. A 106 mg. portion of heyderiol, m.p. 53.5–55° was dissolved in a mixture of 6 ml. of acetic and 4 ml. of hydriodic acids, containing a few crystals of stannous chloride. The resulting liquid was refluxed for 135 min., cooled, diluted with 25 ml. of water, and extracted with 15 ml. of chloroform in two portions. The chloroform extracts were diluted with 10 ml. of acetone and treated with 1.0 g. of ferric chloride hexahydrate for 3 min. Upon addition of 25 ml. of water, the chloroform layer was separated and the aqueous phase washed with 10 ml. of chloroform. The organic extracts were combined, dried with magnesium sulfate, filtered, and evaporated to dryness. The residue was crystallized from methanol-water mixture to give 76 mg. of a dark brown crystalline powder, m.p. 120–121° (78% yield).

An analytical sample was prepared by crystallizations from methanol-water mixtures, m.p. 123.6–124.4°.

Anal. Calcd. for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37. Found: C, 73.09; H, 7.14.

Ultraviolet absorption spectrum (iso-octane): infl. point at 235 mμ, log ε 4.10 (not very pronounced); λ_{max} 259 mμ, log ε 4.33 (quinoid A band); 284–285 mμ, log ε 3.65 (benzenoid B band); 368 mμ, log ε 3.01 (quinoid B band); 450 mμ, log ε 2.66 and infl. point at 470 mμ, log ε 2.63 (quinoid C band). Infrared absorption spectrum: ν_{max} 3340 cm.$^{-1}$ (Nujol) (OH stretching); 1658 cm.$^{-1}$ (conjugated carbonyl); 1615 (conjugated double bond band); two additional bands at 1670 and 1635 (KBr pellet).

Pyrolysis of norheyderioquinone. A 69 mg. portion of norheyderioquinone, m.p. 120–121°, was heated in a Pyrex test tube for 60 min. at 210–220°. During heating a yellow colored sublimate appeared on the walls of the cold part of the vessel. The test tube was cooled, the total pyrolysis product dissolved in 25 ml. of ethyl ether, and extracted with 50 ml. of 10% sodium carbonate solution in three portions. The aqueous extracts appeared violet in color. The color changed to yellow upon acidification with 10% hydrochloric acid and a yellow precipitate appeared. The aqueous mixture was extracted with 25 ml. of chloroform in three portions, the organic extracts dried over sodium sulfate, filtered, evaporated to dryness, and the residue sublimed at 100° and 23-mm. pressure to give 4.5 mg. of 3-hydroxythymoquinone (12% yield), m.p. 160–161° (sealed capillary). Further purification by repeated sublimation raised the melting point of the compound to 166.0–166.5° (sealed capillary), undepressed on admixture with an authentic sample. The infrared spectra of the reaction product and of an authentic sample of 3-hydroxythymoquinone were found to be identical (KBr pellet technique).

Synthesis of heyderiol. To a solution of 3.1 g. of *p*-methoxythymol, n_D^{23} 1.5253, and 2.0 g. of *p*-methoxycarvacrol, m.p. 64–65°, in 125 ml. of carbon tetrachloride there was added a solution of 20 g. of sodium hydroxide in 125 ml. of water. To this vigorously stirred liquid a solution of 9.4 g. of potassium ferricyanide in 100 ml. of water was added dropwise during a 1 hr. period. The yellowish reaction mixture was acidified with concentrated hydrochloric acid and the separated aqueous phase extracted with 30 ml. of chloroform. The organic extracts were combined and evaporated to dryness. The residue was dissolved in 50 ml. of *n* hexane, dried with sodium sulfate, filtered, evaporated to 10 ml., mixed with 1.5 g. of *p* methoxythymol, diluted to 30 ml. with *n*-hexane, and crystallized to −5°. The collected crystalline precipitate was washed with *n*-hexane to give 1.131 g. of libocedrol/*p*-methoxythymol addition complex, m.p. 88.5–90°.

The filtrate from the crystallization was reduced to 20 ml. and extracted with 100 ml. of 10% sodium hydroxide solution in four portions. The aqueous extracts were acidified, extracted with 50 ml. of chloroform in two portions, dried with sodium sulfate, filtered, evaporated to dryness and the residue distilled at 40-mm. pressure to give 2.2 g. of *p*-methoxythymol, containing possibly some *p*-methoxycarvacrol, n_D^{22} 1.5283, b.p. 160–165°.

The extracted *n*-hexane solution was dried with sodium sulfate, filtered, and evaporated to dryness to give 2.5 g. of a viscous residue. The latter was *p*-nitrobenzoylated in the usual way, using 3.0 g. of *p*-nitrobenzoyl chloride, 10 ml. of pyridine, and heating the resulting mixture for 1 hr. on a steam bath. The reaction mixture was cooled, treated with 75 ml. of 3% sodium carbonate solution and extracted with 60 ml. of ethyl ether. The ethyl ether solution was extracted with 50 ml. of 10% sodium carbonate solution, washed with 100 ml. of water, extracted with 100 ml. of 10% hydrochloric acid, washed with 100 ml. of water again, dried with sodium sulfate, filtered, and evaporated to dryness.

The residue was crystallized from 15 ml. of acetone to give 410 mg. of a yellow substance, m.p. 55–75°. The material obtained was dissolved in 30 ml. of hot iso-octane and the solvent evaporated to remove acetone of crystallization. The residue was crystallized from 25 ml. of iso-octane to give 326 mg. of yellow crystals, m.p. 129–133° (6% yield). Further purification by crystallization from acetone and from iso-octane raised the melting point to 132.6–133.2°. Heyderiol was prepared from its *p*-nitrobenzoate through alkaline hydrolysis and crystallization from iso-octane, as described, m.p. 61.2–62.2°. Heyderioquinone was prepared from heyderiol through oxidation with ferric chloride, as described, m.p. 123.2–123.7°. The melting points of the three materials was undepressed on admixture with the corresponding natural compounds, and the infrared spectra of any pair were found to be identical (KBr pellet technique).

Determination of the hydrogen bonding indices. Fig. 2 depicts the infrared spectra of heyderiol and hydroheyderioquinone in the region between 3000 and 4000 cm.$^{-1}$ at various concentrations and in the melt form. Assuming ν_{max} of 3460 cm.$^{-1}$ for the band corresponding to the hydroxyl group of heyderiol, engaged in hydrogen bonding and ν_{max} 3560 cm.$^{-1}$ for the free hydroxyl band (iso-octane solution), the calculation gives 0.30 for the corresponding hydrogen bonding index. In case of hydroheyderioquinone two bands corresponding to the free hydroxyl vibration are present at ν_{max} 3560 and 3600 (iso-octane solution). The

(9) E. Zavarin and A. B. Anderson, *J. Org. Chem.*, 20, 443 (1955).

first one has the same intensity and appears at the same frequency as with heyderiol and apparently stems from the hydroxyl in position 1[10]; the second less intensive one corresponds accordingly to the hydroxyl in position 4. With the concentrated solutions and with the melt there appears, in addition, a strong band resulting from the unresolved hydrogen bond bands of the hydroxyls. With its maximum at 3380 cm.$^{-1}$ (melt) it is shifted to the longer wave length in respect to the hydrogen bond band of heyderiol. Taking this value, one calculates 0.68 for the hydrogen bonding index of hydroxyl in position 4. This is a minimum value since, due to poor resolution, the actual position of the band in question might be at still slightly lower frequency.

(10) Demethylation of a para methoxyl does not seem to influence the position of the free hydroxyl stretching. L. L. Ingraham, J. Corse, G. F. Bailey, F. Stitt, *J. Am. Chem. Soc.*, **74**, 2297 (1952).

All measurements were made at room temperature using hexachlorobutadiene and iso-octane as solvents. For calculation of the concentrations the specific weight of hexachlorobutadiene has been measured as 1.68 at 22°; the specific weights of the phenols used were assumed to be equal to that of *p*-methoxythymal (1.03 at 24°).[10]

Acknowledgments. We are indebted to Mrs. Rosalind M. Smith for determining the ultraviolet and infrared spectra, to Dr. P. Sogo and his coworkers for determining the NMR spectra, to the California Cedar Products Co. for sponsoring a research grant supporting this investigation and to Mr. Charles P. Berolzheimer for his interest and cooperation.

RICHMOND, CALIF.

[CONTRIBUTION FROM THE PHARMACEUTICAL LABORATORY, MEDICAL SCHOOL, KEIO-GIJUKU UNIVERSITY]

Santonin and Related Compounds. XVIII.[1] Tetrahydro-β-santonins[2]

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In addition to the two known tetrahydro compounds (IIBa and IIBb) of β-santonin, two new stereoisomers (IIBc and IIBd) have been obtained. The former isomers were of *trans*-decalin type, and the latters of *cis*-decalin type. IIBa and IIBc were readily isomerized into IIBb and IIBd, respectively. The reverse conversion in each pair of the ketones was effected by hydrolysis of IIBb or IIBd and subsequent relactonization of the resulting acid (IIIBa or IIIBc) under mild conditions. From these results, the four tetrahydro ketones were assigned the stereoformulas (VIIB → XB). On heating with sodium methoxide, the 3-desoxy compound (VBb) from IIBb was converted to VAb under epimerization of the methyl group at the 11-position.

A number of papers[3] concerning the preparation of the tetrahydro derivatives of α-santonin (IA) and the elucidation of their stereochemistry have been published in recent years. Of four possible stereoisomers of these compounds, three (IIA, IIAb, and IIAd) are recorded,[4] and in their stereoformulas the configurations at all the asymmetric centers appear acceptable, except two at the 4-[3f] and 11-position; the latter is the same as in α-santonin.[5] For the purpose of comparison, β-santonin (IB), which is epimeric at the 11-position with α-santonin, was catalytically hydrogenated under similar conditions to the tetrahydro derivatives. Isolation of each isomer of these compounds and assignment of its stereoformula will be recorded in this paper.

It has been stated by Clemo[6] that β-santonin was hydrogenated over palladium-charcoal in acetic acid to two stereoisomers of tetrahydro compounds, m.p. 207–208° (a) and m.p. 125–126° (b), in 25% and 30% yields, respectively. Also it has been disclosed that the use of ethanol in place of acetic acid afforded only the low-melting isomer-b in 66% yield. On repetition, these results were found to be reproducible. To avoid confusion, the previous designations "a" and "b" for these tetrahydro derivatives (IIBa and IIBb, respectively) were employed in this paper. In order to obtain other possible isomers of the tetrahydro compounds (IIB), hydrogenation of β-santonin was explored with a variety of catalysts and of reaction media. When the hydrogenation was carried out over palladium-charcoal in acetone containing either traces of hydrochloric acid or a small amount of methanol, only the isomer-b (IIBb) was obtained in satisfac-

(1) Part XVII, S. Inayama, *J. Org. Chem.*, **23**, 1183 (1958).

(2) This work was supported in part by the Grant in Aid for Scientific Research from the Japanese Ministry of Education.

(3) (a) M. Yanagita and A. Tahara, *J. Org. Chem.*, **20**, 959 (1955). (b) B. Riniker, thesis, E. T. H. Zürich, 1955. (c) O. Kovacs, V. Herout, M. Herak, and F. Sorm, *Collection Czechoslov. Chem. Communs.*, **21**, 225 (1956). (d) A. Tahara, *J. Org. Chem.*, **21**, 442 (1956). (e) M. Yanagita and R. Futaki, *J. Org. Chem.*, **21**, 949 (1956). (f) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4549 (1956). (g) C. Djerassi, R. Riniker, and B. Riniker, *J. Am. Chem. Soc.*, **78**, 6362 (1956). (h) M. Yanagita and H. Ogura, *J. Org. Chem.*, **22**, 1092 (1957).

(4) The synthesis of the fourth isomer of the tetrahydro compound has been achieved, and will be published in a later communication of this series.

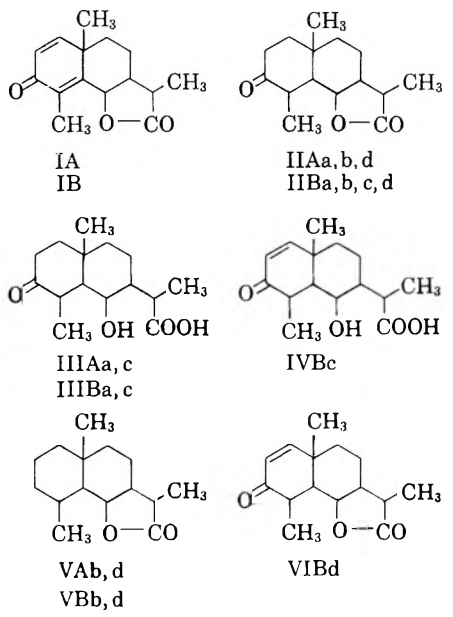
(5) (a) For example see R. B. Woodward and P. Yates, *Chem. & Ind. (London)*, 1391 (1954): *Cf.* M. Yanagita, S. Inayama, M. Hirakura, and F. Seki, *J. Org. Chem.*, **23**, 690 (1958). (b) Y. Abe, T. Miki, M. Sumim, and T. Toga, *Chem. & Ind. (London)*, 953 (1956); and references cited there. (c) W. Cocker and T. B. H. McMurry, *Chem. & Ind. (London)*, 1430 (1956).

(6) G. R. Clemo, *J. Chem. Soc.*, 1343 (1934).

tory yield. On the other hand, use of absolute acetone alone in this system afforded predominantly the other isomer-a in 57% yield. On hydrogenation over platinic oxide in dry benzene, the yield of the isomer-a was raised to 70%. It is noteworthy that in the above hydrogenation, the reduced polarity of the solvent favors the isomer-a, which is less stable than the isomer-b, as described below.

It has been reported by Cocker and McMurry[3f] that when the sodium salt of α-santoninic acid, a lactone-opening product of α-santonin (IA), was hydrogenated over platinum black in aqueous alkaline solution, the salt of the *cis*-fused tetrahydro acid (IIIAc) was obtained as the chief product. By application of this procedure, sodium β-santoninate was reduced over Raney nickel in methanolic alkaline solution, and about two equivalents of hydrogen were absorbed rather rapidly. The crude product was acidified and then heated to completely reform the lactone ring, and after chromatography on alumina, there were obtained two new tetrahydro compounds, m.p. 203–205° and m.p. 139–140°, in 6% and 35% yields, respectively. The former, the melting point of which is close to that of the isomer-a but depressed on admixture with it, is tentatively designated as the tetrahydro ketone-c (IIBc) and the latter isomer as the ketone-d (IIBd). Beside these two isomers, the ketones-a and -b (IIBa and IIBb) were isolated, both in small yields, from the less readily eluted fractions after chromic acid oxidation. When the acidification of the crude hydrogenation products was not followed by external heating, a tetrahydro acid of m.p. 205–206°, together with the ketone-b (IIBb), was obtained in low yield. This acid was tentatively designated as the tetrahydro acid-c (IIIBc). In the alkaline hydrogenation system, substitution of Raney nickel by platinic oxide furnished predominantly the acid-c, accompanied by another acid of the same melting point in 14% yield. These two were easily differentiated by the depressed mixture melting point and the comparison of rotatory powers. The new acid (IVBc) was lactonized to the dihydro ketone-d (VIBd), which was quantitatively hydrogenated over palladium-charcoal in methanol to the tetrahydro ketone-d (IIBd). The Δ^1-structure (VIBd) for this dihydro ketone can be assigned on the basis of its ultraviolet spectrum, λ_{max}^{EtOH} 226 mμ (log ε 3.96), characteristic of α,β-unsaturated ketones with one substituent.[7] Further support for this structure was found in the infrared spectrum which showed the shift (26 cm.$^{-1}$) of the carbonyl band over that of the ketone-d (IIBd).[8]

Clemo[6] has shown that both tetrahydro ketones-a and -b (IIBa and IIBb) were reduced by the Clemmensen method to the same 3-desoxy compound (VBb). From this fact, it may be inferred that, of two asymmetric centers newly formed on hydrogenation of IB, one at the 10-position which appears quite stable to acid possesses the same configuration in these two ketones. Therefore, they must differ in the spatial arrangements of the methyl group at the 4-position which is epimerizable, being in a position α to the carbonyl group. It has been established[3] that catalytic hydrogenation of α-santonin in a neutral medium led preferentially to the *trans*-fused tetrahydro ketones (IIAa or VIIA and IIAb or VIIIA), while in a basic medium the *cis*-isomer (IIAd or XA) is favored.[3f] On analogy with these results, it may be assumed that the fusion of two six-membered rings is *trans* in the ketones-a and -b (IIBa and IIBb), and *cis* in the ketones-c and -d (IIBc and IIBd). Hence, the 3-desoxy compound (VBb) cited above should have a *trans*-relationship of these rings. On warming with dilute ethanolic hydrochloric acid, the ketones-a and -c were readily converted to the isomers-b and -d, respectively. These isomerizations, which apparently involve inversion of the labile methyl group at the 4-position, indicates that this methyl group is axial in the former ketones, and equatorial in the latter two. It follows that the ketones-a, -b, -c, and -d (IIBa, IIBb, IIBc, and IIBd) can be represented by the stereoformulas VIIB, VIIIB, IXB, and XB, respectively. These assignments are in line with those of the corresponding ketones, β, α, and γ[3a,9] (VIIA, VIIIA,

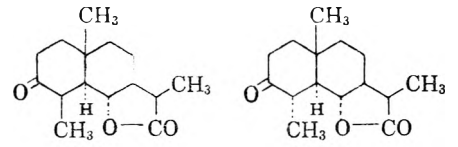


A: α-Santonin series
B: β-Santonin series

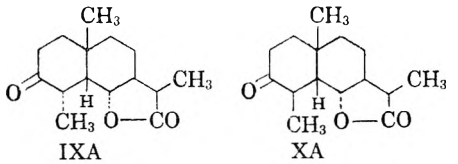
(7) L. F. Fieser and M. Fieser, *Natural Products Related to Phenanthrene*, 3rd ed., Reinhold Publishing Corp., New York, 1947, p. 190.

(8) F. A. Miller in Gilman's *Organic Chemistry, An Advanced Treatise*, John Wiley & Son, Inc., New York, 1953, Vol. III, p. 152.

(9) For the definition of the nomenclature and the numbering used in this paper, see Part XIII of this series (reference 13).



VIIA VIIB VIIIA VIIIB



IXA IXB XA XB

A: α-Santonin series
B: β-Santonin series

and XA) in the α-santonin series, but IXB is now lacking in its epimer (IXA).[4]

It has been reported[10] that β-santonin was epimerized to α-santonin by refluxing with potassium carbonate in xylene. This reaction could be duplicated by use of the commercial reagents, but when the reagents were cautiously dried, β-santonin was substantially recovered unchanged. It is possible that this epimerization occurred with opening of the lactone ring. By the same procedure an attempt was made to transform the above 3-desoxy compound (VBb) into its epimer of the α-santonin series, but it remained unaffected. However, this transformation was readily effected by heating VBb with sodium methoxide in methanol at 170–180°. The product, obtained in 80% yield, was identified as the 3-desoxy compound (VAb), prepared previously from α-tetrahydro-α-santonin (IIAb) by the Clemmensen method.[3c,11] This result gave conclusive evidence for the *trans*-fusion of the six-membered rings in the ketones-a and -b (VIIB and VIIIB). It is notable that in the β-santonin molecule, complete hydrogenation of the dienone ring caused the methyl group of the α-propionic acid residue to be more stable. The relative stability of VBb may be attributed to the effect of the release of strain on saturation of the dienone ring, forming a rigid skeleton of *trans*-decalin type. Attempt to effect similar epimerization of the 3-desoxy derivative (VBd), prepared from the ketone-d (IIBd) by the same Clemmensen procedure, failed. The configuration of this methyl group in the compounds of α- and β-santonin series will be discussed below.

Recently, Cocker and McMurry[3f] have disclosed an interesting finding about the stereochemistry of γ-tetrahydro derivative (IIAd) of α-santonin. The *cis*-fused tetrahydro santoninic acid (IIIAc), described above, was lactonized by heating to give γ-tetrahydro ketone (IIAd), which on treatment with alkali regenerated IIIAc. It was suggested by these workers that since these compounds were reduced to the different hydroxy lactones under similar conditions, they must differ in the configurations of the labile methyl group at the 4-position. This procedure of the interconversion was extended to the tetrahydro compounds in the β-santonin series. The *cis*-tetrahydro ketone-d (IIBd) was treated with warm dilute alkali to give a hydroxy acid-c (IIIBc), which gave back the ketone-d on heating with dilute hydrochloric acid. This result parallels the interconversion between IIAd and IIIAc. Moreover, it was found in this work that brief treatment of the hydroxy acid (IIIBc) with cold concentrated sulfuric acid gave rise to the ketone-c (IIBc) in almost quantitative yield. It is of interest that the conversion of the ketone-d into ketone-c through IIIBc involves a net conversion of the equatorial methyl group at the 4-position into the axial conformation. With a view of the work of Cocker and McMurry,[3f] it is apparent that this inversion has occurred in the stage of the lactone opening. Similarly, the *trans*-ketone (IIBb) was readily converted to the less stable isomer (IIBa) through the acid-a (IIIBa).

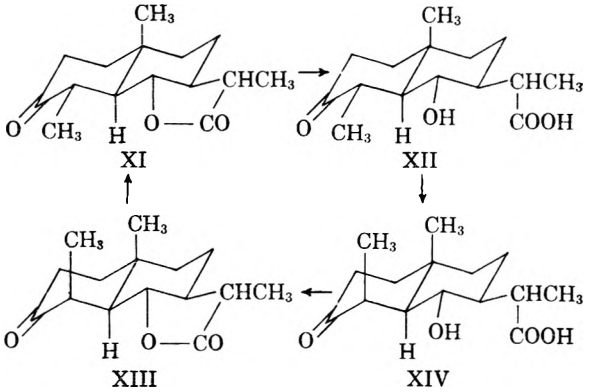
Cocker and McMurry[3f] assigned the methyl groups at the 4-position in the above acid (IIIAc) and the ketone (IIAd) equatorial and axial positions, respectively. The latter orientation (corresponding to IXA) is the reverse of that suggested previously (XA).[3] These assignments are based mainly on the assumption that catalytic hydrogenation of α-santonin into the γ-ketone (XA) involves 1,2-β-addition of hydrogen to the double bond, which requires the introduced hydrogen atoms at the 4- and 10-positions to be *cis* with respect to each other. This argument does not seem valid. Contrary to their opinion, α- and β-santonins, as described above, were catalytically hydrogenated in a neutral medium to furnish fair amounts of tetrahydro compounds, in which the newly entered hydrogen atoms at the referred positions stand in a *trans*-relationship. It seems that the labile methyl group at the 4-position in the initial hydrogenation products from santonins or santoninic acids could be inverted to the more stable conformation during hydrogenation even in a neutral medium or during the isolation of the products.

The steric aspect of the above interconversion between the *trans*-fused ketones-a and -b (IIBa and IIBb) may be reasonably explained in terms of their stereoformulas (VIIB and VIIIB) proposed in the present work. The more stable ketone-b, which can be described by the conformation XI, would initially form a hydroxy acid (XII) on hydrolysis. Examination of the molecular models indicates that in XI, opening of the lactone ring causes a closer proximity of the two equatorial substituents at the 4- and 5-positions. The resulting interaction between these groups, which is associated with the

(10) W. Cocker and T. B. H. McMurry, *J. Chem. Soc.*, 4430 (1955).

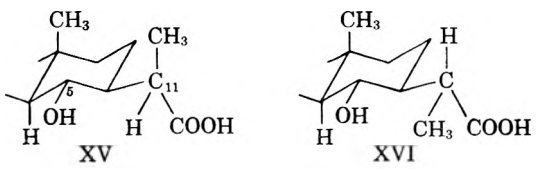
(11) E. Wedekind and K. Tettweiler, *Ber.*, 64, 387 (1931).

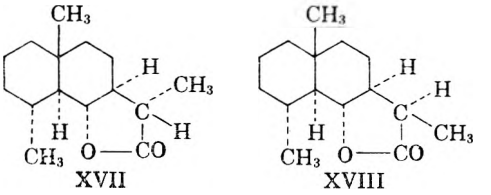
"4,5-effect",[12] is equivalent in strength to that of the *meta*-diaxial effect, as stated previously.[13] In combination with the 2-methyl ketone effect,[14] this compression may force the methyl group at the 4-position into the axial position to give the observed acid-a (XIV), in opposing the newly formed repulsion between the two axial methyl groups.[15]



These steric factors resemble closely those suggested for explanation of the relative stabilities of epimers of 30-nortaraxastan-20-ones in which the axial methyl group at the 19-position is favored over the equatorial one.[16] It is obvious that lactonization of the acid-a (XIV) under mild conditions forms the ketone-a (XIII) which readily regenerates the more stable isomer (XI). The interconversion between the *cis*-fused ketones-c and -d (IXB and XB) is presumed to involve a similar steric aspect, but because of complexity of conformational analysis of these formulas, it is difficult to assess the relative stabilities of these ketones. An effort to establish the steric aspects in the interconversions of the tetrahydro ketones (IIA and IIB) is now being made in this laboratory.

In conclusion, we should like to discuss the configurations of the methyl group at the 11-position in α- and β-santonins. The above cited epimerization of the 3-desoxy compound (VBb) into VAb possibly occurs under cleavage of the lactone ring. The hydroxy acid resulting from V can be partially described, respectively, by the most favorable conformation XV or XVI, in which the ring carbon at the 5-position and the carboxyl group are as far apart as possible. Examination of molecular models shows that, of these two structures, XV is sterically more favored than XVI by one less *meta*-diaxial interaction between the hydroxyl group at the 5-position and the methyl group at the 11-position. It follows that VAb and VBb must be represented by the stereoformulas XVII and XVIII, respectively. This gave strong support for the revised configurations of the methyl group in α- and β-santonins (IA and IB), which are the same as in XVII and XVIII respectively.





EXPERIMENTAL[17]

All melting points were uncorrected. Rotations were determined in a 0.5-dm. microtube, unless otherwise noted.

β-Santonin (IB). This was obtained from "santonin residues" of Carnegies of Welwyn Limited (Welwyn Garden City, Hertfordshire, England). The residues, white crystals, m.p. 142–147°, were washed with chloroform to remove α-santonin, and recrystallized from ethanol to give in 50–60% yield β-santonin as white plates, m.p. 215°, $[\alpha]_D^{18}$ −140.0° (c 0.20; $CHCl_3$) and $[\alpha]_D^{24}$ −138.2° (c 0.43; EtOH); λ_{max}^{EtOH} 240 mμ (log ε 4.09). Reported,[6] m.p. 216–218°, $[\alpha]_D^{19}$ −137.5° ($CHCl_3$). With Brady's reagent,[13] it formed quantitatively a *2,4-dinitrophenylhydrazone*, which was recrystallized from chloroform-methanol (1:1) to deep red fine needles, m.p. 258°; $\lambda_{max}^{CHCl_3}$ 258 mμ (log ε 4.15) and 395 mμ (log ε 4.44).

Anal. Calcd. for $C_{21}H_{22}N_4O_6$: C, 59.15; H, 5.20; N, 13.14. Found: C, 58.95; H, 5.27; N, 13.33.

Catalytic hydrogenation of β-santonin (IB) *in a neutral or acidic medium.* (*a*) By an effective modification of the method reported by Clemo,[6] β-santonin was converted to the tetrahydro compounds (IIB). β-Santonin (IB, 0.85 g.) was hydrogenated in the presence of 4% palladium-charcoal (0.2 g.) in 10 cc. of glacial acetic acid. About 2 molar-equivalents (165 cc.) of hydrogen was absorbed within 30 min. and the gas uptake ceased. After filtration of the catalyst, the reaction solution was evaporated to a small volume, and a little ethyl acetate was added. There was obtained 0.21 g. (24.2%) of the *tetrahydro ketone-a* (IIBa), m.p. 197°. Further recrystallization from ethyl acetate furnished plates, m.p. 209–210°; $[\alpha]_D^{24}$ +131.8° (c 0.22; EtOH, 1-dm. tube); $\nu_{C=O}^{CHCl_3}$ 1770 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1704 cm.$^{-1}$ Reported, m.p. 207–208°.[6]

The mother liquor of crystallization of IIBa was evaporated to a small volume, and a little ethanol was added. On standing, 0.15 g. (17.3%) of the *tetrahydro ketone-b* (IIBb), separated as white plates, m.p. 95–100°. Recrystallization from dilute ethanol raised the melting point to 125–126°. Reported, 125–126°.[6] The mother liquor from the recrystallization of IIBb gave a sirup, which afforded an additional 0.09 g. (total 27.7%) of IIBb, m.p. 123°, after warming with dilute hydrochloric acid in ethanol.

(12) W. Klyne, *Progress in Stereochemistry*, Academic Press Inc., New York, 1954, Vol. 1, p. 53.

(13) M. Yanagita and H. Ogura, *J. Org. Chem.*, **23**, 443 (1958) (Paper XIII of this series).

(14) W. Klyne, *Experientia*, **12**, 119 (1956).

(15) When the preparation of this manuscript was being made, J. C. Banerji, D. H. R. Barton, and R. C. Cookson [*J. Chem. Soc.*, 5041 (1957)] have published almost the same opinion on the conformational analysis of the tetrahydro derivatives in α-santonin series.

(16) T. R. Ames, J. L. Beton, A. Bowers, T. G. Halsall, and E. R. H. Jones, *J. Chem. Soc.*, 1905 (1954).

(17) Microanalyses were by Miss C. Shibuya, and the ultraviolet measurements by Miss M. Suzuki, both of this school.

(*b*) β-Santonin (IB, 0.50 g.) was hydrogenated over 0.10 g. of 3% palladium-charcoal in 20 cc. of acetone containing one drop of concentrated hydrochloric acid. About 2 molar-equivalents (88 cc.) of hydrogen was absorbed within 15 min. After filtration of the catalyst, the filtrate was evaporated under reduced pressure to leave a colorless sirup, which gave 0.35 g. (68.6%) of *tetrahydro-β-santonin-b* (IIBb), m.p. 113°, from an ether solution by addition of petroleum ether. Further recrystallization from dilute ethanol forms colorless plates, m.p. and mixed m.p. 125°; $[\alpha]_D^{14}$ +84.3° (c 1.6: $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1764 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1704 cm.$^{-1}$

A *semicarbazone*, obtained in 97% yield, was recrystallized from ethanol to colorless prisms, m.p. 241° (decomp.).

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.57; H, 8.51; N, 13.84.

With Brady's reagent, it formed in 70% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized from ethyl acetate to fine yellow needles, m.p. 222–223°; $\lambda_{max}^{CHCl_3}$ 364.5 mμ (log ε 4.40) and 300 mμ (log ε 3.37).

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09; N, 13.02. Found: C, 58.55; H, 5.82; N, 13.00.

(*c*) β-Santonin (2.00 g.) was hydrogenated over 0.2 g. of 9% palladium-charcoal in a mixture of 50 cc. of acetone and 15 cc. of methanol. Hydrogen (400 cc., 2.2 molar-equivalents) was absorbed. Worked up as above, the residual sirup furnished the ketone (IIBb, 1.04 g.) m.p. 112°, from an ethanol solution by addition of a little water. Recrystallization from dilute ethanol afforded 0.93 g. of colorless plates, m.p. and mixed m.p. 123°. The sirup, obtained from the mother liquor of IIBb, was warmed with dilute hydrochloric acid in methanol to give an additional 0.50 g. (total 70.4%) of IIBb, m.p. and mixed m.p. 123°.

(*d*) The hydrogenation of IB (2.00 g.) was carried out under the same conditions as described above in (c), except only dry acetone (50 cc.) was used instead of the mixture of solvents. Hydrogen (420 cc., 2.3 molar-equivalents) was absorbed. After removal of the catalyst, the solution was evaporated under reduced pressure to a small bulk, giving 1.15 g. (57%) of the *tetrahydro ketone-a* (IIBa), colorless plates, m.p. 200°. Recrystallization from ethyl acetate gave colorless plates, m.p. and mixed m.p. 207°.

(*e*) β-Santonin (IB, 0.50 g.) was hydrogenated over platinic oxide (0.03 g.) in dry benzene (20 cc.), and absorption of about 2 molar-equivalents (100 cc.) of hydrogen required 5 hr. On working up as described in (*d*), the *ketone-a* (IIBa, 0.21 g., 41%), m.p. 204°, was obtained. Recrystallization from ethyl acetate afforded colorless plates, m.p. and mixed m.p. 212°: $[\alpha]_D^{16}$ +116.0° (c 4.0; $CHCl_3$). The mother liquor from the crystallization gave additional 0.15 g. (total 70%) of IIBa, m.p. 188°.

It forms quantitatively a *semicarbazone*, which was recrystallized from ethanol to fine white needles, m.p. 255° (decomp.): $[\alpha]_D^{16}$ −25.3° (c 0.48; pyridine).

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.90; H, 7.79; N, 13.38.

With Brady's reagent, it was converted in 76.4% yield to the 2,4-dinitrophenylhydrazone of the ketone-b (IIBb), which was recrystallized from ethyl acetate to yellow fine needles, m.p. and mixed m.p. 221°.

Hydrogenation of β-santonin (IB) *in basic medium.* (*a*) β-Santonin (IB, 0.50 g.) was dissolved in warm alkali solution (0.5 g. of potassium hydroxide in 10 cc. of methanol and 1 cc. of water), and the clear solution was shaken under an atmosphere of hydrogen in the presence of Raney nickel (prepared from 3 g. of alloy) until the gas absorption was complete. In 3 hr., 110 cc. (2.4 molar-equivalents) of hydrogen was consumed. After removal of the catalyst, the solution was evaporated under reduced pressure, and the residual oil was warmed with concentrated hydrochloric acid to reform the lactone ring and then was taken up in ether. Evaporation of the dried ether solution gave a colorless oil (0.48 g.) which was chromatographed on alumina (15 g.). The elution with petroleum ether–benzene (3:2) afforded 0.18 g. (35%) of the *tetrahydro ketone-d* (IIBd), colorless plates, m.p. 135–136°. Recrystallization from the same solvent mixture and then from dilute ethanol raised the melting point to 139–140°; $[\alpha]_D^{19}$ +71.1° (c 0.90; $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1767 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1701 cm.$^{-1}$ It showed obvious depression of the melting point (98–100°) on admixture with the above ketone-b (IIBb), m.p. 125–126°.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.65; H, 8.63.

It formed in 82% yield a *semicarbazone*, which was recrystallized from ethanol to fine colorless needles, m.p. 215° (decomp.).

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: C, 62.52; H, 8.20; N, 13.67. Found: C, 62.48; H, 8.25; N, 13.79.

With Brady's reagent, IIBd gave in 60% yield a *2,4-dinitrophenylhydrazone*, which was recrystallized to golden yellow plates, m.p. 194°; $\lambda_{max}^{CHCl_3}$ 365 mμ (log ε 4.26) and 300 mμ (log ε 3.20).

Anal. Calcd. for $C_{21}H_{26}N_4O_6$: C, 58.59; H, 6.09. Found: C, 58.52; H, 6.25.

The following fractions eluted with benzene gave 0.03 g. (6%) of the *tetrahydro ketone-c* (IIBc), m.p. 147°. Recrystallization from benzene afforded white needles, m.p. 198° and mixed m.p. 200° with a sample (IIBc) described below. It was converted to the ketone-d (IIBd) with 2,4-dinitrophenylhydrazine or with acid, which will be described below in more detail.

The last fractions eluted with methanol furnished a colorless sirup (0.25 g.), which could not be crystallized. The sirup was oxidized with chromic acid–pyridine, and from the neutral fraction, 0.08 g. (16%) of IIBa, m.p. 200°, which was recrystallized from ethanol to colorless prisms, m.p. and mixed m.p. 209–210°. A sirup from the mother liquor of IIBa was dissolved in a little ethanol, and a little water was added. On standing in a refrigerator, 0.04 g. (8%) of IIBb separated as white plates, m.p. 120°, which was raised by recrystallization from dilute ethanol to 123° (mixed melting point).

(*b*) As described above in (*a*), β-santonin (5.00 g.) in potassium hydroxide solution (5.0 g. of potassium hydroxide in 40 cc. of methanol and 20 cc. of water) was hydrogenated in the presence of Raney nickel (from 15 g. of alloy). About 2 molar-equivalents (1000 cc.) of hydrogen were absorbed, and the oily product was mixed with concentrated hydrochloric acid and the mixture, which was not externally heated, was extracted with ethyl acetate. The acetate solution was shaken with aqueous bicarbonate, and was evaporated to leave a sirup (3.08 g.) which solidified partly. The residue (1.52 g.) was chromatographed on alumina (50 g.), and the elution with petroleum ether–benzene (4:1) furnished the *ketone-b* (IIBb) as crude crystals (0.63 g.), melting in the range 75–105°. Recrystallization from dilute ethanol gave colorless plates, m.p. and mixed m.p. 124°.

The bicarbonate solution, removed from the neutral fraction, was acidified and extracted with ethyl acetate. Evaporation of the ethyl acetate solution left a sirup (2.00 g.), which solidified partly. From a methanolic solution by addition of water, the sirup gave 0.85 g. (16%) of the *hydroxy acid-c* (IIIBc) as colorless needles, m.p. 198°. Recrystallization from dilute ethanol raised the melting point to 204–206°; $[\alpha]_D^{26}$ +9.05° (c 2.87; EtOH).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.04; H, 8.66.

(*c*) Hydrogenation of β-santonin (IB, 5.00 g.) was carried out under the same conditions as described in (b), except platinic oxide (0.16 g.) was used as catalyst in place of Raney nickel. About 2 molar-equivalents (929 cc.) of hydrogen were absorbed. The acid fraction, a sirup (4.00 g.) which solidified partly, gave 0.75 g. (14%) of the *Δ¹-dihydro acid* (IVBc), colorless prisms, m.p. 203–205°, from a methanol solution by addition of water. Recrystallization from dilute ethanol raised the melting point to 204–206°; $[\alpha]_D^{28}$ −54.8° (c 1.93; EtOH) and $[\alpha]_D^{28}$ −33.2° (c 3.13; pyridine). It showed obvious depression (about 20°) of the melting

point on admixture with the tetrahydro acid-c (IIIBc), m.p. 204–206°, described above.

Anal. Calcd. for $C_{15}H_{22}O_4$: C, 67.68; H, 8.33. Found: C, 67.69; H, 8.49.

Catalytic hydrogenation of IVBc with palladium-charcoal in methanol afforded quantitatively the tetrahydro acid-c (IIIBc), m.p. 198°. A pure sample showed m.p. and mixed m.p. 204° (from dilute ethanol).

The mother liquor of crystallization of IVBc gave 1.50 g. (27%) of the *acid-c* (IIIBc), m.p. 198°, which on recrystallization from dilute ethanol showed m.p. and mixed m.p. 203–204°. A colorless sirup (1.6 g.), obtained from the mother liquor of IIIBc, was chromatographed on silica gel (20 g.), and the elution with benzene–ethyl acetate (7:3) afforded additional 0.33 g. (total 32%) of IIIBc, m.p. 195°.

The neutral fraction, a colorless sirup (1.10 g.) was dissolved in warm 10% potassium hydroxide, and the clear solution was acidified with cooling. After standing at room temperature for 5 hr., the separated oil was extracted with ethyl acetate and the dried acetate solution was evaporated to leave a sirup (0.75 g.), which deposited 0.26 g. of white needles, m.p. 154°, from an ethanol solution by addition of water. Further recrystallization from dilute ethanol raised the melting point to 165°, undepressed on admixture with the tetrahydro acid-a (IIIBa) described below.

Δ^1-Dihydro-β-santonin (VIBd). The Δ^1-dihydro acid (IVBc, 0.75 g.), described in the preceding paragraph, was refluxed with *p*-toluenesulfonic acid (0.05 g.) in 50 cc. of benzene for 5 hr. After washing with aqueous bicarbonate and then water, the solution was dried and evaporated to leave 0.69 g. (99%) of the *Δ^1-dihydro-β-santonin* (VIBd) as colorless plates, m.p. 157°. Recrystallization from ethanol raised the melting point to 158–159°; $[\alpha]_D^{28}$ +31.7° (c 3.53; $CHCl_3$); λ_{max}^{EtOH} 226 mμ (log ε 3.96); $\nu_{C=O}^{CHCl_3}$ 1675 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{20}O_3$: C, 72.55; H, 8.12. Found: C, 72.40; H, 8.09.

With Brady's reagent, it formed almost quantitatively a *2,4-dinitrophenylhydrazone*, which was recrystallized from methanol-chloroform to fine yellow needles, m.p. 204°; $\lambda_{max}^{CHCl_3}$ 258 mμ (log ε 4.44) and 375 mμ (log ε 4.75).

Anal. Calcd. for $C_{21}H_{24}N_4O_6$: C, 58.87; H, 5.65; N, 13.08. Found: C, 58.54; H, 5.76; N, 13.25.

Catalytic hydrogenation of the dihydro ketone (VIBd, 0.03 g.) with 5% palladium-charcoal (0.01 g.) in methanol (5 cc.) resulted in a quantitative yield (0.03 g.) of the tetrahydro ketone-d (IIBd), m.p. 130°. Recrystallization from dilute ethanol raised the melting point to 140° (mixed m.p.).

Hydroxy acid-a (IIIBa) *from the tetrahydro ketone-b* (IIBb). The ketone-b (IIBb, 0.10 g.) was added to 10 cc. of 5% aqueous sodium hydroxide, and the mixture was warmed on a water bath for 1.5 hr. After cooling, the clear solution was washed with ether, acidified with 5% dilute hydrochloric acid under ice cooling, and extracted with ethyl acetate. Evaporation of the dried acetate solution furnished 0.07 g. (65%) of the acid-a (IIIBa), m.p. 144°. Recrystallization from dilute ethanol gave white needles, m.p. 165°; $[\alpha]_D^{22}$ −51.6° (c 1.24; EtOH).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 66.92; H, 8.65.

Acid treatment of the hydroxy acid-a (IIIBa). (a) *With cold concentrated sulfuric acid.* The powdered acid-a (IIIBa, 0.01 g.), above described, was added to concentrated sulfuric acid with ice cooling, and was dissolved to a clear solution in about two minutes. Immediately, the solution was poured into ice water, and the separated solid was taken up in ether. The ether solution was washed with aqueous sodium bicarbonate and then with water. Evaporation of the dried ether solution left 5 mg. (54%) of the pure ketone-a (IIBa) as colorless plates, m.p. and mixed m.p. 209°.

(b) *With dilute hydrochloric acid on heating.* A solution of the above acid-a (IIIBa, 0.03 g.) in methanol (1 cc.) and 5% hydrochloric acid (1 cc.) was heated to reflux for 1 hr. On cooling, the solution deposited 0.02 g. (71%) of the ketone-b (IIBb) as colorless plates, m.p. 120°. A pure sample had m.p. and mixed m.p. 125–126° (from dilute ethanol).

Isomerization of the ketone-a (IIBa) *to the ketone-b* (IIBb). A solution of the ketone-a (IIBa, 0.05 g.) in ethanol (3 cc.) containing 3% hydrochloric acid (0.5 cc.) was warmed for 30 min. on a water bath. On cooling, the solution deposited the ketone-b (IIBb, 0.035 g., 70%), m.p. 123°. A pure sample had m.p. and mixed m.p. 124–125° (from dilute ethanol).

Hydroxy acid-a (IIIBc) *from the tetrahydro ketone-d* (IIBd). The hydrolysis of IIBd (0.02 g.) was carried out as described above for IIBb, giving the acid-c (IIIBc, 0.015 g., 72%), m.p. 198°. Recrystallization from benzene afforded colorless leaflets, m.p. and mixed m.p. 204–206°; $[\alpha]_D^{28}$ +9.74° (c 1.23; EtOH).

Anal. Calcd. for $C_{15}H_{24}O_4$: C, 67.13; H, 9.02. Found: C, 67.27; H, 9.14.

Acid treatment of the hydroxy acid-c (IIIBc.) (a) *With cold concentrated sulfuric acid.* As described above for IIIBa, the acid-c (IIIBc, 0.33 g.) was treated with concentrated sulfuric acid (1.5 cc.) and the ketone-c (IIBc, 0.29 g., 94%) was obtained as colorless plates, m.p. 160°. Recrystallization from ethyl acetate raised the melting point to 205°; $[\alpha]_D^{17}$ +26.3° (c 0.53; $CHCl_3$); $\nu_{C=O}^{CHCl_3}$ 1764 cm.$^{-1}$ and $\nu_{C=O}^{CHCl_3}$ 1709 cm.$^{-1}$ It showed obvious depression (*ca.* 20°) of the melting point on admixture with the starting acid-c.

Anal. Calcd. for $C_{15}H_{22}O_3$: C, 71.97; H, 8.86. Found: C, 71.73; H, 8.90.

A *semicarbazone*, obtained in 81% yield, was recrystallized from ethanol afforded white crystalline powder, m.p. 258° (decomp.).

Anal. Calcd. for $C_{16}H_{25}N_3O_3$: N, 13.67. Found: N, 13.73.

With Brady's reagent, it forms in 60% yield a 2,4-dinitrophenylhydrazone, m.p. 192° and mixed m.p. 193°, of the ketone-d (IIBd).

(b) *With dilute hydrochloric acid on heating.* As described above for IIIBa, the acid-c (IIIBc, 0.90 g.) was heated with 5% hydrochloric acid (30 cc.) and methanol (10 cc.) to regenerate the ketone-d (IIBd, 0.78 g., 93%) as colorless plates, m.p. 133°. Recrystallization from dilute ethanol raised the melting point to 138–139° (mixed m.p.).

(c) *With p-toluenesulfonic acid.* The acid-c (IIIBc, 0.15 g.) was refluxed with *p*-toluenesulfonic acid (0.01 g.) in benzene (12 cc.) for 5 hr. After cooling, the mixture was washed with aqueous sodium bicarbonate, then dried and evaporated to give the ketone-d (IIBd, 0.13 g., 92%) as colorless plates, m.p. 135–137°. Recrystallization from dilute ethanol raised the melting point to 139–140° (mixed m.p.).

Isomerization of the ketone-c (IIBc) *to the ketone-d* (IIBd). As described above for IIBa, the ketone-c (IIBc, 0.02 g.) was converted with hydrochloric acid to the ketone-d (IIBd, 0.015 g.), colorless plates, m.p. 133°. A pure sample showed m.p. and mixed m.p. 139° (from dilute ethanol).

3-Desoxytetrahydro-β-santonin-b (VBb). This was prepared from the ketone-b (IIBb) by a slight modification of the procedure previously reported.[6] The ketone-b (0.50 g.) in 1 cc. of toluene was heated to reflux for 24 hr. with zinc amalgam (prepared from 1.2 g. of zinc and 0.05 g. of mercuric chloride) in 1.7 cc. of concentrated hydrochloric acid and 1 cc. of water. One half cc. each of concentrated hydrochloric acid was added to the refluxed reaction 2 times during a period of 4 hr. After cooling, ether was added to the reaction mixture, and the organic layer was separated, washed with water, dried, and evaporated. There was obtained 0.40 g. (85%) of the 3-desoxy compound-b (VBb) as colorless prisms, m.p. 72°. Recrystallization from petroleum ether raised the melting point to 76°; $[\alpha]_D^{17}$ +87.6° (c 1.67; EtOH). Reported, m.p. 75–76°.[6]

Isomerization of the 3-desoxy compound-b (VBb) *to* VAb. The above desoxy compound (VBb, 0.15 g.) was added to sodium methoxide solution (from 5 cc. of 99% methanol

and 0.5 g. of sodium metal), and was heated in a sealed tube at 170–180° for 2 hr. After cooling, the solution was diluted with water, acidified with hydrochloric acid, and warmed for 15 min. on a water bath. The solution was extracted with ether, and the ether solution was washed with aqueous bicarbonate, dried, and evaporated to leave 0.12 g. (80%) of colorless leaflets, m.p. 150°. Recrystallization from dilute ethanol raised the melting point to 153°; $[\alpha]_D^{18}$ +21.9° (c 2.47; EtOH). It showed no depression of the melting point on admixture with 3-desoxy-α-tetrahydro-α-santonin (VAb)[3b,c] m.p. 154°; $[\alpha]_D^{31}$ +20.8° (c 0.87; EtOH), prepared from IIAb by the Clemmensen reduction.

3-Desoxytetrahydro-β-santonin-d (VBd). By the Clemmensen method described above for preparing VB, the ketone-d (IIBd, 0.29 g.) was reduced to an oily product, which was fractionated to a colorless oil (VBd, 0.22 g., 80%), b.p. 73–75° at 3 mm. The oil (0.17 g.) was chromatographed on alumina (10 g.), and the elution with petroleum ether–benzene (2:1) gave 0.13 g. of colorless sirup, which solidified almost completely; m.p. 88–89°; $[\alpha]_D^{19}$ +60.0° (c 1.27; $CHCl_3$).

Anal. Calcd. for $C_{15}H_{24}O_2$: C, 76.22; H, 10.24. Found: C, 76.35; H, 10.01.

Attempt on isomerization of VBd into the corresponding compound (VAd)[3a] in α-santonin series by the procedure described for VBb was unfruitful.

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SHINJUKU-KU, TOKYO, JAPAN

[CONTRIBUTION FROM THE CITRUS EXPERIMENT STATION OF THE UNIVERSITY OF FLORIDA]

Derivatives of (+)-Limonene. I. Esters of *trans*-*p*-Menthane-1,2-diol[1]

WILLIAM F. NEWHALL

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The hitherto unreported diacetate, dipropionate and dibutyrate esters of trans-*p*-menthane-1,2-diol have been synthesized from (+)-limonene in 50 per cent yield. Partial hydrogenation of (+)-limonene followed by hydroxylation with performic acid affords a crystalline mixture of *trans*-*p*-menthane-1,2-diols in 60 per cent yield. The diols are converted in 90–95 per cent yield to the diesters by reaction with the appropriate acid anhydride.

This paper describes a convenient synthesis of *trans*-*p*-menthane-1,2-diol and three of its diester derivatives. The preparation of *trans*-*p*-menthane-1,2-diol by the hydrogenation of *trans*-$\Delta^{8(10)}$-*p*-menthene-1,2-diol has been reported by Schmidt[2] and others.[3] Improved yields of this saturated diol have been obtained in this laboratory by first hydrogenating the exocyclic double bond of (+)-limonene and then hydroxylating the endocyclic double bond by reaction with performic acid.

Hydrogenation of freshly distilled (+)-limonene[4] (I) without solvent, at low pressure, over a 5 per cent platinum on Darco G-60 catalyst proceeds smoothly to afford Δ^1-*p*-menthene (II) in virtually quantitative yield. It is imperative to use only freshly distilled material, because the catalyst is rapidly poisoned by compounds (probably peroxides) formed in (+)-limonene stored in contact with air for as short a period as five days. The hydrogenation is highly exothermic and absorption of hydrogen almost ceases when one mole has been absorbed per mole of (+)-limonene. It has been found practicable to use the same catalyst for as many as thirty consecutive hydrogenations. Spent catalyst is easily reactivated by washing with acetone and drying for one hour at 110°. This ease of partial hydrogenation of (+)-limonene was first described by Vavon,[5] who used a heat deactivated platinum catalyst. More recently Fujita and Matsuura[6] accomplished the same partial hydrogenation using Adams' platinum catalyst in methanol solution.

Hydroxylation of Δ^1-*p*-menthene (II) by the gradual addition of one equivalent of preformed performic acid followed by hydrolysis of the intermediate monoformate esters with alcoholic potassium hydroxide, affords a crystalline mixture of *trans*-*p*-menthane-1,2-diols (III) in 60% over-all yield from (I). Direct addition of II to the performic acid solution results in yields of III 20–25% less than obtained by the inverse addition procedure. Separation of the diols III by fractional crystallization affords 40–45% of one diol melting at 89° and 8–12% of another diol melting at 55°. By analogy with the work of Jefferies and Milligan[7] and Cole and Jefferies,[8] on the racemic *trans*-*p*-menthane-1,2-diols, the higher melting, more abundant diol probably has the conformation of their compound (I) (1-hydroxyneocarvomenthol) and the lower melting diol corresponds in structure to

(1) Florida Agricultural Experiment Station Journal Series, No. 720.

(2) H. Schmidt, *Ber.*, 82, 11 (1949).

(3) H. Meerwein, A. Ogait, W. Prang, and A. Serini, *J. prakt. Chem.*, 113, 9 (1926).

(4) Samples of citrus d-limonene were supplied by Kuder Citrus Pulp Co., Lake Alfred, Fla.

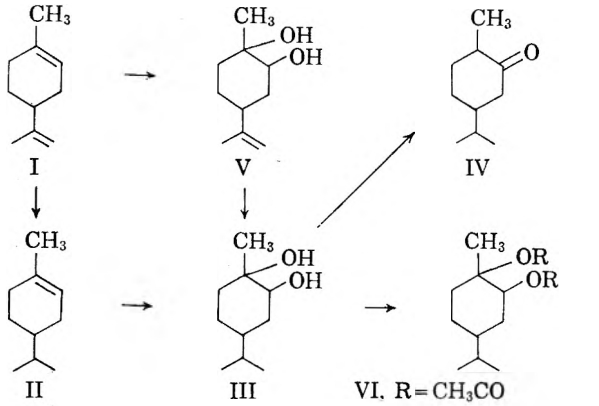
(5) M. G. Vavon, *Bull. soc. chim.* IV, 15, 282 (1914).

(6) K. Fujita and T. Matsuura, *J. Sci. Hiroshima Univ.* 18A, 455 (1955).

(7) P. R. Jefferies and B. Milligan, *J. Chem. Soc.*, 4384 (1956).

(8) A. R. H. Cole and P. R. Jefferies, *J. Chem. Soc.*, 4391 (1956).

their compound (II) (1-hydroxyisocarvomenthol). However, the infrared absorption of these optically active diols was not considered conclusive enough to establish conformations. Both *trans* diols are



VI, R = CH_3CO
VII, R = CH_3CH_2CO
VIII, R = $CH_3CH_2CH_2CO$

dehydrated by refluxing in 10% sulfuric acid to the same tetrahydrocarvone[2,7] (IV). The higher melting isomer may also be prepared in poor yield (14%) by performic acid hydroxylation of (+)-limonene (I) to $\Delta^{8(10)}$-*p*-menthene-1,2-diol (V) followed by catalytic hydrogenation. In this case only one unsaturated diol (V) could be isolated from the hydroxylation. Performic acid hydroxylation of (+)-limonene is, in contrast to the peracetic acid hydroxylations reported in the literature,[3,9,10] much too vigorous and a large part of the (+)-limonene is converted to water soluble polymers.

The higher melting diol is converted in 90–95% yield to the diacetate (VI), dipropionate (VII), or dibutyrate (VIII) ester by refluxing with the appropriate acid anhydride. The mixture of *trans*-diols (III) may also be converted directly, in comparable yield, to give a mixture of isomeric diesters. In this way saturated glycol esters may be prepared from (+)-limonene (I) in 50–55% yield.

EXPERIMENTAL

Preparation of 5% platinum on charcoal catalyst. The general procedure outlined by Kaffer[11] was followed with one modification, no hydrazine hydrate was used in the final stage of the preparation.

Δ^1-*p-Menthene* (II). One hundred and twenty milliliters (100.8 g.) of freshly distilled (+)-limonene (I) (b.p. 175–176°, $[\alpha]_D^{23}$ + 118.7°, n_D^{23} 1.4722) was hydrogenated at room temperature in a Parr series 3910 low pressure hydrogenation apparatus at a starting pressure of 52 pounds using 1.3 g. of 5% platinum on Darco G-60 catalyst. One equivalent of hydrogen was consumed after 60 min. The temperature of the reaction flask rose to approximately 60° during hydrogenation. Removal of the catalyst by filtration afforded 121 ml. (97.6%) of Δ^1-*p*-menthene (II) (b.p. 174–176°, $[\alpha]_D^{23}$ + 109, n_D^{23} 1.4557). The physical constants for Δ'-*p*-menthene reported by Fujita and Matsuura[6] are: b.p. 77.5–78° at 35 mm., n_D^{25} 1.4533, $[\alpha]_D^{25}$ + 100.0°.

trans-p-Menthane-1,2-diols (III). A mixture of 200 ml. of 90% formic acid and 75.2 g. (0.752 moles) of 34% hydrogen peroxide was added dropwise over a period of 1 hr. to 120 ml. (0.717 moles) of Δ^1-*p*-menthene (II). The mixture was stirred and cooled in a water bath to maintain a temperature of 35° during the addition. Stirring at 35° was continued for an additional 2 hr. Five grams of sodium bisulfite was added to destroy peroxides and most of the formic acid was removed under vacuum at 50°, using a film evaporator. One hundred ml. of 95% ethanol was added to the colorless, oily residue and sufficient ethanolic potassium hydroxide to bring the *p*H to 11–12. This mixture was stirred for 3 hr. at room temperature, made to *p*H 6 with concentrated hydrochloric acid and all of the alcohol removed under vacuum at 50°. The residue was taken up in ether, the aqueous phase discarded and the ether solution dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the residual oil (100.6 g.) was distilled. At 102–108° (1 mm.) 74.3 g. (60% from I) of *trans-p*-menthane-1,2-diols (III) distilled as a colorless, viscous oil. This oil slowly crystallized on standing at room temperature. The mixed diols were dissolved in 200 ml. of hot benzene, the solution was cooled, and 400 ml. of petroleum ether (30–60°) was added. The higher melting *trans*-diol crystallized as colorless prisms, m.p. 84–87°, 52.6 g. (43%). Several recrystallizations from a mixture of benzene and petroleum ether afforded material melting at 86.6–88.6° and having a rotation of $[\alpha]_D^{23}$ + 48° (10% acetone solution).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.73; H, 11.70. Found: C, 70.13; 11.56.

The filtrate from the above diol was evaporated to dryness under vacuum and the residue dissolved in 100 ml. of petroleum ether. The lower melting *trans*-diol crystallized as colorless needles, m.p. 51–54°, 9.6 g. (7.8%). Several recrystallizations from petroleum ether afforded material melting at 54–55°, $[\alpha]_D^{23}$ + 25° (10% acetone solution).

Anal. Calcd. for $C_{10}H_{20}O_2$: C, 69.73; H, 11.70. Found: C, 68.88, H, 11.79.

Tetrahydrocarvone (IV). Ten grams of *trans-p*-menthane-1,2-diol (III) (higher melting isomer, m.p. 87–89°) was refluxed for 2 hr. in 100 ml. of 10% sulfuric acid. During refluxing, 8.5 g. of colorless, steam distillable oil was collected in an oil separatory trap. Purification of this oil through the semicarbazone derivative afforded 5.0 g. (56%) of tetrahydrocarvone (IV), b.p. 55–56 (1 mm.), n_D^{23} 1.4545, $[\alpha]_D^{23}$ + 18 (reported,[2] b.p. 218–220°/745 mm.; n_D^{20} 1.4544; α_D^{20} + 13.3).

Anal. Calcd. for $C_{10}H_{18}O$: C, 77.87; H, 11.76. Found: C, 77.72; H, 11.76.

Semicarbazone, m.p. 185–189° (reported,[2] 190–191°).

Dehydration of the *trans*-diol melting at 54–55° by the same procedure afforded a comparable yield of tetrahydrocarvone (IV). A mixture of the semicarbazone derivative with the semicarbazone prepared above showed no melting point depression.

$\Delta^{8(10)}$-*p-Menthene-1,2-diol* (V). A mixture of 30 ml. (0.184 mole) of (+)-limonene (I), 100 ml. of 90% formic acid, and 24 ml. (0.227 mole) of 29% hydrogen peroxide was stirred and cooled in a water bath to maintain a temperature of 35° for 1 hr. Unreacted (+)-limonene (10.8 ml.) was separated and the formic acid layer was run immediately into excess, aqueous sodium carbonate solution. The colorless oily upper phase was separated and dissolved in ethanolic potassium hydroxide (*p*H 10–11). After standing for 2.5 hr. at room temperature, the solution was brought to *p*H 6 with concentrated hydrochloric acid. Most of the ethanol was removed under vacuum and 100 ml. of water was added. The unsaturated diol crystallized as the hydrate in colorless plates. Removal of water of crystallization in a vacuum desiccator over sulfuric acid afforded 4.0 g. (19.6% conversion yield) of crystalline $\Delta^{8(10)}$-*p*-menthene-1,2-diol (V), m.p. 62–67°. Several recrystallizations from benzene–

(9) J. Sword, *J. Chem. Soc.*, 127, 1632 (1925).

(10) B. A. Arbusow and B. M. Michailow, *J. prakt. Chem.*, 127, 92 (1930).

(11) H. Kaffer, *Ber.*, 57, 1263 (1924).

petroleum ether (30–60°) afforded colorless prisms, m.p. 70–71.6°, $[\alpha]_D^{23}$ + 41 (10% acetone solution).

Anal. Calcd. for $C_{10}H_{18}O_2$: C, 70.55; H, 10.66. Found: C, 70.66; H, 10.66.

Hydrogenation of $\Delta^{8(10)}$*-p-menthene-1,2-diol.* Five grams of $\Delta^{8(10)}$-*p*-menthene-1,2-diol was dissolved in 150 ml. of 95% ethanol and hydrogenated at room temperature, using 2 g. of 5% platinum on Darco G-60 catalyst. The hydrogenation was complete in 10 min. The catalyst was removed by filtration and the filtrate concentrated to about 10 ml. Dilution with water afforded colorless crystals which were dried in a vacuum desiccator over concd. H_2SO_4. The dried product weighed 4.6 g. (92%) and melted at 86.4–88.4°. There was no melting point depression on admixture with a sample of *trans-p-menthane*-1,2-diol (III) (m.p. 86.6–88.6°) prepared by the hydroxylation of Δ^1-*p*-menthene (II).

Trans-p-menthane-1,2-diol-diacetate (VI). Thirty grams of *trans-p*-menthane-1,2-diol (III) (m.p. 89°) was refluxed for 2 hr. in 150 ml. of acetic anhydride containing 0.5 g. of anhydrous sodium acetate. The solution was poured into water and stirred to decompose excess anhydride. The diester was extracted with three portions of ethyl ether. The combined ether extracts were washed three times with sodium bicarbonate solution, twice with water, and dried over anhydrous sodium sulfate. After removal of the ether under reduced pressure, the residual oil was distilled. At 99° (0.8 mm.) 41 g. (92%) of colorless, slightly viscous oil was collected. The diacetate obtained by distillation was sufficiently pure for analysis $[\alpha]_D^{23}$ + 93, n_D^{23} 1.4498.

Anal. Calcd. for $C_{14}H_{24}O_4$: C, 65.60; H, 9.44; Sapon. equiv., 128. Found: C, 65.34; H, 9.70; Sapon. equiv., 135.

Trans-p-menthane-1,2-diol-dipropionate (VII). Thirty grams of *trans-p*-menthane-1,2-diol (III) (m.p. 89°) was refluxed for 2 hr. in 150 ml. of propionic anhydride containing 0.5 g. of anhydrous sodium acetate. Excess anhydride was decomposed by water and the diester was extracted with ether as described in the case of the diacetate ester. After removal of the ether under reduced pressure, the residual oil was distilled. At 114° (0.8 mm.) 46 g. (94%) of colorless, slightly viscous oil was collected. The dipropionate obtained by distillation was sufficiently pure for analysis $[\alpha]_D^{23}$ + 83, n_D^{23} 1.4478.

Anal. Calcd. for $C_{16}H_{28}O_4$: C, 67.57; H, 9.92; Sapon. equiv., 142. Found: C, 67.78; H, 9.96; Sapon. equiv., 146.

Trans-p-menthane-1,2-diol-dibutyrate (VIII). Thirty grams of *trans-p*-menthane-1,2-diol (III) (m.p. 89°) was refluxed for 2 hr. in 150 ml. of butyric anhydride containing 0.5 g. of anhydrous sodium acetate. Excess anhydride was decomposed by water and the diester was extracted with ether as described in the case of the diacetate ester. After removal of the ether under reduced pressure, the residual oil was distilled. At 131° (0.8 mm.) 50 g. (92%) of colorless, slightly viscous oil was collected. The dibutyrate obtained by distillation was sufficiently pure for analysis $[\alpha]_D^{23}$ + 74, n_D^{23} 1.4486.

Anal. calcd. for $C_{18}H_{32}O_4$: C, 69.19; H, 10.33; Sapon. equiv., 156. Found: C, 69.26; H, 10.47; Sapon. equiv., 154.

LAKE ALFRED, FLA.

[CONTRIBUTION FROM THE CHEMICAL LABORATORY OF NORTHWESTERN UNIVERSITY]

α-Deoxykojic Acid and Some of Its Derivatives

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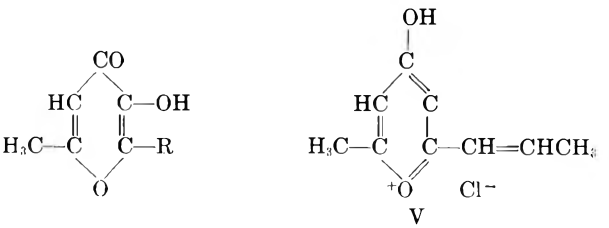
The allyl ether of α-deoxykojic acid was prepared and rearranged to 6-allyl-α-deoxykojic acid, from which the 6-propenyl and 6-propyl analogs were made. 3,5-Dinitrobenzoates were satisfactory derivatives for these compounds.

In connection with studies on kojic acid and related compounds it became of interest to prepare α-deoxykojic acid[1] and certain of its derivatives.

α-Deoxykojic acid (I) was synthesized from kojic acid by halogenation (thionyl chloride) to yield α-chloro-α-deoxykojic acid, followed by catalytic reduction of the latter. The allyl ether of I was prepared from allyl bromide, adapting conditions[2] employed earlier with kojic acid. The ether was an oil at room temperature that crystallized readily at ice temperature from one run but not from another. It isomerized rapidly to 6-allyl-α-deoxykojic acid (II) at elevated temperatures and gave evidence for slow isomerization at room temperature.

II was a crystalline solid, giving a strong violet color with ferric chloride. When it was treated with dry hydrogen chloride in ethanol it changed to a salt-like compound (V), the hydrochloride of 6-propenyl-α-deoxykojic acid (III). This compound lost hydrogen chloride on standing but more



V

I, R = H
II, R = $CH_2CH{=}CH_2$
III, R = $CH{=}CHCH_3$
IV, R = $CH_2CH_2CH_3$

rapidly on heating to yield III. The latter was prepared more readily by treatment with base. V, III, and a mixture thereof all melted at the same temperature which would indicate that hydrogen chloride is lost prior to the attainment of the melting temperature, and that what melts is impure III. The 6-propenylkojic acid hydrochloride of McLamore and co-workers[2b] also melts a few degrees below the melting point of 6-propenylkojic

(1) The α represents position on the side chain. α-Deoxykojic acid also has been called allomaltol by Yabuta, *J. Chem. Soc.*, **125**, 575 (1924).

(2) (a) C. D. Hurd and R. J. Sims, *J. Am. Chem. Soc.*, **71**, 2440 (1949); (b) W. M. McLamore, E. Gelblum, and A. Bavley, *J. Am. Chem. Soc.*, **78**, 2816 (1956).

acid, but these workers did not report a mixed melting point determination.

It is of interest that the corresponding hydrochloride of I could not be as easily characterized. It was considerably more soluble in alcohol and, although it gave all qualitative tests in agreement with the proposed structure, titration gave consistently high neutralization equivalents. This might be accounted for either by partial loss of hydrogen chloride during isolation or by solvation of this species.

Both II and III could be hydrogenated readily to 6-propyl-α-deoxykojic acid (IV) using palladized charcoal as catalyst.

3,5-Dinitrobenzoates of I, II, III, IV were readily prepared. They proved to be excellent derivatives since the several melting points were widely separated. To prepare these esters, however, low temperatures and short reaction times were desirable to avoid side reactions.

Other reagents tested for derivatives were not satisfactory. From IV and phenyl isocyanate no urethan was obtained. II and IV, on reaction with acetic anhydride and pyridine, yielded oily products; some tar was formed from II as well. Prolonged treatment of II with benzoyl chloride and pyridine resulted in tar. III gave rise to a crystalline acetate but it was not studied further since the other two acetates were oils.

EXPERIMENTAL

α-Chloro-α-deoxykojic acid. Some of this material, m.p. 166–167°, was prepared by reaction of thionyl chloride and kojic acid, but most of it was generously donated by Chas. Pfizer and Co., who supply it under the name "chlorokojic acid." The latter was recrystallized prior to use, otherwise the reduction (below) proceeded very slowly.

α-Deoxykojic acid (I). Directions for this synthesis were essentially those of Brown.[3] The catalyst used was palladium (10%) on carbon. The reduction was done in a Parr apparatus on batches of up to 30 g. of α-chloro-α-deoxykojic acid. Methanol was taken as solvent and it was found that addition of up to 15% of water did not affect the yield, but was convenient for better solubilization of the sodium acetate used to neutralize the hydrogen chloride that was formed. The pressures used ranged from 25 to 40 lbs./inch,[2] and the theoretical amount of hydrogen was usually absorbed within 15–30 min. Yields were good (80–92%). The product melted at 152° after recrystallization from ethyl acetate.

Infrared spectra were taken on a Baird double beam recording spectrophotometer, using potassium bromide pellets. The following bands were observed for I: 3.10, 6.05, 6.18, 6.28, 6.86 (weak), 6.94, 7.23, 7.31, 7.83, 8.00, 8.14, 8.38, 8.67 with shoulder at 8.53, 9.48w, 9.75w, 10.90, 11.28, 11.94, 12.96, 13.34w, and a broad band at about 14.30μ.

α-Deoxykojic acid hydrochloride. One gram of I was dissolved in 25 cc. of warm absolute ethanol and the solution was saturated with dry hydrogen chloride. Solid separated only after addition of 75 cc. of ether. A total of 0.90 g. was obtained in several crops, m.p. 149° with some darkening above 110°. The material gave an immediate precipitate with silver nitrate, and it responded like an acid of mineral strength with Davidson's A-II indicator.[4] The ferric chloride test was positive, giving the same color as that from I. Titration to phenolphthalein end point gave neutralization equivalents of 93 and 95, whereas the calculated value for I is 126, for its hydrochloride 81, and for its monoethanolate 104. On acidification of the solution, crystals were obtained that were identified as I.

α-Deoxykojyl allyl ether. One tenth mole of α-deoxykojic acid was dissolved in 150 cc. of methanol, then 0.1 mole of sodium methoxide was added to the hot solution, followed by water until the salt was completely dissolved. Allyl bromide (0.11 mole) was added and the yellow solution refluxed for 150 min. It was then evaporated in an air stream and the resulting mixture of oil and crystals was extracted with chloroform until the extracts were colorless. The extract was washed with 25-cc. portions of 10% sodium carbonate solution until the chloroform layer gave no ferric chloride test, and then once more (7 washings). The carbonate washings were re-extracted with two 50-cc. portions of chloroform. The combined chloroform solutions were washed with water, dried with sodium sulfate, stirred with Norit and filtered. Chloroform was removed at diminished pressure and the oily residue was dissolved in ether-ligroin. On standing at 5° large crystals separated which melted at room temperature except for a few small crystals which were identified as III. Crystals of the ether which were collected at 5° gave no coloration with ferric chloride solution.

In another run this ether could not be obtained crystalline. When the oil (negative ferric chloride test) was taken up in benzene and refluxed for 11 hr. the benzene layer gave a strong violet color with ferric chloride, indicating some isomerization of the ether even at this relatively low temperature of heating. In this ferric chloride test, one drop of solution was placed on filter paper, the solvent was evaporated, then a drop of the ferric chloride solution was added. Hence, no further attempts were made to purify this ether for analysis, but instead it was rearranged to II.

6-Allyl-α-deoxykojic acid (II). The solution of the above ether was warmed at reduced pressure to remove solvents, then was heated at 180° and 11 mm. for 20 min. The material was dissolved in acetone and methanol, decolorized, and concentrated. There separated 8.9 g. of cream colored crystals in three crops, m.p. 151–153°. The yield, based on I, was 53%. The sample for analysis was sublimed at 20 mm., m.p. 157–158°. In its ultraviolet spectrum, it showed λ_{max} 275 mμ, log ε 3.82. The infrared spectrum had the following characteristic bands: 3.10, 6.04, 6.19, 6.30, shoulder at 6.48, 6.85, 6.97, 7.22, 7.39, 7.72w, 8.10 broad, 8.40, 8.99, 9.54, 9.99, 10.22, 10.85, 11.32, 13.05, 13.70, and a broad band around 14μ.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.23; H, 5.86.

6-Propenyl-α-deoxykojic acid hydrochloride (V). One gram of II was dissolved in hot absolute ethanol (20 cc.). Dry hydrogen chloride was bubbled in slowly for an hour. The solution was left at 20° for two days after which time clusters of pale reddish violet needles formed which were filtered off and dried in the air. Later, a second crop of crystals was obtained. Total yield 0.85 g., or 70%; m.p. 148–149°. It gave an intense greenish color with ferric chloride. It was essentially insoluble in ether, but the trace that did dissolve was recognizable by the ferric chloride coloration.

Anal. Calcd. for $C_9H_{11}ClO_3$: C, 53.33; H, 5.47. Found: C, 53.40; H, 5.65.

Titration of the hydrochloride also was confirmatory: 0.0547 g. of it consumed 2.72 cc. of 0.192*N* sodium hydroxide (phenolphthalein end point), giving a neutralization equivalent of 104. The theoretical value is 101.5, but since the end point for the titration of the enolic hydroxyl was not very sharp the value is satisfactory for the proposed structure.

6-Propenyl-α-deoxykojic acid (III). The solution from the above titration was acidified with acetic acid. Crystals gradually formed which were collected, washed with water and methanol, and dried at 80°; yield, 0.02 g. There was considerable loss during washing since III is soluble in methanol,

(3) M. G. Brown, *J. Chem. Soc.*, 2558 (1956).

(4) D. Davidson, *J. Chem. Ed.*, 19, 221, 532 (1942).

It is also readily soluble in ether, an observation in marked contrast to the insolubility of the hydrochloride. The m.p. was 148–149°. The sample for analysis was purified by sublimation; m.p. 151–152°, mixed m.p. with II was 123–131°. The product gave a green color with ferric chloride.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.06. Found: C, 65.26; H, 5.87.

The ultraviolet spectrum of III showed λ_{max} 310 mμ, log ε 4.17. The important infrared bands were: 3.10, 3.40w, 3.46w, 6.03, 6.12, 6.21, 6.32, 6.84, 6.93, 7.18, 7.39, 7.58, 8.07, 8.20, 8.44, 9.50, 10.00, 10.29, 10.43, 10.90, 11.40, 12.95, and a broad band around 14.70 μ.

6-Propyl-α-deoxykojic acid (IV). To crude II (5.0 g.), dissolved in 150 cc. of methanol, was added 25 mg. of 10% palladium-on-carbon and the suspension was shaken in a Parr apparatus at about 30 lbs./inch.[2] The uptake of hydrogen ceased after 5 min. The suspension was filtered, the solvent was removed, and the residue was recrystallized from a mixture of methanol and ethyl acetate. The product separated in creamy crystals, yield 3.5 g. (70%), m.p. 128–131°. Sublimation afforded pure IV, m.p. 132.5–133.5°. From the yellow mother liquor 1.5 g. of less pure material was recovered, from which some pure IV could be obtained on sublimation, the rest decomposing.

The product was considerably more soluble in ethyl acetate, acetone, and methanol than I, but it was less soluble in water. It gave a deep violet color with ferric chloride.

When 0.3 g. of crude III was hydrogenated analogously, 0.28 g. of cream colored crystals was obtained, m.p. 131–132.5°. The mixed m.p. with the above crystals also was 132–133.5°. The infrared spectra of the compound from the two sources were identical, with these bands: 3.09, 3.39, 3.41, 3.49, 6.04, 6.18, 6.28, 6.85, 6.97, 7.20, 7.37 with shoulders at 7.43 and 7.48, 7.74, 8.06, 8.18, 8.35, 9.08 with shoulders at 9.11 and 9.20, 9.50 with shoulder at 9.65, 10.19, 10.29, 10.29, 10.43, 11.35, 11.63, 12.60w, 13.01, and a broad band around 14.20μ.

Anal. Calcd. for $C_9H_{12}O_3$: C, 64.26; H, 7.19. Found: C, 64.39; H, 7.29.

3,5-Dinitrobenzoates of I, II, III, IV. About 0.2 g. of I, II, III, or IV was dissolved in 5 cc. of dry pyridine at room temperature, mixed with 0.35 g. of 3,5-dinitrobenzoyl chloride, and stirred for 5 min. The solution of I remained clear, that of II turned deep red-brown, that of III became a thick slurry, and that of IV yielded a thin slurry. Each reaction mixture was then heated on a hot plate for 30 sec. and the flasks were then cooled under tap water. Then 10 cc. of ice water was added to each mixture and the resulting precipitate was collected on a filter, washed with water, and dried over calcium chloride at room temperature and 10 mm. Yields were between 0.3 and 0.4 g.

The products were recrystallized from chloroform-ligroin with the use of Norit, and then from benzene-hexane. Fine, colorless crystals were obtained for each product. These melting points were observed for the several dinitrobenzoates: from I, 215–216°; from II, 96.5°; from III, 234–235°; from IV, 125°. The infrared spectra of the derivatives had the following peaks in common: 3.27 (aromatic CH), 5.72 (benzoate carbonyl), 5.97 (pyrone carbonyl), 6.47 and 7.44 (nitro), 12.58 (sym. trisubstituted benzene), and the four spectra were generally similar up to about 9.55μ. A good region for differentiation of the derivatives was 9.55–11.90μ where the individual compounds exhibited the following bands: I. 9.75, 9.92, 10.47, 10.73, 10.96, 11.25, 11.90. II. 10.10, 10.34, 10.59, 10.85, 10.94, 11.23, 11.39, 11.90. III. 9.99, 10.23 (shoulder 10.43), 10.66, 10.85, 10.92, 11.30, 11.90. IV. 9.94, 10.49, 10.65, 10.84, 10.92, 11.29, 11.60, 11.90μ.

Explosions were encountered in analyzing all of the dinitrobenzoates but they seemed not to affect the values for the esters from I, III, IV. The explosion with the dinitrobenzoate of II, however, did make analysis unrealizable, for duplicate analyses (C, H, N) were inconsistent and varied widely. These and other microanalyses were performed by Miss Hilda Beck.

Anal. of dinitrobenzoates.

From I. Calcd. for $C_{13}H_8N_2O_8$: C, 48.76; H, 2.52. Found: C, 48.37; H, 2.54.

From III. Calcd. for $C_{16}H_{12}N_2O_8$: C, 53.33; H, 3.36. Found: C, 53.71; H, 3.10.

From IV. Calcd. for $C_{16}H_{14}N_2O_8$: N, 7.73. Found: N, 7.57.

EVANSTON, ILL.

[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF KANSAS]

The Structure of 2-Substituted Pyrrolines[1,2]

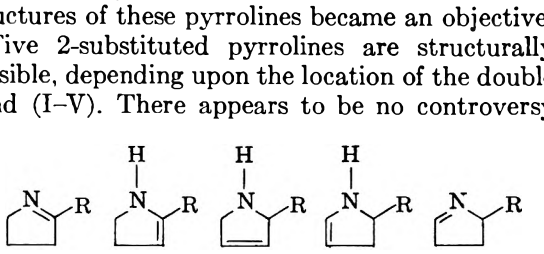
J. H. BURCKHALTER AND J. H. SHORT[4]

Received January 24, 1958

Of the five possible structures which may be written for 2-substituted pyrrolines upon the basis of the location of the double bond, only the Δ^1- and Δ^3-pyrrolines have been shown conclusively to exist. The present work confirms the existence of the former rather than a Δ^2 structure. An attempt to synthesize 2-phenyl-Δ^4-pyrroline resulted in failure.

While employing a number of 2-substituted pyrrolines in the synthesis of a group of desired 2-substituted pyrrolidines,[5] it became apparent from a survey of the literature that much confusion existed concerning the structures of the intermediate 2-substituted pyrrolines, and a determination of the structures of these pyrrolines became an objective.

Five 2-substituted pyrrolines are structurally possible, depending upon the location of the double bond (I–V). There appears to be no controversy



(1) Based upon a portion of the Ph.D. Thesis of J. H. Short, University of Kansas, 1954.

(2) During the preparation of this manuscript, a recent report on the structure of 2-phenylpyrrolines was noted.[3]

(3) M. C. Kloetzel, J. Z. Pinkus, and R. M. Washburn, *J. Am. Chem. Soc.*, 79, 4222 (1957).

(4) Parke, Davis & Co., Fellow. Present address, Abbott Laboratories, North Chicago, Ill.

(5) J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, 23, 1281 (1958).

concerning the existence and identity of Δ^3-pyrrolines (III); compounds of this structure are the usual[6] but not the exclusive[7,8] products obtained from the partial reduction of substituted pyrroles. However, confusion has centered around the existence of Δ^1-pyrrolines (I and V) and Δ^2-pyrrolines (II and IV). Several workers have arbitrarily assigned a Δ^2 structure to their compounds,[9,10] while Cloke and colleagues suggest either the Δ^1- or Δ^2-pyrroline form or a tautomeric mixture of the two.[11]

It is surprising that so many workers have accepted the Δ^2-pyrroline structure without question since analogous open chained vinyl amines have been considered to exist in only a few special cases where conjugated systems are involved.[12] But using infrared spectral data, Witkop has recently challenged even some of these assignments as vinyl amines (eneamines).[13] Further, by the same means, Witkop has come to the conclusion that there are probably no authentic secondary Δ^2-pyrrolines.[14] Of course, tertiary Δ^2-pyrrolines, such as 1-methyl-2-substituted-Δ^2-pyrrolines are well known.[15]

Maginnity and Cloke, using the Zerevitinov method of determining active hydrogen, apparently were the first workers to choose the Δ^1-pyrroline (I) over the Δ^2-pyrroline (II) structure upon a rational basis.[16] Since none of the pyrrolines tested liberated appreciable quantities of active hydrogen, Δ^1-pyrrolines were indicated.

The following pyrrolines were synthesized as described in the publication which follows,[5] and their infrared spectra were determined: 2-phenyl-, 2-(p-methoxyphenyl)-, 2-(2-thienyl)-, 2-(4-biphenylyl)-, 2-(9-phenanthryl) and 2-(1-naphthyl)-. All show a strong absorption peak at about 6.20μ which may be attributed to C=N bonding, and none show absorption in the 3.00μ region where the NH group is known to absorb.[17] The infrared spectra, therefore, confirm the Δ^1-pyrroline (I) structure for these substances.

Two different methods of preparation, as illustrated by schemes C and D for 2-(*m*-methoxyphenyl)pyrroline,[5] gave rise to the same pyrroline. The samples had identical boiling points and refractive indices. The picrates had the same melting points, and there was no depression upon admixture. Sizable portions of the two picrates were combined and recrystallized with no change in melting point. Further, the two pyrrolines gave identical infrared and ultraviolet absorption spectra. Both gave infrared peaks at 6.26 μ, while neither absorbed in the 3.00 region in confirmation of the absence of the NH group. Thus, the Δ^1-pyrroline structure is indicated.

Although the active hydrogen determinations of Maginnity and Cloke imply that 2-benzylpyrroline exists solely in the Δ^1-pyrroline form,[16] the infrared spectrum of this substance suggests a tautomeric equilibrium, with the Δ^1-pyrroline form predominating. If 2-benzylpyrroline actually exists as a tautomeric mixture, then three structures must be considered. In addition to the normal Δ^1-pyrroline (I), there is the Δ^2-pyrroline formulation (II), and the structure with an exocyclic double bond. It can be seen that the double bonds of I and II are not in positions of conjugation with the phenyl group. If 2-benzylpyrroline actually exists as a tautomeric equilibrium between I and a structure possessing the vinylamine group, then the exocyclic structure would appear to be a more logical choice than II since the former would be favored by the conjugation of the phenyl group with the double bond.

Samples of 2-benzylpyrroline from several different runs were subjected to infrared analysis. Strong absorption was observed at about 6.10μ, which represents the absorption of the C=N group. It will be noticed that the C=N absorption of this compound is at a slightly shorter wavelength than the C=N absorption of the compounds already discussed. This shift in wavelength presumably occurs because the C=N group of 2-benzyl-Δ^1-pyrroline (I) is not in conjugation with the phenyl group (or other aryl group), as is the case with other 2-substituted pyrrolines. The absorption peak of a double bond such as is under consideration here is displaced to a slightly longer wave length when in a position of conjugation as compared to a position of nonconjugation.[17] Also, ultraviolet absorption spectra of these substances confirmed the conclusion that the double bond of 2-benzylpyrroline is not conjugated with the phenyl group, while the double

(6) H. Fischer and H. Orth, *Die Chemie des Pyrrols*, Vol. I, Akademische Verlagsgesellschaft, Leipzig, 1934, p. 319.

(7) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

(8) A. Sonn, *Ber.*, **68**, 148 (1935); **72**, 2150 (1939).

(9) S. Gabriel, *Ber.*, **42**, 1238 (1909); R. Hielscher, *Ber.*, **31**, 277 (1898); J. Dhont and J. P. Wibant, *Rec. trav. chim.*, **63**, 81 (1944); H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

(10) E. B. Knott, *J. Chem. Soc.*, 186 (1948); J. B. Cloke, *J. Am. Chem. Soc.*, **51**, 1174 (1929); P. Lipp and H. Seeles, *Ber.* **62**, 2456 (1929); L. C. Craig, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, **53**, 1931; D. F. Starr, H. Bulbrook, and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932).

(11) J. B. Cloke and T. S. Leary, *J. Am. Chem. Soc.*, **67**, 1249 (1945); J. B. Cloke *et al.*, *J. Am. Chem. Soc.*, **67**, 1587 (1945); 2155 (1945).

(12) S. A. Glickman and A. C. Cope, *J. Am. Chem. Soc.*, **67**, 1017 (1945); A. Seher, *Arch. Pharm.*, **284**, 371 (1951); S. Kanao and K. Shinozuka, *J. Pharm. Soc., Japan*, **50**, 148 (1930) [*Chem. Zentr.*, **102**, I, 1743 (1931)]; Krabbe and Schmidt, *Ber.*, **72**, 381 (1939).

(13) B. Witkop, *J. Am. Chem. Soc.*, **78**, 2873 (1956).

(14) B. Witkop, *J. Am. Chem. Soc.*, **76**, 5597 (1954).

(15) L. C. Craig, *J. Am. Chem. Soc.*, **55**, 295, 2543 (1933); R. Lukeš, *Collection Czechoslov. Chem. Comm.*, **2**, 531 (1930) [*Chem. Abstr.*, **25**, 102 (1931)].

(16) P. M. Maginnity and J. B. Cloke, *J. Am. Chem. Soc.*, **73**, 49 (1951).

(17) H. M. Randall, R. G. Fowler, N. Fuson, and J. R. Dangl, *Infrared Determination of Organic Compounds*, D. Van Nostrand Co., Inc., New York, N. Y., 1949; and F. A. Miller in H. Gilman, *Organic Chemistry*, John Wiley & Sons, Inc., New York, N. Y., 1953, Vol. 3, pp. 122–157

bond of the 2-phenyl analogs, for example, is in a position of conjugation.

Close inspection of the infrared spectrum of 2-benzylpyrroline shows weak absorption in the 3.05–3.10μ region which is presumably due to the NH group. However, active hydrogen determinations were negative in confirmation of Maginnity's observation.[16] Since the only groups with which we are concerned here are known to absorb in the 3.00μ region are NH and OH, absorption in this region and the absence of active hydrogen must be considered to be anomalous.

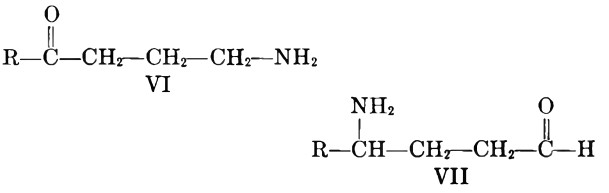
In order to determine if this anomalous result also obtains in the naphthalene series, 2-(2-naphthylmethyl)pyrroline was prepared and its infrared spectrum determined. Unlike that of 2-benzylpyrroline, the spectrum of this compound is entirely in agreement with a Δ^1-pyrroline structure, since no adsorption was observed in the 3.00μ region.

Other anomalous results, however, have been observed with 2-methylpyrroline by Evans, who found weak absorption at 3.02μ.[18] This observation was confirmed; our 2-methylpyrroline shows absorption at 3.07μ which is apparently due to the presence of an NH group. The C=N group absorbs at 6.11μ. Since there is no other double bond in the compound, the 2-pyrroline structure (II) cannot be rationalized on the basis of conjugation. Again Maginnity found no active hydrogen in 2-methylpyrroline,[16] so the absorption at 3.07μ must also be considered anomalous in agreement with the results of Evans.

For purposes of comparison, the infrared spectra of the saturated 2-phenylpyrrolidine and 1-methyl-2-phenylpyrrolidine[5] were determined. The former substance has a strong absorption peak at 3.02μ which is attributed to the NH group, and double bond absorption in the 6.20 region is absent. The latter compound, as expected, shows no absorption in either the 3.00 or 6.20μ region.

The evidence at hand in regard to the structure of pyrrolines obtained by Procedures C, D, and E,[5] as well as from other ring closure reactions,[8,9] indicates that these compounds exist chiefly, if not exclusively, as Δ^1-pyrrolines (I). Thus, it has not yet been demonstrated that Δ^2-pyrrolines (II) can exist as such.

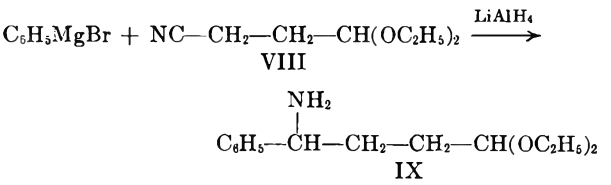
Although five isomeric structures (I–V) may be written for any given substituent (*e.g.*, phenyl), no more than two isomers (I and III) are known actually to exist. Examples of the fifth isomer (V) are unknown at the present time, although it should be capable of separate existence from I by analogy with such isomeric pairs as *N*-methylenebenzylamine and *N*-benzylidinemethylamine.[19] Further, if Δ^1-pyrrolines are considered to arise from an intramolecular condensation involving an amino group and a carbonyl group, it can be seen that I and V differ in the relative position of the substituent to the two functional groups in the intermediate amino carbonyl compound. The ring closure of a γ-aminopropyl ketone (VI) gives rise to pyrrolines of type I. Cyclization of γ-amino-γ-substituted-butyraldehydes (VII), on the other hand, would be expected to lead to the isomeric Δ^1-pyrrolines (V).



VI

VII

In attempting the synthesis of a type V compound through an aldehyde (VII, R = phenyl), phenylmagnesium bromide was allowed to react with diethyl β-cyanopropionacetal (VIII), and the Grignard complex was subjected to the reducing action of lithium aluminum hydride. The compound isolated from the reaction proved to be the desired diethyl γ-amino-γ-phenylbutyracetal (IX). Under



VIII IX

the influence of mineral acid, it was hoped IX could be converted to the corresponding amino aldehyde which might then undergo intramolecular condensation to the desired 5-phenyl-Δ^1-pyrroline (V, R = phenyl). However, V was not obtained since the aldehyde seemed to have a greater tendency to polymerize than to undergo the desired reaction. A similar attempt using model compound X (IX, where phenyl is replaced with hydrogen) also failed.

EXPERIMENTAL

Diethyl γ-aminobutyracetal X. A mixture of 16 g. (0.1 mole) of diethyl β-cyanopropionacetal,[20] 100 ml. of ethanol saturated with ammonia, and about 5 g. of Raney nickel catalyst (Davison and Co., water slurry) was shaken at room temperature at an initial hydrogen pressure of 60 p.s.i. The theoretical amount of hydrogen was absorbed in 10 hr. After removal of the catalyst and solvent, the residue was subjected to vacuum distillation to obtain 15 g. (91%) of colorless oil, b.p. 79–81° (10 mm.), n_D^{20} 1.4290. The recorded boiling points are 84° (11 mm.) and 93° (15 mm.).[20]

Diethyl γ-amino-γ-phenylbutyracetal (IX). According to the procedure of Pohland and Sullivan,[21] 110 ml. (0.33 mole) of a 3*N* ether solution of phenylmagnesium bromide (Arapahoe Special Products) was allowed to react with 47 g. (0.3

(18) G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951).

(19) C. K. Ingold and C. W. Shoppee, *J. Chem. Soc.*, 1199 (1929).

(20) R. H. F. Manske, *Can. J. Research*, **5**, 598 (1931).

(21) A. Pohland and H. R. Sullivan, *J. Am. Chem. Soc.*, **75**, 5898 (1953).

mole) of diethyl β-cyanopropionacetal.[20] The Grignard adduct was reduced with 14 g. (0.37 mole) of lithium aluminum hydride. After hydrolysis of the reaction mixture with 400 ml. of 10% ammonium chloride solution the reaction was worked up as described[21] to give a colorless oil, b.p. 90–107° (0.3 mm.). The material was redistilled and a middle cut, 37 g. (53%), was collected, b.p. 103–107° (0.3 mm.), n_D^{20} 1.5026.

Anal. Calcd. for $C_{14}H_{23}NO_2$: C, 70.85; H, 9.77. Found: C, 70.47; H, 9.45.

Acknowledgment: Appreciation is expressed to Parke, Davis & Co. for fellowship funds, and to Mr. R. Bruce Scott and Dr. George Moersch of the Research Division of that Company and to Dr. Calvin Stevens of Wayne State University for the determination and interpretation of the early infrared spectra.

LAWRENCE, KAN.

[CONTRIBUTION FROM THE LABORATORY OF PHARMACEUTICAL CHEMISTRY, SCHOOL OF PHARMACY, UNIVERSITY OF KANSAS]

Synthesis of Nicotine Analogs[1]

J. H. BURCKHALTER AND J. H. SHORT[2]

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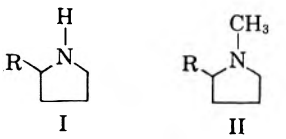
A number of 2-substituted pyrrolidines and *N*-methylpyrrolidines have been synthesized as possible antihypertensive agents.

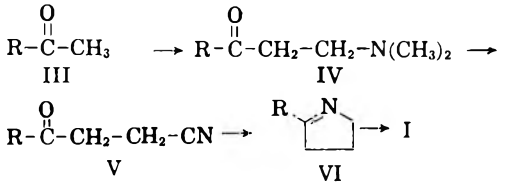
One of the many physiological effects of nicotine, 1-methyl-2-(3-pyridyl)pyrrolidine (II, R = 3-pyridyl), when administered in large doses, is a marked lowering of the blood pressure.[3] The toxicity of nicotine precludes its clinical use; however, it might be



I II

possible, by incorporating groups other than 3-pyridyl in the pyrrolidine nucleus, to obtain substances useful for the treatment of hypertension. With this objective in mind, 2-(2-naphthyl) pyrrolidine (I, R = 2-naphthyl) and its *N*-methyl derivative (II, R = 2-naphthyl) have already been prepared.[4] These compounds were found to reverse epinephrine-induced hypertension in the dog, with the latter the more effective of the two.[5] In view of these results, it seemed worthwhile to synthesize a number of compounds represented by I and II.

The preparation of the pyrrolines and pyrrolidines was undertaken by three different synthetic procedures. The first method, described as Procedures C and F in the Experimental section, has been used by Rupe and Gisiger[6] and by Knott.[7] It depends upon the reductive cyclization of a β-aroylpropionitrile (V) to a pyrroline (VI) or pyrrolidine (I).



III IV V VI

The starting material for this series of reactions was a substituted acetophenone (III) or a similar aryl methyl ketone. The ketone was allowed to react with paraformaldehyde and dimethylamine hydrochloride in the manner of the Mannich reaction to give an aryl β-dimethylaminoethyl ketone (IV). The Mannich base was then used to alkylate potassium cyanide to give a β-aroylpropionitrile (V).[8] The nitrile, in turn, was subjected to low pressure hydrogenation in the presence of Raney nickel catalyst. If the reaction mixture was shaken until no more hydrogen was absorbed, the uptake corresponded to three moles and the product isolated was a 2-arylpyrrolidine (I). When the hydrogenation was interrupted after two moles of hydrogen had been absorbed, the substance obtained was a 2-aryl-Δ^1-pyrroline (VI).[9] Since the first two moles of hydrogen were absorbed much faster than the third mole, the isolation of the pyrrolines offered no difficulty.

This series of reactions was successful for the synthesis of I, where R = phenyl, *m*-methoxyphenyl, *p*-methoxyphenyl, and 1-naphthyl. Also, a small amount of 2-(4-biphenylyl)pyrrolidine (I, R = 4-biphenylyl) was isolated as the hydrochloride by this procedure. Because of the failure of the intermediate keto nitrile to absorb hydrogen, 2-(2-

(1) Based upon a portion of the Ph.D. Thesis of J. H. Short, University of Kansas, 1954.

(2) Parke, Davis & Co. Fellow. Present address, Abbott Laboratories, North Chicago, Ill.

(3) L. S. Goodman and A. Gilman, *The Pharmacological Basis of Therapeutics*, 2nd ed., The Macmillan Co., New York, N. Y., 1955, p. 622.

(4) J. H. Burckhalter and R. Meyer, unpublished results.

(5) Dr. Graham Chen, private communication.

(6) H. Rupe and F. Gisiger, *Helv. Chim. Acta*, **8**, 338 (1925).

(7) E. B. Knott, *J. Chem. Soc.*, 186 (1948).

(8) E. B. Knott, *J. Chem. Soc.*, 1190 (1947).

(9) For structure studies, see J. H. Burckhalter and J. H. Short, *J. Org. Chem.*, **23**, 1278 (1958).

TABLE I

β-ACYLPROPIONITRILES (V)

No.	Acyl Group	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Benzoyl[a]	A	43	75–76[h]					
2	*p*-Methoxybenzoyl[b]	B	81	95–96[h,i]					
3	*m*-Methoxybenzoyl[b]	B	88	52–53[j]					
4	*m*-Hydroxybenzoyl[c]	B	54	97–99[k]					
5	*p*-Phenylbenzoyl[d]	B	50	171–172[h]	$C_{16}H_{13}NO$	81.67	81.56	5.57	5.69
6	1-Naphthoyl[e]	A	45	60–61	$C_{14}H_{11}NO$	80.36	80.59	5.30	5.47
7	2-Naphthoyl[a,f]	B	51	117–118					
8	9-Phenanthroyl[g]	B	61	150–151[h]	$C_{18}H_{13}NO$	83.38	83.15	5.05	5.09

[a] Preparation described by Knott.[8] [b] Variation in Knott's procedure[8] increased yield. [c] No yield given by Knott.[8] [d] For intermediate β-dimethylamino-*p*-phenylpropiophenone, see W. L. Nobles and J. H. Burckhalter, *J. Am. Pharm. Assoc.*, 47, 77 (1958). [e] The oil which separated during reflux period was extracted with ether and distilled, b.p. 179–184° (0.3 mm.), n_D^{25} 1.6204. It solidified when alcohol was added. Recrystallized from Skelly B. [f] Prepared by Dr. Robert Meyer of this laboratory.[4] Recrystallized from methanol. [g] For intermediate 3-dimethylamino-1-(9-phenanthryl)-1-propanone hydrochloride, see J. van de Kamp and E. Mosettig, *J. Am. Chem. Soc.*, 58, 1568 (1936). [h] Recrystallized from alcohol. [i] B.p. 154–162° (0.4 mm.). [j] After distilling at 154–156° (0.5 mm.), the oil solidified. [k] Recrystallized from dilute alcohol.

thienyl)pyrrolidine (I, R = 2-thienyl) could not be obtained in this manner. Apparently, the sulfur of the thiophene ring poisoned the catalyst. Lithium aluminum hydride also failed to effect the desired reduction. The hydrogenation of β-9-phenanthroylbutyronitrile (V, R = 9-phenanthroyl) failed to yield any product. Since more than three moles of hydrogen was absorbed, it appeared that the phenanthrene ring was partially hydrogenated.

This method for the preparation of pyrrolines and pyrrolidines suffers from several limitations. It is, of course, limited to those ketones which undergo the Mannich reaction. The most serious drawback, however, is the small number of Mannich bases (IV) that may be used to alkylate potassium cyanide. Only Mannich bases possessing an aryl group adjacent to the carbonyl group appear to form β-keto nitriles (V), since no successful application of this reaction to wholly aliphatic ketonic Mannich bases has been reported.[10] Also, during the course of this work unsuccessful attempts were made to prepare the corresponding β-keto nitriles (V) from 2-diethylaminomethylcyclohexanone hydrochloride and 5-dimethylamino-1-phenyl-1-penten-3-one (the Mannich base from benzalacetone, IV, R = β-phenylvinyl).

Most of the keto nitriles (V, Table I) are low-melting solids, and some of them tended to separate as oils on recrystallization. This difficulty was circumvented by vacuum distillation of the crude products before recrystallization.

Knott prepared the isomeric β-naphthoylpropionitrile (V, R = 1-naphthoyl) and β-2-naphthoylpropionitrile (V, R = 2-naphthoyl) from the corresponding Mannich bases.[8] He reported melting points of 113–114° and 114°, respectively, for the two compounds. Burckhalter and Meyer[4] confirmed Knott's synthesis of the 2-isomer, but were unable to obtain the 1-isomer as a solid. Instead only an oil was isolated which was not characterized. Although Knott converted β-2-naphthoylpropionitrile to 2-(2-naphthyl)-Δ^1-pyrroline (VI, R = 2-naphthyl), he did not report any further transformations of his so-called β-1-naphthoylpropionitrile.[7] So, the preparation of the latter compound was repeated, and an oil, which could be purified by distillation, was obtained. When allowed to stand in alcohol at room temperature, it crystallized. The white solid obtained in this manner, after two recrystallizations from petroleum ether (60–70°), melted at 61° (Table I, Compound 6). That this compound, rather than Knott's melting at 113–114°, is β-1-naphthoylpropionitrile was proved by partial hydrogenation to 2-(1-naphthyl)-Δ^1-pyrroline (Table II, Compound 6), which has been prepared by Maginnity from 1-naphthylmagnesium bromide and γ-chlorobutyronitrile.[11] As a result of these observations, it seems likely that the compound assumed by Knott to be β-1-naphthoylpropionitrile is actually β-2-naphthoylpropionitrile, since he recorded the same melting point for both compounds. He did not report a mixed melting point.

2-(*m*-Hydroxyphenyl)-Δ^1-pyrroline (VI, R = *m*-hydroxyphenyl) has been obtained as a white, crystalline solid from the corresponding keto nitrile by the absorption of two moles of hydrogen.[7] Continued hydrogenation, however, failed to yield any of the desired 2-(*m*-hydroxyphenyl)pyrrolidine. The theoretical amount of hydrogen was absorbed, but the product appeared to be a resin. This material was soluble in both acid and base. It formed an oily picrate, and could not, according to Knott, be distilled. Repetition of this work resulted in a confirmation of Knott's observations except that the substance was found to distil over a wide range. The distillate solidified to a glassy solid.

(10) J. H. Brewster and E. L. Eliel, *Org. Reactions*, 7, 108 (1953).

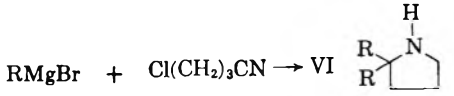
(11) P. M. Maginity and J. B. Cloke, *J. Am. Chem. Soc.*, 73, 49 (1951).

A different approach to 2-(*m*-hydroxyphenyl)pyrrolidine also failed. An attempt to demethylate 2-(*m*-methoxyphenyl)pyrrolidine (I, R = *m*-methoxyphenyl) by the action of hydriodic acid gave a resinous product similar to that obtained by the hydrogenation procedure. An attempt to methylate the crude reaction product to obtain 2-(*m*-hydroxyphenyl)-1-methylpyrrolidine (II, R = *m*-hydroxyphenyl) also failed.

The action of hydriodic acid on 2-(*m*-methoxyphenyl)-Δ^1-pyrroline (VI, R = *m*-methoxyphenyl) gave rise to a substance identical with Knott's 2-(*m*-hydroxyphenyl)-Δ^1-pyrroline (VI, R = *m*-hydroxyphenyl). Examination of the infrared absorption spectrum of the latter compound gave conclusive proof that the double bond was unaffected by the hydriodic acid.

Had the preparation of 2-(*m*-hydroxyphenyl)pyrrolidine been successful, it would have been interesting to see if this compound would undergo an internal Mannich reaction in the presence of formaldehyde to give a benzodehydropyrrolizidine ring system. Such an intramolecular Mannich reaction has apparently never been reported.

The second approach to pyrrolines, Procedure D, was first described by Cloke[12] and by Lipp and Seeles.[13] It involves the action of a Grignard reagent on γ-chlorobutyronitrile to give a pyrroline (VI). Apparently, any Grignard reagent may be used. Those pyrrolines (VI) which could not be

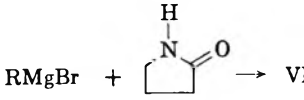


VII

prepared by Procedure C were obtained by this route (Table II). The only disadvantage of Procedure D is the low yields, which seldom exceed 50% and are frequently much lower.

When the crude product from the Grignard reaction was subjected to vacuum distillation, some high-boiling residue always remained in the still pot. The preparation of 2-benzyl-Δ^1-pyrroline (VI, R = benzyl) was run on a larger scale than usual in order to obtain enough of the higher boiling fraction to identify. It was considered to be either a polymer of 2-benzyl-Δ^1-pyrroline or else 2,2-dibenzylpyrrolidine (VII, R = benzyl). Analysis of the picrate indicated structure VII to be correct, and infrared spectrum of the free base confirmed the absence of a double bond.

The third approach to pyrrolines, Procedure E, involves the action of a Grignard reagent on 2-pyrrolidone. Only one example of this reaction has



been recorded in the literature. When Lukeš, Štorm, and Arnold[14] investigated the reaction of propylmagnesium bromide with 2-pyrrolidone, they found the main product to be 2-propylpyrrolidine (I, R = propyl), obtained in unstated yield. Their proof of structure rested on a comparison of the melting points of the picrate and benzenesulfonamide derivatives with those obtained from 2-propylpyrrolidine synthesized by another method. The alternate synthetic procedure was not stated. The melting points of the two derivatives do agree excellently with those reported by Gabriel[15] who synthesized 2-*n*-propylpyrrolidine by a ring closure reaction. In addition to the main product, Lukeš and co-workers obtained a small amount of a higher boiling fraction. This material consisted of a mixture of 2,2-di-*n*-propylpyrrolidine (VII, R = *n*-propyl) and an unidentified base, $C_{10}H_{25}N$, containing one double bond and three propyl groups.

On the basis of two examples studied, the third approach (Procedure E) proved to be unsatisfactory for the preparation of pyrrolines (VI). From phenylmagnesium bromide and 2-pyrrolidone, there was obtained only an 18% yield of 2-phenyl-Δ^1-pyrroline (VI, R = phenyl), while *p*-methoxyphenylmagnesium bromide gave only a 6% yield of 2-(*p*-methoxyphenyl)-Δ^1-pyrroline (VI, R = *p*-methoxyphenyl). These compounds were identical with those prepared by Procedure C. In both cases no other basic materials were obtained from the reaction mixtures. The yields could not be improved by means of various modifications of the experimental procedures.

Table II summarizes the data obtained on the pyrrolines, which were synthesized by Procedure C, D, or E of the Experimental section.

The pyrrolines (VI) obtained by the foregoing procedures were reduced to the corresponding pyrrolidines (I, Table III) by low pressure hydrogenation using Raney nickel catalyst according to Procedure F or H. Lithium aluminum hydride also proved capable of effecting the desired reduction (Procedure G).

The pyrrolidines (I) were converted to the 1-methyl derivatives (II, Table IV by the formaldehyde-formic acid method.[16]

PHARMACOLOGICAL RESULTS

Adrenergic blocking effect.[17] At a dose level of 10 mg./kg. I.V. in dogs, the following substances failed to reverse epinephrine-induced hypertension. Compounds 1, 3, 4, 7, 8, and 9 of Table III and

(12) J. B. Cloke, *J. Am. Chem. Soc.*, 51, 1174 (1929).

(13) P. Lipp and H. Seeles, *Ber.*, 62, 2456 (1929).

(14) R. Lukeš, F. Štorm, and Z. Arnold, *Collection Czechoslov. Chem. Comm.*, 12, 641 (1947) [*Chem. Abstr.*, 42, 5899 (1948)].

(15) S. Gabriel, *Ber.*, 42, 1264 (1909).

(16) R. N. Icke, B. B. Wisegarver, and G. A. Alles, *Org. Syntheses*, Coll. Vol. III, 723 (1955).

(17) We wish to thank Dr. Graham Chen, Research Laboratories, Parke, Davis & Co., Detroit, Mich., for the test results.

TABLE II

2-SUBSTITUTED-Δ^1-PYRROLINES (VI)

No.	Substituent	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Phenyl[a]	C	83	44–45[l]					
		E	18						
	Picrate[a]			200–202[m]					
2	*p*-Methoxyphenyl[a]	C	76	77–78[n]					
		E	6						
	Picrate[a]			179–180[m]					
3	*m*-Methoxyphenyl	C	90[g]		$C_{11}H_{13}NO$	75.40	75.50	7.48	7.44
		D	46						
	Picrate			147–148[m]	$C_{17}H_{16}N_4O_6$	50.50	50.45	3.99	3.99
4	*m*-Hydroxyphenyl[a]		75[h]	158–160[o]					
	Picrate[a]			205–206[m]					
	Hydrochloride			252–253[p]	$C_{10}H_{12}ClNO$	60.76	61.06	6.12	6.22
5	Biphenylyl	D	76	159–160[m]	$C_{16}H_{15}N$	86.84	87.00	6.83	6.87
	Picrate			205–206[m]	$C_{22}H_{18}N_4O_7$	58.66	58.53	4.03	4.06
	Hydrochloride			236–237[p]	$C_{16}H_{16}ClN:{}^1/_2H_2O$	72.03	71.86	6.42	6.34
6	1-Naphthyl[b]	C	87	35–36[q]					
	Picrate[b]			176–177[m]					
7	9-Phenanthryl	D	28	123–124[m]	$C_{18}H_{15}N$	88.13	87.89	6.16	6.43
	Picrate			212–213[r]	$C_{24}H_{18}N_4O_7$	60.76	60.87	3.82	3.95
8	9-Anthryl	D	14	151–152[n]	$C_{18}H_{15}N$	88.13	88.61	6.16	6.35
	Picrate			214–215[m]	$C_{24}H_{18}N_4O_7$	60.76	60.89	3.82	3.92
9	2-Thienyl[a,c]	D	45	57.5–58.5[n]					
10	Benzyl[d]	D	39		$C_{11}H_{13}N$[t]	82.97	83.07	8.23	8.00
	Picrated[d]			114–115[m]					
11	1-Naphthylmethyl	D	22[i]						
	Picrate			195–196[m]	$C_{21}H_{18}N_4O_7$	57.53	57.61	4.14	4.07
12	2-Naphthylmethyl	D	26[j]		$C_{15}H_{15}N$	86.08	85.69	7.22	7.50
	Picrate			211–212[m]	$C_{21}H_{18}N_4O_7$	57.53	57.79	4.14	4.44
13	Methyl[e]	D	12[k]						
	Picrate[f]			123–124[m,s]					

[a] Described by Knott.[7] [b] Described by Maginnity and Cloke.[11] [c] Described by Kirchner and Johns.[21] [d] Described by D. F. Starr, H. Bulbrook and R. M. Hixon, *J. Am. Chem. Soc.*, **54**, 3971 (1932). [e] Described by R. Hielscher, *Ber.*, **31**, 277 (1898). [f] Described by G. G. Evans, *J. Am. Chem. Soc.*, **73**, 5230 (1951). [g] B.P. 95–96° (0.3 mm.), n_D^{25} 1.5692. [h] Made from compound 3 by demethylation with 47% hydriodic acid. [i] B.p. 135–139° (0.4 mm.), n_D^{25} 1.6144. [j] B.p. 135–136° (0.3 mm.), n_D^{20} 1.6228. Hydrochloride, m.p. 207° from isopropanol. [k] B.p. 99–101°, n_D^{20} 1.4296. [l] Recrystallized from Skelly A. [m] From alcohol. [n] From Skelly B. [o] From alcohol-benzene. [p] From isopropyl alcohol. [q] From Skelly A-B. [r] From alcohol-acetone. [s] Mixed m.p. with picric acid gave a marked depression. [t] Analyses by Clark Microanalytical Laboratories, Urbana, Ill. No active hydrogen was found at either 25 or 100° by the Zerevitinov procedure.

Compounds 1, 2, 3, 5, 6, and 9 of Table IV. At the same dose level, Compounds 5 of Table III and 8, 10, and 11 of Table IV effected a partial reversal of epinephrine-induced hypertension, and Compounds 4 and 7 of Table IV caused a complete reversal. It is of interest to note that the demethylated derivative of Compound 4, or 2-(*m*-hydroxyphenyl)-1-methylpyrrolidine (Compound 5 of Table IV), actually caused a rise in blood pressure above the level caused by epinephrine alone.

Nicotinolytic Activity.[18] Although 2-phenylpyrrolidine and 1-methyl-2-phenylpyrrolidine failed to show any adrenergic blocking activity, they both antagonized the hypertensive effect of small doses, 0.02–0.03 mg./kg., of nicotine in the dog.

1-Methyl-2-phenylpyrrolidine alone, caused an evanescent rise in blood pressure, its pressor potency being about $^1/_{25}$th that of nicotine. The nicotine pressor response was immediately reduced about 50% by 5 mg./kg. of 1-methyl-2-phenylpyrrolidine with return to normal in about one hour. At a dose level of 10–12 mg./kg., it immediately abolished, or nearly abolished, the nicotine pressor effect with return to 50–70% at 1 hr. and to normal at 2 hr. The effect of stimulation of the vagus nerve (causing a decrease in the heart rate) was markedly reduced by 10 mg./kg., but only slightly affected by 5 mg./kg. of the material.

2-Phenylpyrrolidine alone caused an initial evanescent rise in blood pressure, its pressor potency being about $^1/_{40}$th that of nicotine. The nicotine pressor response was immediately reduced about 20% by 1 mg./kg. of the substance, about 50% by 2.5 mg./kg., about 75% by 6 mg./kg., and about 90% by 10 mg./kg. The effect was more prolonged than that of 1-methyl-2-phenylpyrrolidine and persisted with lessening degree for 2–3 hr. This compound also blocked stimulation of the vagus nerve.

(18) The nicotinolytic tests were carried out by Dr. Paul S. Larson through the cooperation of Parke, Davis & Co., Detroit, Mich.

TABLE III

2-SUBSTITUTED-PYRROLIDINES (I)

No.	Substituent	Procedure	Yield, %	M.P., °C.	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Phenyl[a]	F	82[e]						
	Picrate[a]			148–149[m]					
2	*p*-Methoxyphenyl[a]	F	91[f]						
	Picrate[a]			134–135[m,n]	$C_{17}H_{18}N_4O_3$	50.24	50.19	4.47	4.36
3	*m*-Methoxyphenyl	F	83[g]		$C_{11}H_{15}NO$	74.54	74.65	8.53	8.70
	Picrate			127–128[m]	$C_{17}H_{18}N_4O_8$	50.24	50.38	4.47	4.39
4	Biphenylyl	G	54[h]	58–59[o]	$C_{16}H_{17}N$	86.05	85.69	7.67	7.68
		H	85						
	Picrate			182–183[m]	$C_{22}H_{20}N_4O_7$	58.40	58.63	4.46	4.39
	Hydrochloride			177–178[p]	$C_{16}H_{18}ClN$	73.97	74.15	6.98	6.70
5	2-Naphthyl[b]	F	72[i]		$C_{14}H_{16}N$	85.24	85.22	7.67	8.38
	Picrate			174–175[m]					
	Hydrochloride			149–150[q]	$C_{14}H_{16}ClN$[t]				
6	9-Phenanthryl	G	94	94–95[o,r]	$C_{18}H_{17}N$	87.41	87.53	6.93	6.93
	Picrate			245–246[s]	$C_{24}H_{20}N_4O_7$	60.50	60.33	4.23	4.23
7	2-Thienyl[c]	G	88[j]						
	Picrate[c]			189–190[m]					
8	Benzyl[d]	H	92[k]						
	Picrate[d]			139–140[m]					
9	1-Naphthylmethyl	H	87[l]						
	Picrate			171–172[m]	$C_{21}H_{20}N_4O_7$	57.27	57.00	4.58	4.64
	Hydrochloride			167–168[s]	$C_{15}H_{18}ClN$	72.71	72.54	7.32	7.70

[a] Described by Knott.[7] [b] Prepared by Dr. Robert Meyer[2] from Compound 7, Table I. When that intermediate was prepared by the procedure of Knott (our Procedure A), it melted at 114°, and reduction stopped at the pyrroline stage (m.p. 95–96°), even when heat was applied. [c] Described by Kirchner and Johns.[21] [d] Footnote *d* of Table II. [e] B.p. 99–100° (4.5 mm.), n_D^{20} 1.5472. [f] B.p. 108–112° (1 mm.), n_D^{20} 1.5504. [g] B.p. 103–105° (1 mm.), n_D^{25} 1.5496. [h] B.p. 153–156° (0.2 mm.). [i] B.p. 139–141 (0.5 mm.). [j] B.p. 78–81° (1.5 mm.), n_D^{25} 1.5625. [k] B.p. 96–97° (2 mm.), n_D^{20} 1.6368. [l] B.p. 127–140° (0.7 mm.), n_D^{25} 1.5998. [m] Recrystallized from alcohol. [n] Knott[7] gave m.p. 172–173°. [o] From Skelly B. [p] From isopropyl alcohol. [q] From alcohol-ether. [r] From methyl alcohol. [s] From alcohol-acetone. [t] Anal. for Cl: Calcd. 15.17; found. 15.06.

EXPERIMENTAL[19]

β-Keto nitriles. Procedure A. According to Knott's procedure[8] the Mannich base and potassium cyanide were heated at reflux temperature in aqueous solution.

Some of the lower melting nitriles tended to precipitate as oils on recrystallization. This difficulty was obviated by vacuum distillation of the product before recrystallization.

Procedure B. To a solution of the Mannich base in water containing an equivalent of concentrated hydrochloric acid was added, beneath the surface of the liquid, an aqueous solution of potassium cyanide (hood.). The reaction mixture was then heated under reflux for 30 min. This is the procedure of Haggett and Archer.[20]

Pyrrolines.[21] *Procedure C.* The procedure described by Knott was followed.[7] A solution of the β-keto nitrile in ethanol was hydrogenated over Raney nickel catalyst at four atmospheres of hydrogen pressure. The reaction was interrupted when two moles of hydrogen had been consumed.

Procedure D. According to the procedure developed by Kirchner and Johns[22] for the preparation of 2-(2-thienyl)-Δ¹-pyrroline, a Grignard reagent was allowed to act upon γ-chlorobutyronitrile (Custom Chemical Lab.), and the reaction mixture was worked up as described.

Procedure E. Two moles of Grignard reagent was allowed to react with one mole of 2-pyrrolidone (Cliffs-Dow Co.), and the reaction mixture worked up according to Procedure D.

Pyrrolidines. Procedure F. According to the procedure described by Knott,[7] the β-keto nitriles were subjected to low pressure hydrogenation, according to Procedure C, until no more hydrogen was absorbed. The uptake corresponded to three moles.

Procedure G. The pyrrolines could be conveniently reduced to the pyrrolidines by lithium aluminum hydride (Metal Hydrides, Inc.) in ether by the usual procedure.[23] The reaction mixture was hydrolyzed with ammonium chloride solution and worked up in the usual manner.

Procedure H. Low pressure catalytic hydrogenation also proved to be a satisfactory method for the conversion of pyrrolines to pyrrolidines. The procedure followed was the same as described for the preparation of pyrrolidines directly from β-keto nitriles (Procedure F).

N-Methylpyrrolidines. The pyrrolidines were methylated by means of the formaldehyde-formic acid method. The procedure followed was that described by Icke, Wisegarver, and Alles[16] for the methylation of β-phenylethylamine.

2,2-Dibenzylpyrrolidine. Benzylmagnesium chloride, prepared from 127 g. (1 mole) of benzyl chloride, was allowed to react with 83 g. (0.8 mole) of γ-chlorobutyronitrile in the manner described for the preparation of 2-(2-thienyl)-Δ¹-pyrroline.[22] After removal of the drying agent and solvent, the residue was subjected to vacuum distillation to give 50 g. (39%) of 2-benzyl-Δ¹-pyrroline. After distillation of the pyrroline, considerable residue remained in the still pot. From

(18) Microanalyses were carried out by Mr. C. M. Beazley, Skokie, Ill. and by Drs. Strauss and Weiler, Oxford, England.

(19) E. Haggett and S. Archer, *J. Am. Chem. Soc.*, **71**, 2255 (1949).

(20) *Chem. Abstr.* names Δ¹-pyrrolines as derivatives of 3,4-dihydro-2H-pyrrolenine. For example, 2-phenyl-Δ′-pyrroline would be 3,4-dihydro-5-phenyl-2*H*-pyrrolenine.

(21) J. G. Kirchner and I. B. Johns, *J. Am. Chem. Soc.*, 62, 2183 (1940).

(23) R. F. Nystrom and W. C. Brown, *J. Am. Chem. Soc.*, **70**, 3738 (1948).

TABLE IV

2-SUBSTITUTED-1-METHYLPYRROLIDINES (II)

No.	Substituent	Yield, %	B.P. or M.P., °C.	Refractive Index (n_D)	Formula	Analysis C Calcd.	Analysis C Found	Analysis H Calcd.	Analysis H Found
1	Phenyl[a]	72	83–84 (6 mm.)	1.5242 (20°)					
	Picrate[a]		148–149[f,g]						
2	*p*-Methoxyphenyl[a]	71	87–90 (0.5 mm.)	1.5310 (20°)					
	Picrate[a]		155–156[f]						
3	*p*-Hydroxyphenyl[a,b]	50	158–159[h]						
	Picrate[a]		184–185[i]						
4	*m*-Methoxyphenyl	75	76–77 (0.6 mm.)	1.5290 (25°)	$C_{12}H_{17}NO$	75.35	75.22	8.96	9.24
	Picrate		143–144[f]		$C_{18}H_{20}N_4O_8$	51.42	51.70	4.80	4.89
5	*m*-Hydroxyphenyl[c] Hydrochloride	41	181–182[j]		$C_{11}H_{16}ClNO$	61.82	61.79	7.55	7.53
6	4-Biphenylyl	92	145–148 (0.3 mm.)[k]		$C_{17}H_{19}N$	86.03	85.40	8.07	8.30
	Picrate		182–183[f,g]		$C_{23}H_{22}N_4O_7$	59.22	59.48	4.75	5.02
	Hydrochloride		170–171[j]		$C_{17}H_{20}ClN$[o]	74.57	74.52	7.36	7.42
	Methiodide		212–214[m]		$C_{18}H_{22}IN$	57.00	56.97	5.85	5.81
7	2-Naphthyl[d]	80	102–103 (0.2 mm.)						
	Picrate		139–140[f]		$C_{21}H_{20}N_4O_7$	57.27	57.00	4.58	4.97
8	9-Phenanthryl	91	89–90[n]		$C_{19}H_{19}N$	87.31	87.21	7.33	7.32
	Picrate		160–161[f]		$C_{25}H_{22}N_4O_7$	61.22	61.47	4.52	4.54
	Hydrochloride		220–221[l]		$C_{19}H_{20}ClN$[p]	74.37	74.50	6.90	6.77
	Methiodide		245–246[m]		$C_{20}H_{22}IN$	59.56	59.72	5.50	5.66
9	2-Thienyl	63	47–48 (0.3 mm.)	1.5363 (25°)	$C_{19}H_{13}NS$	64.62	64.22	7.83	7.75
	Picrate		123–124[f]		$C_{15}H_{16}N_4O_7S$	45.45	46.23	4.07	4.13
10	Benzyl[e]	89	69–70 (0.3 mm.)	1.5186 (25°)	$C_{12}H_{17}N$	82.23	82.46	9.78	9.66
	Picrate		144–145[f]		$C_{18}H_{20}N_4O_7$	53.46	53.80	4.99	5.14
11	1-Naphthylmethyl	78	120–121 (0.5 mm.)	1.5828 (25°)	$C_{16}H_{19}N$	85.28	84.86	8.50	9.00
	Picrate		166–167[f]		$C_{22}H_{22}N_4O_7$	58.14	58.38	4.88	4.96

[a] Described by L. C. Craig, *J. Am. Chem. Soc.*, **55**, 2543 (1933). [b] Prepared from Compound 2 by demethylation with hydriodic acid. [c] Prepared from Compound 4 by demethylation with hydriodic acid, then isolated as the hydrochloride. [d] Prepared by Dr. Robert Meyer. [e] Described by R. Lukeš, *Chem. Listy*, **27**, 392, 409 (1933); *Chem. Abstr.*, **29**, 1720 (1935), but no physical constants are given. [f] From alcohol. [g] Showed a marked depression when mixed with the picrate of intermediate pyrrolidine. [h] From dilute alcohol. [i] From water. [j] From acetone-ether-methyl alcohol. [k] Crystallized by dissolving in Skelly A at room temperature and cooling in a Dry Ice bath. m.p. 40–41°. [l] From alcohol-ether. [m] From absolute alcohol. [n] From Skelly B or methanol. [o] 4.22% water was removed by analyst at 110° before C—H analysis. [p] Contains also 1.5% water.

this residue there was obtained 9 g. of 2,2-dibenzylpyrrolidine, b.p. 137–151° (1 mm.). The material was redistilled, and the fraction boiling over the range 169–172° (1.5 mm.) was collected, n_D^{25} 1.5878. The product was a light yellow oil.

A *picrate* was prepared and recrystallized five times from alcohol, once with the aid of decolorizing charcoal, m.p. 176.5–177.5°.

Anal. Calcd. for $C_{24}H_{24}N_4O_7$: C, 59.99; H, 5.04. Found: C, 60.03; H, 5.09.

LAWRENCE, KAN.

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

Pyridine Derivatives. I. Preparation of 3-Chloro-2-pyridone and 6-Chloro-2-pyridone

M. P. CAVA AND N. K. BHATTACHARYYA

Received May 6, 1958

The synthesis of the previously unknown 3-chloro-2-pyridone is reported, and a convenient synthesis of 6-chloro-2-pyridone is described.

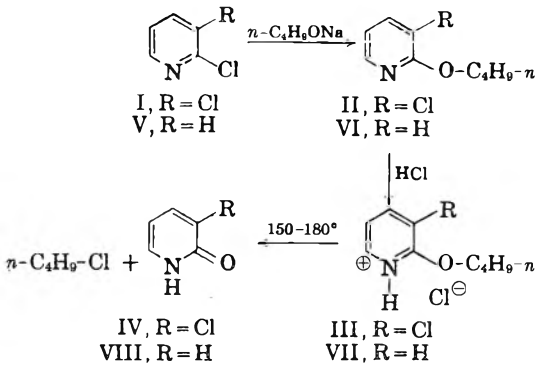
Of the four possible monochloro derivatives of 2-pyridone, only 3-chloro-2-pyridone (IV) has not been described previously. The one recorded observation of the direct chlorination of 2-pyridone mentions 3,5-dichloro-2-pyridone as a product, but 5-chloro-2-pyridone was the only monochlorinated pyridone found in the reaction mixture.[1]

A suitable starting material for an unambiguous synthesis of 3-chloro-2-pyridone is 2,3-dichloropyridine (I), which is readily available from 3-aminopyridine by chlorination to 2-chloro-3-aminopyridine,[2] followed by the replacement of the amino group of the latter by chlorine.[3]

The hydrolysis of the more reactive 2-chlorine atom of 2,3-dichloropyridine to a pyridone function was accomplished conveniently by a two-step process. Treatment of 2,3-dichloropyridine with excess sodium *n*-butoxide in *n*-butyl alcohol for 22 hr. on the steam bath gave, in 64% yield, 3-chloro-2-*n*-butoxypyridine (II). The acid-catalyzed cleavage of 2-alkoxypyridines to 2-pyridones by mineral acids is well known, but the conditions employed may be drastic and inconvenient, *e.g.*, hydrochloric acid under pressure at 160°.[4] A simple and convenient method for the cleavage of mixed aliphatic-aromatic ethers consist in heating the appropriate ether with the thermally stable pyridine hydrochloride.[5]

It was assumed in the case of a 2-alkoxypyridine that the ether and the hydrochloride reagent could be combined in the same molecule; this was found indeed to be possible. When dry hydrogen chloride was passed into an ethereal solution of 3-chloro-2-*n*-butoxypyridine the crystalline hydrochloride (III) of the latter separated in quantitative yield. The dry salt decomposed smoothly at 150–180°, evolving *n*-butyl chloride and leaving a residue which, on crystallization from benzene, afforded pure 3-chloro-2-pyridone (IV), m.p. 180–181°, in 69% yield.

The stepwise hydrolytic procedure described above was found to be equally applicable to the simpler model case of 2-chloropyridine (V). The conversion of 2-chloropyridine to 2-*n*-butoxypyridine (VI) proceeded in 85% yield; pyrolysis of the oily hydrochloride (VII) of the latter at 150°–180° gave *n*-butyl chloride and 2-pyridone (VIII), both essentially in quantitative yield. By contrast, the cleavage of 2-*n*-butoxypyridine by concentrated hydrochloric acid at 98° proceeded very slowly, 75% of the unhydrolyzed ether being recovered after 14 hours of heating.



Of the remaining monochloro-2-pyridones, the one least convenient to prepare has been 6-chloro-2-pyridone (XVI), the only described synthesis of which involves heating the difficultly accessible 6-bromo-2-ethoxypyridine with hydrochloric acid under pressure.[6] A simple new synthesis of 6-chloro-2-pyridone adaptable to large scale preparations, has been developed starting from the commercially available 6-methyl-2-aminopyridine (IX). Diazotization of this amine in cold fuming hydrochloric acid, as described by Seide,[7] gave 2-methyl-6-chloropyridine (X) in 56% yield. Sodium permanganate oxidation of 2-methyl-6-chloropyridine[8] gave, in 61% yield, 6-chloropicolinic acid (XI), esterified by methanolic hydrogen chloride, in 83% yield, to methyl 6-chloropicolinate (XII), m.p. 95–96°. Reaction of this methyl ester with hydrazine produced, in 92% yield, 6-chloropicolinic hydrazide (XIII), m.p. 154–155°. Diazotization of

(1) M. Dohrn and R. Dirksen, U. S. Patent 1,706,775; *Chem. Abstr.*, 23, 2189 (1929).

(2) O. Schickh, A. Binz, and A. Schultz, *Ber.*, 69, 2593 (1936).

(3) H. J. den Hertog, J. C. M. Schogt, J. de Bruyn, and A. de Klerk, *Rec. trav. chim.*, 69, 673 (1950).

(4) C. R. Kolder and H. J. den Hertog, *Rec. trav. chim.*, 72, 285 (1953).

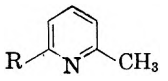
(5) V. Prey, *Ber.*, 74, 1221 (1941).

(6) H. J. den Hertog and J. de Bruyn, *Rec. trav. chim.* 70, 182 (1951).

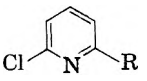
(7) O. A. Seide, *J. Russ. phys. chem. Soc.*, 50, 534 (1918).

(8) Oxidation of this compound using potassium permanganate is mentioned in Swiss Patent 227,124.

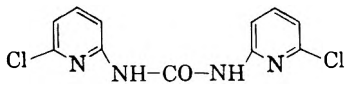
the hydrazide gave 6-chloropicolinic azide (XIV) which, without purification, was decomposed directly in warm 50% aqueous acetic acid to 6-chloro-2-aminopyridine (XV), m.p. 65–67°; the over-all yield of pure amine from the hydrazide was 64%. As a by-product of the azide decomposition there was isolated, in 7% yield, bis(6-chloro-2-pyridyl) urea (XVII), m.p. 250–251°. Finally, the 6-chloro-2-aminopyridine was diazotized in aqueous sulfuric acid, giving 6-chloro-2-pyridone (XVI) in a yield of 70%.



IX: R = NH_2
X: R = Cl



XI, R = COOH
XII, R = $COOCH_3$
XIII, R = $CONH—NH_2$
XIV, R = CON_3
XV, R = NH_2
XVI, R = OH



XVII

EXPERIMENTAL[9]

3-Chloro-2-(n-butoxy)pyridine (II). To a solution of sodium (12.3 g.) in dry *n*-butyl alcohol (180 ml.) was added a solution of 2,3-dichloropyridine[3] (20.0 g.) in the minimum necessary volume of dry *n*-butyl alcohol. The mixture was heated for 22 hr. on the steam bath with occasional shaking, cooled, and made strongly acid by the addition of concentrated hydrochloric acid. The butanol solution was decanted from the sodium chloride precipitate, which was washed first with methanol, then with ether. The combined organic extracts were diluted with water, the mixture was made strongly basic with sodium hydroxide, and the organic layer separated. The aqueous layer was extracted further with several portions of ether. The combined organic extracts were washed with water, dried (sodium sulfate), and distilled. The desired chloroether (16 g., 66%) was collected at 72–75° (2 mm.). On redistillation an analytical sample was obtained, b.p. 75° (2 mm.).

Anal. Calcd. for $C_9H_{12}ClNO$: C, 58.22; H, 6.48; N, 7.55; Cl, 19.15. Found: C, 57.82; H, 6.71; N, 7.39; Cl, 19.06.

3-Chloro-2-pyridone (IV). Dry hydrogen chloride gas was passed into a cooled solution of 3-chloro-2-(*n*-butoxy)-pyridine (15.0 g.) in dry ether (200 ml.) until no further solid separated. The white precipitate of hydrochloride (15.0 g.) was filtered off, washed with ether, followed by 30–60° petroleum ether, and sucked dry. The dried hydrochloride was placed in a round-bottomed flask provided with a water separator, and the flask was heated in a sand bath. The bath temperature was raised from 150 to 180° over a period of 90 min., when *n*-butyl chloride (2.3 ml.) collected in the separator. The flask was cooled and the white crystalline 3-chloro-2-pyridone (5.5 g., 64%), m.p. 180–181°, was rubbed with a little benzene, filtered and dried. After recrystallization from a large volume of benzene glistening flakes, m.p. 180–181°, were obtained.

Anal. Calcd. for C_5H_4NOCl: C, 46.40; H, 3.09; N, 10.80; Cl, 27.42. Found: C, 46.54; H, 3.17; N, 10.47; Cl, 27.44.

2-(n-Butoxy)pyridine (VI). To a solution of sodium *n*-butoxide prepared from sodium hydride (7.5 g.) and *n*-butyl alcohol (100 ml.) was added 2-chloropyridine (11.6 g.). The mixture was heated for 10 hours on the steam bath, cooled, and a mixture of water (200 ml.) and concentrated hydrochloric acid (40 ml.) added. The butanol layer was separated and extracted three times with a small volume of dilute hydrochloric acid. The original aqueous acid phase was combined with the acid wash solutions, and residual butanol removed by ether extraction. The aqueous solution was cooled, made strongly basic by addition of aqueous sodium hydroxide, and the separated basic oil extracted by ether. Evaporation of the dried ether extracts left an oil, most of which distilled at 55–65° (3–4 mm.). Redistillation gave pure 2-(*n*-butoxy)pyridine (13.2 g., 85%), b.p. 65–66° (4 mm.).

Anal. Calcd. for $C_9H_{13}NO$: C, 71.52; H, 8.63; N, 9.28. Found: C, 71.59; H, 8.57; N, 9.50.

Ether cleavage of 2-(n-butoxy)pyridine (VI). Dry hydrogen chloride was passed through an ethereal solution of the butyl ether VI (8.0 g.) when the hydrochloride separated as a thick oil: the oil did not crystallize on rubbing or after adding methanol. The methanolic solution of the hydrochloride was evaporated and the residue heated gradually to 220°; during the heating *n*-butyl chloride (5.0 ml.) distilled over. Distillation of the residue at 132–133° (2 mm.) gave 2-pyridone (5.0 g., 99%) as a viscous mass, solidifying to crystals, m.p. 65–70°. The identity of the crude pyridone was confirmed by its infrared spectrum.

6-Chloropicolinic acid (XI). To a gently refluxing and rapidly stirred suspension of 2-methyl-6-chloropyridine[7] (69 g.) in water (700 ml.) was added, during 1 hr., a solution of sodium permanganate (215 g.) in water (300 ml.). Heating and stirring were continued for an additional 3 hr., and the mixture was then steam distilled. From the distillate unchanged 2-methyl-6-chloropyridine (23.0 g.) was recovered. The oxidation mixture was filtered from manganese dioxide and the colorless filtrate concentrated to 300 ml., cooled, and acidified with concentrated hydrochloric acid. The fine white precipitate of acid XI was filtered, washed carefully with ice water, air dried and finally oven dried at 95°: yield 35.0 g. (61%, based on unrecovered starting material), m.p. 192–194° (reported[10] 190°).

Methyl 6-chloropicolinate (XII). A suspension of finely powdered 6-chloropicolinic acid (31.0 g.) in 12% methanolic hydrogen chloride (200 ml.) was refluxed for six hours. The clear solution was concentrated on the steam bath (aspirator pressure), diluted with cold water, and the precipitated ester extracted into a large volume of ether. After washing with water and aqueous sodium bicarbonate, the dried extract was evaporated slowly and the residual mass of needles (28.0 g., 83%; m.p. 95–96°) washed with 30–60° petroleum ether and dried. Recrystallization from absolute ethanol afforded the analytical sample as long white needles, m.p. 96–97°.

Anal. Calcd. for $C_7H_6NO_2Cl$: C, 48.90; H, 3.50; N, 8.17; Cl, 20.70. Found: C, 49.13; H, 3.71; N, 8.02; Cl, 20.89.

6-Chloropicolinic hydrazide (XIII). A solution of the methyl ester XII (28.0 g.) in a mixture of absolute ethanol (150 ml.) and anhydrous hydrazine (11 ml.) was refluxed for 2.5 hr. The clear solution was evaporated under vacuum and the solid residue crystallized from aqueous ethanol to give a microcrystalline white powder (26.0 g., 92%, m.p. 154–155°). The melting point was not appreciably changed (155–156°) after recrystallization from ethanol.

Anal. Calcd. for $C_6H_6N_3ClO$: C, 42.00; H, 3.51; N, 24.50, Cl, 20.71. Found: C, 42.10, H, 3.60; N, 24.28; Cl, 20.87.

Curtius degradation of 6-chloropicolinic hydrazide. A solution of the hydrazide XIII (37.0 g.) in *N* hydrochloric acid (250 ml.) was cooled to −5° and a solution of sodium nitrite (20.0 g.) in water (100 ml.) was added dropwise with good stirring, taking care that the temperature of the acid solution remained below 0° by cooling. The white precipitate of *6-chloropicolinic azide* (XIV) was filtered, washed with ice-water and sucked almost dry: a sample melted at 102–103° with gas evolution. The crude azide was

(9) Analyses carried out by Galbraith Laboratories, Knoxville, Tenn. Melting points are uncorrected.

dissolved in 50% aqueous acetic acid (400 ml.) and the solution heated on the steam bath. After 1 hr. gas evolution had ceased. The solution was cooled and the precipitate of crude *bis(6-chloro-2-pyridyl)urea* (XVII; 4.5 g., 7.6%, m.p. 230–240°) was removed by filtration. Recrystallization of a sample of XVII from benzene-ethanol gave voluminous white needles, m.p. 250–251°.

Anal. Calcd. for $C_{11}H_8N_4Cl_2O$: C, 46.62; H, 2.83; N, 19.80; Cl, 25.10. Found: C, 46.72; H, 2.81; N, 19.90; Cl, 25.09.

The acetic acid filtrate from the crude urea was cooled (ice bath) and neutralized to *p*H 7 by the gradual addition of 20% aqueous sodium hydroxide. The precipitate (21.2 g.) was filtered, air dried, and sublimed at 75–90° (2 mm.) to give colorless granular crystals of 6-chloro-2-aminopyridine (XV; 18.0 g., 64%; m.p. 65–67°). The melting point was not altered by resublimation.

Anal. Calcd. for $C_5H_5N_2Cl$: C, 46.67; H, 3.91; N, 21.80; Cl, 27.62. Found: C, 47.16; H, 3.99; N, 21.67; Cl, 27.72.

6-Chloro-2-pyridone (XVI). To a stirred and cooled (0–5°) solution of 6-chloro-2-aminopyridine (10.0 g.) in 6*N* sulfuric acid (70.0 ml.) was added, in small portions, solid sodium nitrite (10.0 g.). After careful neutralization of the resulting cold suspension to *p*H 5 with aqueous sodium hydroxide the crude pyridone (9.0 g.) was filtered, washed with a very small amount of ice water and air dried. Recrystallization from benzene (charcoal treatment) afforded the pure pyridone XVI (6.9 g., 70%) as fine white needles, m.p. 125–126° (reported[6] 128.5–129°).

Anal. Calcd. for C_5H_4NOCl: C, 46.40; H, 3.09; N, 10.80; Cl, 27.42. Found: C, 46.43; H, 3.17; N, 10.95; Cl, 27.39.

Acknowledgment. This work was supported by a contract with The U. S. Army Chemical Corps, Fort Detrick, Fredrick, Md.

COLUMBUS 10, OHIO

[CONTRIBUTION NO. 1368 FROM THE STERLING CHEMISTRY LABORATORY OF YALE UNIVERSITY]

Preparation of Some α-(2-Thienyl)-β-arylethylamines[1]

A. J. HILL AND R. A. BROOKS

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A series of seven α-(2-thienyl)-β-arylethylamine hydrochlorides has been prepared from the corresponding ketones by Leuckart reaction. The necessary ketones were made from the arylacetyl chlorides by a Friedel-Crafts reaction with thiophene or from the arylacetonitriles by reaction with 2-thienylmagnesium iodide or 2-thienyllithium.

Reports of the analgesic potentialities of α,β-diphenylethylamines[2–6] suggested the substitution of the 2-thienyl group for either or both phenyl groups in these compounds. The substitution of 2-thienyl for phenyl in physiologically active compounds may result in little or no change in properties[7,8] but occasionally activity is markedly enhanced.[9,10]

The route selected for the preparation of the 2-thienyl isosteres of α,β-diphenylethylamines was *via* the arylacetyl chlorides, employing a Friedel-Crafts reaction to produce the ketones, followed by conversion to the amines with a Leuckart reagent. The necessary arylacetic acids were to be prepared from the hydrocarbons by chloromethylation, cyanation, and hydrolysis. In practice, it was found possible to use this route with phenylacetyl chloride and *p*-methoxyphenylacetyl chloride to give the ketones (I and II, Table I). Stannic chloride and iodine were effective catalysts for the reaction with thiophene. The investigation was also extended to include the 1-naphthyl-substituted ketone (III, Table I). With 2-thienylacetyl chloride,[11] on the other hand, no ketone could be obtained with either stannic chloride or iodine. Hydrogen chloride was freely evolved but only tarry products were obtained. An alternative preparation of the ketone by the use of 2-thienylacetonitrile and 2-thienylmagnesium iodide[12] or 2-thienyllithium[13] also failed, only polymeric materials being obtained. This failure was attributed to the involvement of the α hydrogen atoms of the nitrile. Bisalkylation at the α positions permitted successful reaction to give the ketone (IV, Table I). The corresponding phenyl ketone (V, Table I) was also prepared as well as the diethyl analog (VI, Table I).

Application of a Leuckart reaction was uniformly successful to convert the ketones to the primary amines (VII–XI, Table II). The yield of the amine (XII, Table II) from the diethyl ketone (VI, Table

(1) From the doctoral dissertation of Robert A. Brooks; Yale University; present address: Jackson Laboratory, E. I. du Pont de Nemours and Co., Inc., Wilmington 99, Del.

(2) E. C. Dodds, W. Lawson, and P. C. Williams, *Nature*, **151**, 614 (1943); *Proc. Roy. Soc. (London)*, B **132**, 119 (1944).

(3) L. H. Goodson, C. J. W. Wiegand, and J. S. Splitter, *J. Am. Chem. Soc.*, **68**, 2174 (1946).

(4) R. B. Moffett and W. M. Hoehn, *J. Am. Chem. Soc.*, **69**, 1792 (1947).

(5) W. D. McPhee and E. S. Erickson, Jr., *J. Am. Chem. Soc.*, **68**, 624 (1946).

(6) H. G. O. Holck, *J. Am. Pharm. Assoc., Sci. Ed.*, **39**, 354 (1950).

(7) H. Gilman and R. M. Pickens, *J. Am. Chem. Soc.*, **47**, 245 (1925).

(8) H. Erlenmeyer, *Biochem. Z.*, **252**, 22 (1932); **262**, 196 (1933).

(9) F. F. Blicke and F. Leonard, *J. Am. Chem. Soc.*, **68**, 1934 (1946).

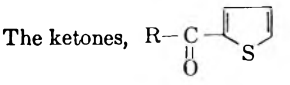
(10) F. F. Blicke and M. U. Tsao, *J. Am. Chem. Soc.*, 66, 1645 (1944).

(11) P. Cagniant, *Bull. soc. chim. France*, 847 (1949).

(12) R. Kitchen and R. B. Sandin, *J. Am. Chem. Soc.*, **67**, 1645 (1945).

(13) H. Gilman and D. A. Shirley, *J. Am. Chem. Soc.*, **71**, 1870 (1949).

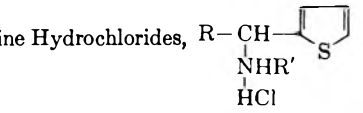
TABLE I

The ketones, 

	R	B.P., °C.	M.P., °C.	Source[a]	% Yield
I	$C_6H_5CH_2$—	165 (5 mm.)	51	AC	82
II	p-$CH_3OC_6H_4CH_2$—	165 (2 mm.)	..	AC	47
III	1-$C_{10}H_7CH_2$—	262 (18 mm.)	85	AC	74,[b] 70[c]
IV	2-$C_4H_3SC(CH_3)_2$—	134 (1.5 mm.)	...	N	...
V	$C_6H_5C(CH_3)_2$—	135 (2 mm.)	87.5	N	70,[d] 44[e]
VI	$C_6H_5C(C_2H_5)_2$—	...	86	N	31,[d] 23[e]

[a] AC: *via* the acid chloride; N: *via* the nitrile. [b] Use of stannic chloride. [c] Use of iodine. [d] Use of 2-thienylmagnesium iodide. [e] Use of 2-thienyllithium.

TABLE II

The Amine Hydrochlorides, 

	R	R′	M.P., °C.	Yield, %	Empirical Formula	Nitrogen Anal. Calcd.	Found
VII	$C_6H_5CH_2$—	H	220	56	$C_{12}H_{14}ClNS$	5.84	5.96
VIII	p-$CH_3OC_6H_4CH_2$—	H	...	57	$C_{13}H_{16}ClNOS$	5.19	5.39
IX	1-$C_{10}H_7CH_2$—	H	221	58	$C_{16}H_{16}ClNS$	4.83	5.23
X	2-$C_4H_3SC(CH_3)_2$—	H	243	24[a]	$C_{12}H_{16}ClNS_2$	5.11	5.29
XI	$C_6H_5C(CH_3)_2$—	H	255	42	$C_{14}H_{18}ClNS$	5.23	5.16
XII	$C_6H_5C(C_2H_5)_2$—	H	...	...	$C_{16}H_{21}NS$[b]	5.40	5.17
XIII	$C_6H_5CH_2$—	—CH_3	166	4,[c] 32[d]	$C_{13}H_{16}ClNS$	5.52	5.57

[a] Yield from nitrile. [b] Free amine, hydrochloride unstable. [c] Use of modified Leuckart reaction. [d] Use of Decker reaction.

I) was low. One secondary amine (XIII, Table II) was prepared by a modified Leuckart reaction using *N*-methylformamide and, in better yield, by a Decker reaction.

EXPERIMENTAL

Benzyl 2-thienyl ketone (I) was prepared from phenylacetyl chloride and thiophene using stannic chloride as described by Spurlock.[14] After crystallization from 50% alcohol the ketone was obtained as plates. The *2,4-dinitrophenylhydrazone* melted at 180°.

Anal. Calcd. for $C_{18}H_{14}N_4O_4S$: N, 14.65. Found: N, 14.43.

p-Methoxyphenylacetonitrile was prepared from *p*-methoxyphenylacetyl chloride[15] by reaction with potassium cyanide in boiling acetone containing 10% water; b.p. 93–96° (4 mm.); n_D^{20} 1.5325; yield 75%.

p-Methoxyphenylacetic acid. Hydrolysis of *p*-methoxyphenylacetonitrile gave very low yields of the acid. Consequently, the acid was prepared *via* the imino ester hydrochloride and ester without isolation of these compounds. A solution of 20 g. (0.136 mole) of *p*-methoxyphenylacetonitrile in 6.3 g. (0.136 mole) of absolute alcohol and 50 ml. of ether was treated with 7.5 g. (0.205 mole) of dry hydrogen chloride at 0°. The solution was then allowed to stand in the cold for several hours. Water (50 ml.) was added and the ether was removed. Potassium hydroxide (20 g., 0.357 mole) in 100 ml. of 95% alcohol was added and the solution was refluxed for 3 hr. As much alcohol as possible was removed by distillation at atmospheric pressure on a steam bath. All ether-soluble material was extracted and the remaining solution was made strongly acidic with dilute hydrochloric acid. An oil which separated was dissolved in ether. After drying and removal of the ether the product was obtained as a solid which was crystallized from carbon tetrachloride and petroleum ether; m.p. 86°; yield 14 g. (62%).

p-Methoxyphenylacetyl chloride was prepared from the acid by reaction with thionyl chloride; b.p. 126–130° (14 mm.); yield 90%.

p-Methoxybenzyl 2-thienyl ketone (II). Iodine (0.15 g.) was added to a solution of 8.5 g. (0.046 mole) of *p*-methoxyphenylacetyl chloride in 7.7 g. (0.092 mole) of thiophene. The mixture was shaken until the iodine had dissolved and then was refluxed for 6 hr. A volume of water and two volumes of ether were added. The ether layer was separated, washed with 25 ml. of 5% sodium carbonate solution and with water. After drying, the ether and excess thiophene were removed. Distillation of the residue gave 5 g. of product. Crystallization from 85% alcohol gave needles with no clear cut melting point.

Anal. Calcd. for $C_{13}H_{12}O_2S$: S, 13.80. Found: S, 13.86.

1-(2-Thienyl)-2-(1-naphthyl)ethanone-1 (III). (*a*) A solution of 19 g. (0.073 mole) of stannic chloride in 25 ml. of benzene was cooled to −10° and a solution of 15 g. (0.073 mole) of 1-naphthylacetyl chloride,[16] 6.1 g. (0.073 mole) of thiophene, and 30 ml. of benzene was added during 1.5 hr. The mixture was then stirred at room temperature for 1 hr. Water (50 ml.) containing 1 ml. of concentrated hydrochloric acid was added. The benzene layer was separated, washed with 50 ml. of 5% sodium carbonate solution and with water. After drying, the benzene was removed and the residue distilled. The product was a liquid which solidified on cooling; yield 13.7 g. Crystallization from 80% alcohol raised the melting point to 85°.

(*b*) The use of iodine in place of stannic chloride gave 12.1 g. of product.

Ethyl 2-thienyliminoacetate hydrochloride. Dry hydrogen chloride (1.25 moles) was passed into a solution of 24.6 g.

(14) J. J. Spurlock, *J. Am. Chem. Soc.*, **75**, 1115 (1953).
(15) A. Ofner, *Helv. Chim. Acta*, 18, 951 (1935).
(16) F. E. King and T. Henshall, *J. Chem. Soc.*, 417 (1945).

(0.20 mole) of 2-thienylacetonitrile[17] and 9.2 g. (0.20 mole) of absolute alcohol in 50 ml. of ether. During addition of the gas the temperature was maintained at 0°, and following attainment of the correct weight the flask was placed in an ice box. After several hours, clumps of needles formed; m.p. 97.5°; yield 18 g. (43%).

Anal. Calcd. for $C_8H_{12}ClNOS$: N, 6.80. Found: N, 7.07.

Ethyl 2-thienylacetate[18] was prepared by the hydrolysis of ethyl 2-thienyliminoacetate hydrochloride.

2-Thienylacetic acid.[18] Saponification of 11 g. (0.065 mole) of ethyl 2-thienylacetate gave 7.5 g. (81%) of the acid; m.p. 73°. Recrystallization from carbon tetrachloride and petroleum ether yielded plates melting at 76°. Preparation of 2-thienylacetic acid from 2-thienylacetonitrile without isolation of the intermediate imino ester hydrochloride and ester gave an improvement in yield to 88% overall.

2-Thienylacetyl chloride was prepared from 2-thienylacetic acid and thionyl chloride by the method of Cagniant.[11] All attempts to condense this product with thiophene failed to give the ketone.

α-Methyl-(2-thienyl)acetonitrile. (*a*) A solution of 41.3 g. (0.341 mole) of 2-thienylacetonitrile in 250 ml. of ether was cooled to 0°. During 30 min. 13.3 g. (0.341 mole) of powdered sodium amide was added. The mixture was stirred for 15 min. at room temperature and then 48.8 g. (0.341 mole) of methyl iodide was added dropwise. The mixture was refluxed for 2 hr. and hydrolyzed with 200 ml. of cold water. The ether layer was separated and dried. After removal of the ether the residue was distilled to give 25 g. (53%) of liquid; b.p. 94° (10 mm).

(*b*) Substitution of lithium amide for sodium amide in the above procedure gave a 58.5% yield of the nitrile.

Anal. Calcd. for C_7H_7NS: N, 10.21. Found: N, 10.07.

α,α-Dimethyl-(2-thienyl)acetonitrile. (*a*) Sodium amide (7.1 g., 0.182 mole) was suspended in 250 ml. of ether at 0° and, during 1 hr., 25 g. (0.182 mole) of α-methyl-(2-thienyl)acetonitrile was added. The mixture was stirred for 30 min. at room temperature and 25.8 g. (0.182 mole) of methyl iodide was dropped in. The mixture was refluxed for 1 hr., hydrolyzed with 200 ml. of water, and the ether layer separated. After drying the nitrile was distilled; b.p. 93–95° (11 mm); yield 13 g. (47%).

(*b*) Substitution of lithium amide for sodium amide raised the yield to 70.5%.

Anal. Calcd. for C_8H_9NS: N, 9.27. Found: N, 9.16.

1,2-Di-(2-thienyl)-2,2-dimethylethanone-1 (IV). A solution of 40 g. (0.265 mole) of α,α-dimethyl-(2-thienyl)acetonitrile in 100 ml. of ether was added slowly to a solution of 2-thienyllithium prepared from 6.9 g. (1.0 mole) of lithium, 68.5 g. (0.50 mole) of *n*-butyl bromide, and 42 g. (0.50 mole) of thiophene in 150 ml. of ether.[13] The mixture was refluxed for 12 hr. and then poured over ice. The ether layer was separated and dried. After removal of the ether the residue was stirred at 100° with 20% hydrochloric acid for 4 hr. The acidic solution was extracted with ether and the extracts were washed and dried. After removal of the solvent the residue was distilled to give 4 g. of the ketone and 16 g. of unchanged α,α-dimethyl(2-thienyl)-acetonitrile.

Anal. Calcd. for $C_{12}H_{12}OS_2$: S, 27.14. Found: S, 27.35.

It was found possible to substitute 2-thienylmagnesium iodide for 2-thienyllithium in this preparation. Yields were improved by replacing the ether with xylene and heating the reaction mixture at 100° for 18 hr. before hydrolysis. The crude product was used directly in the preparation of the amine (IX).

1-(2-Thienyl)-2-phenyl-2,2-dimethylethanone-1 (V). (*a*) To 0.30 mole of 2-thienyllithium in 500 ml. of ether[13] was added 14.5 g. (0.10 mole) of α,α-dimethylphenylacetonitrile.[19] After refluxing for 12 hr. the reaction mixture was poured over 200 g. of ice mixed with 100 ml. of saturated ammonium chloride solution. The ether layer was separated, washed, and dried. Hydrogen bromide was passed into the ether solution. Five grams of a yellow solid, believed to be the imide hydrobromide of the ketone (V), precipitated. This material was heated for 1 hr. with 25 ml. of 20% hydrochloric acid. The precipitated oil was dissolved in ether. After removal of the ether the gummy residue was crystallized from 95% alcohol. Needles were obtained; yield 3.2 g. The ether solution from which the hydrobromide had precipitated was distilled to remove the solvent and the residue was heated at 100° for 1 hr. with 100 ml. of 20% hydrochloric acid. The mixture was extracted with ether and the extracts were dried. After removal of the ether the product was distilled and crystallized from 95% alcohol; yield 7 g. The phenylhydrazone was prepared and crystallized from 90% alcohol.

Anal. Calcd. for $C_{20}H_{20}N_2S$: N, 8.74. Found: N, 8.70.

(*b*) To 0.20 mole of 2-thienylmagnesium iodide in 250 ml. of ether[12] was added 6 g. (0.041 mole) of α,α-dimethylphenylacetonitrile. The solution was refluxed briefly and then the ether was replaced by xylene. The xylene solution was heated at 100° for 12 hr., refluxed for 2 hr. and distilled to remove the xylene. The residue was hydrolyzed with ice and then heated at 100° for 1 hr. with 150 ml. of 20% hydrochloric acid. The product was dissolved in ether and dried. After removal of the ether the product was distilled; yield 6.6 g.

1-(2-Thienyl)-2-phenyl-2,2-diethylethanone-1 (VI). (*a*) To 0.30 mole of 2-thienyllithium in 500 ml. of ether was added 17.3 g. (0.10 mole) of α,α-diethylphenylacetonitrile.[20] After refluxing for 16 hr. the reaction mixture was hydrolyzed with ice and dilute hydrochloric acid. The ether layer was dried and the ether removed. The residual oil was stirred at 100° for 1 hr. with 100 ml. of 25% hydrochloric acid. Eight grams of a solid precipitated on cooling and was filtered. This was the hydrochloride of the ketimine of the ketone (VI). It was soluble in hot 95% alcohol, gave a precipitate with silver nitrate and reacted with potassium hydroxide to give a brown oil. Prolonged boiling with dilute alcohol followed by cooling caused the precipitation of the ketone; yield 6 g.

(*b*) The use of 2-thienylmagnesium iodide in place of 2-thienyllithium as described for the ketone (V) increased the yield to 8 g.

Anal. Calcd. for $C_{16}H_{18}OS$: S, 12.40. Found: S, 12.54.

Preparation of the amines. The following procedure is typical of those used to prepare the primary amines found in Table II. *α-(2-Thienyl)-β-phenylethylamine hydrochloride* (VII). Twenty-four grams of 85–90% formic acid was added dropwise to 24 g. of powdered ammonium carbonate. The mixture was slowly distilled until the temperature reached 165°. Then 20.2 g. (0.10 mole) of benzyl 2-thienyl ketone (I) was added. The temperature was raised to 180–185° and maintained for 8 hr. Two volumes of water were added to the cooled mixture which caused solidification. The water was decanted, 20 ml. of concentrated hydrochloric acid was added, and the mixture was refluxed for 1 hr. Two hundred ml. of water and 200 ml. of ether were added, the water layer was separated and treated with 2 g. of activated charcoal. Filtration gave a light brown solution which was made basic with sodium hydroxide. The precipitated oil was dissolved in ether. After washing and drying, the ether solution was saturated with hydrogen chloride. A precipitate of 13.4 g. was dissolved in absolute alcohol and reprecipitated with ether. A sample was treated with alkali to liberate the base; b.p. 171° (10 mm). Another sample was converted to the acetyl derivative; m.p. 99–100°.

Anal. Calcd. for $C_{14}H_{15}NOS$: N, 5.71. Found: N, 5.67.

(17) F. F. Blicke and F. B. Zienty, *J. Am. Chem. Soc.*, **63**, 2945 (1941).

(18) F. Ernst, *Ber.*, **19**, 3281 (1886).

(19) A. Haller and E. Bauer, *Compt. rend.*, **155**, 1582 (1912).

(20) F. Bodroux and F. Taboury, *Compt. rend.*, **150**, 1241 (1910).

N-Methyl-α-(2-thienyl)-β-phenylethylamine hydrochloride (XIII). (*a*) A mixture of 20.2 g. (0.10 mole) of benzyl 2-thienyl ketone (I) and 23.6 g. (0.40 mole) of *N*-methylformamide was refluxed for 12 hr. Two volumes of water were added, the organic layer was separated and refluxed for 2 hr. with 30 ml. of concentrated hydrochloric acid. Water (50 ml.) was added and the mixture extracted with two 75-ml. portions of ether. After drying, the extracts were saturated with hydrogen chloride. An oil which separated was dissolved in absolute alcohol and ether was added to precipitate the product; yield 1.1 g.

(*b*) α-(2-Thienyl)-β-phenylethylamine (22 g., 0.108 mole) and 11.5 g. (0.108 mole) of benzaldehyde were warmed for 15 min. on a steam bath. Water which was liberated was removed under vacuum. Then 15.3 g. (0.108 mole) of methyl iodide was added. The resulting solution was heated at 100° for 12 hr. in a sealed tube. The reaction mass was boiled for 30 min. with 50 ml. of 95% alcohol, the alcohol was removed, and 100 ml. of water was added. This solution was filtered, treated with 2 g. of activated charcoal, filtered, and cooled. The addition of sodium hydroxide caused an oil to separate which was extracted with 100 ml. of ether. The extract was dried and mixed with 50 ml. of anhydrous ether saturated with hydrogen chloride. A precipitate which formed was dissolved in a minimum of absolute alcohol and reprecipitated with ether; yield 9 g.

NEW HAVEN, CONN.

[CONTRIBUTION FROM THE DOW CHEMICAL CO., EASTERN RESEARCH LABORATORY]

Aminophenols. I. The Reaction of *o*-Aminophenol with Chloracetic Acid and Some Comments on the Formation of Phenmorpholones[1]

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The reaction between *o*-aminophenol and chloroacetic acid has been reinvestigated; the products obtained have been identified, their structures proved, and optimum conditions of formation established. A number of examples are presented of the ring-closure of *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids to 2- and 3-phenmorpholones, respectively, and the similarity to the ring-chain tautomerism of α-(β-hydroxyethylamino)ketones is noted.

Vater[2] reported that *N*-(*o*-hydroxyphenyl)glycine (I) may be prepared by the alkylation of *o*-aminophenol with chloroacetic acid. Repetition of his work yielded an entirely different product and, inasmuch as no published account more recent than Vater's[2] is available, we investigated the reaction in some detail. We now find that by varying the experimental conditions there may be isolated at least five major products (I–V), all in yields of 60% or better.

Though the reaction of mono- or disubstituted amines with chloroacetic acid in the presence of a suitable acid acceptor is a well known method for the preparation of *N*-mono- and disubstituted glycines,[3] it is usually difficult to stop the reaction at the introduction of a single acetic acid group, and separation of the mono- from the diproduct can be tedious.[4] In general, the formation of the monoglycine is favored by an excess of amine,[5] while the diglycine is usually obtained in good yield when excess chloroacetic acid is used.[6] When no added base is present (hydroxide, acetate, etc.) then the amine itself acts as acceptor of the acid liberated and, to avoid decreasing the yield, must be present in excess. These principles are demonstrated amply in the discussion which follows.

The introduction of a mono- or dicarboxymethyl group in *o*-aminophenol (as in I or IIa) offers a favorable opportunity for intramolecular lactonization of the carboxyl with the *o*-phenolic function to form the stable six membered phenmorpholone ring. However, the fact that we found this condensation to be remarkably facile in specific cases only, prompted us to extend our investigations to related systems and to correlate these with some previously reported ring closures. Thus, the formation of 2- and 3-phenmorpholones from *o*-hydroxyphenylglycines and *o*-aminophenoxyacetic acids is presented as a logical adjunct to our study of the reaction of *o*-aminophenol with chloroacetic acid.

Formation of the products. Table I represents a summary of the products obtained from over 20 runs in which the experimental conditions and ratio of reagents were varied systematically. The products, or mixtures, obtained from this reaction are controlled largely by two factors: (1) the ratio of the reactants, *o*-aminophenol and chloroacetic acid, and (2) the *p*H of the solution. That both these factors are equally important can be seen from a casual inspection of Table I. Thus, for example, maintaining the ratio of reactants constant and changing the *p*H slightly, as in runs 3 and 4, give different products, and this is equally true of runs 6 and 8 where the *p*H is constant and the ratio is changed.

Since chloroacetic acid is a strong acid, the *p*H

(1) Presented in part before the Organic Section of the 131st Meeting of the American Chemical Society, Miami, Fla. April 1957.

(2) H. Vater, *J. prakt. Chem.*, **29**, 289 (1884).

(3) M. Sahyun, *Outline of Amino Acids and Proteins*, Reinhold Publishing Co., N. Y., 1944, p. 95.

(4) P. J. Meyer, *Ber.*, **14**, 1325 (1881); *Ber.*, **35**, 580 (1902).

(5) Rebuffat, *Gazz. chim. ital.*, **17**, 234 (1888), **20**, 122 (1891).

(6) *Org. Syntheses*, Coll. Vol. II, 2nd ed., 397 (1943).

TABLE I

Run No.	o-Amino-phenol, Mol.	Chloro-acetic Acid, Mol.	NaOH, Mol.	Approx. pH	Product[a] I	II	III	IV	Total[b] o-Amino-phenol Accounted for, %
1	1	1	0	4	..	..	..	60	90
2	1	2	0	3	..	..	..	90	90
3	1	1	1	7	20	..	50	..	80
4	1	1	2	8[c]	20	20	..	..	90
5	1	4	4	7	..	50	45	..	95
6	1	4	6	8[c]	..	80	..	..	80
7	2	1	0	6	[d]	..	50	..	70
8	2	1	2	8[c]	60	..	..	..	90
9	4	1	..	6	20	..	..	..	85
10	1	4	6	10		(50% of V)			

[a] Based on reactant present in least amount. [b] The difference between this figure and the o-aminophenol converted to product represents o-aminophenol actually isolated as such. [c] Excess base added dropwise so as to maintain the pH at 7–8. [d] I is present in filtrate, but was not isolated.

will not rise significantly above 7 until more than one mole of strong base (sodium hydroxide in this case) is present per mole of acid. Thus at a low pH; *i.e.*, when no excess of acid acceptor over chloroacetic acid is present (runs 1 and 2), no alkylation occurs, but it is possible to isolate the salt, *o*-aminochloracetate (IV). This compound is entirely dissociated into its components at pH <2 and >7, but is stable and is obtained in optimum yield at pH 3. On the other hand, when the pH is high enough to dissociate the phenolic protons, *O*-alkylation as well as *N*-alkylation will take place, this being a common method for the preparation of aryloxyacetic acids.[7] Therefore, when conditions called for a large excess of base (runs 4 and 6), *O*-alkylation was avoided by maintaining the pH at 7–8 by addition of the hydroxide solution as needed. In the one case where the pH was allowed to reach 10 (run 10) reaction occurred rapidly at both the amino and phenolic functions, and the major product was the disodium salt of [*o*-(carboxymethoxy)phenyl]iminodiacetic acid (V).

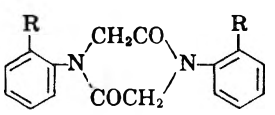
The monosubstituted glycine (I) was obtained in good yield only with a twofold excess of *o*-aminophenol at a pH of 7–8 (run 8). This is interpreted as a mass action effect wherein the excess phenol represses the formation of the disubstituted glycine, IIa. Conversely, with an excess of chloracetic acid, as in runs 5 and 6, the (ring-closed) dialkylated II, rather than I, is obtained. The situation is further complicated by the strong tendency for II to condense with unreacted aminophenol to give III. However, this occurs only in neutral or slightly acid solution and at a pH of 8, III is rapidly hydrolyzed back to II. This explains why in run 5 at a neutral pH, a mixture of both II and III is obtained, whereas in run 6, where the pH is maintained at 8, only II was realized. Finally, with equimolar amounts of reagents on the neutral or slightly acid side (runs 3 and 7) there was obtained a mixture of I and III with, the latter predominating. We may assume that here the initial mixture consisted of I and II, the latter being converted to the insoluble III by condensation with excess *o*-aminophenol.

Structure of the products. *N*-(*o*-hydroxyphenyl) glycine (I), which crystallized from water as the monohydrate, existed entirely as the Zwitterion in analogy to *N*-phenylglycine. According to Vater,[2] I loses water on heating to form an "anhydride" and Beilstein[8] erroneously concludes that the structure of this product is the lactone VII. We now find that though quantitative dehydration of I at 140° under vacuum does indeed show that two moles of water are lost (including one mole of water

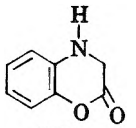
(7) R. L. Shriner, R. C. Fuson, and D. Y. Curtin, *The Systematic Identification of Organic Compounds*, John Wiley and Sons, Inc. N. Y., 4th Ed., p. 263.

(8) *Beilstein*, Vol. 27 (Hauptwerk), p. 190.

of hydration), the actual dehydration product is not VII, but 2,5-dioxo-1,4-di-(*o*-hydroxylphenyl)-piperazine (VI). An analogous bimolecular con-



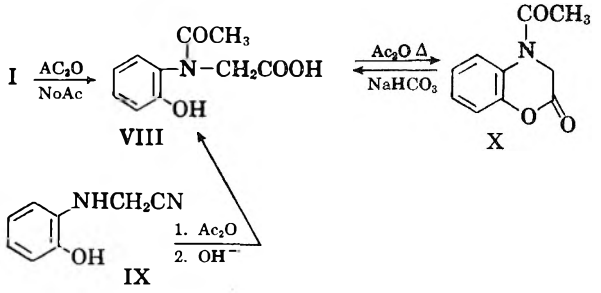
VI R=OH
VI-a R=H



VII

densation occurs with *N*-phenylglycine which on heating to 150° forms VIa.[9] The absence of a lactone carbonyl band and its insolubility in bicarbonate rule out VII as the dehydration product, while supporting evidence for VI is obtained from the strong amide-I band at 6.08μ in its spectrum. An attempt to prepare VII by treating I with hydrochloric acid yielded only *N*-(*o*-hydroxyphenyl)-glycine hydrochloride, and it was concluded that in this case lactonization does not readily take place.[9a]

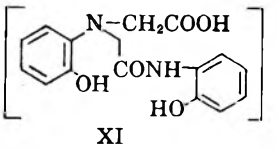
When I was treated with acetic anhydride–sodium acetate, *N*-acetylation occurred to yield the water-insoluble sodium salt of VIII, which was converted to pure VIII on acidification. This compound has been prepared by Shimo[10] by the acetylation of *N*-(*o*-hydroxyphenyl)glycinonitrile (IX) and subsequent hydrolysis of the nitrile. He does not mention the hydrolysis of IX to I. We found



that no acetylation of the phenolic function of VIII took place under mild conditions, while in boiling acetic anhydride ring closure occurred to yield *N*-acetylphenmorpholone-2 (X). Unlike compounds such as II, and others discussed below, which are not isolatable in the open-chain form, X is readily saponified back to VIII by bicarbonate and VIII does not lactonize even in warm 6*N* hydrochloric acid.

All attempts to isolate *N*-(*o*-hydroxyphenyl)-iminodiacetic acid (IIa) led only to the lactone, 2-phenmorpholone-4–acetic acid (II). Thus, when the aqueous alkaline reaction mixture from run 6 was made strongly acid and warmed, it at once deposited II in good yield. The lactone II was soluble in bicarbonate and required approximately two equivalents of base for titration in aqueous alcohol. However, acidification of an alkaline solution of II to *p*H 4 (the estimated *p*H of the free acid IIa) and extraction with ether afforded only unchanged II, again indicating that the free acid is not capable of isolation. In contrast to the *N*-monosubstituted glycine (I), II is insoluble in strong acid and does not form a stable hydrochloride. In addition, its infrared spectrum shows a normal carboxyl band (~5.84μ) and, therefore, it does not exist as a Zwitterion.

When II[11] was refluxed with aqueous *o*-aminophenol it was converted almost quantitatively to III, thus providing evidence for the structure of the latter. This amide formation in aqueous solution would seem to be highly unusual, if not unique, were it occurring by the elimination of water between the amine and carboxyl groups, a reaction which is usually conducted at high temperatures under dehydrating conditions.[12] It is more likely that amide formation occurs by attack of the amino group on the lactone function to yield the nonisolatable intermediate XI which spontaneously



XI

lactonizes to give III. The fact that I, in which the lactone function is absent, does not react further with *o*-aminophenol lends support to this argument. The ready formation of the amide bond of III is paralleled by its rapid hydrolysis in base; by merely dissolving III in warm bicarbonate, *o*-aminophenol precipitates on cooling. The structure of III is supported also by its infrared spectrum which contains absorptions characteristic of a phenol, γ,δ-unsaturated δ-lactone and secondary amide.

Treatment of III with excess acetic anhydride in the presence of sodium acetate yielded the monoacetyl derivative, XII, which on hydrolysis with cold, dilute base afforded not the expected *o*-aminophenol or *o*-aminophenylacetate, but only *o*-hydroxyacetanilide. This conflicting piece of evidence was resolved by the realization that after hydrolysis at the amide function, an oxygen to nitrogen rearrangement had taken place. Such re-

(9) P. J. Meyer, *Ber.*, **10**, 1967 (1877).

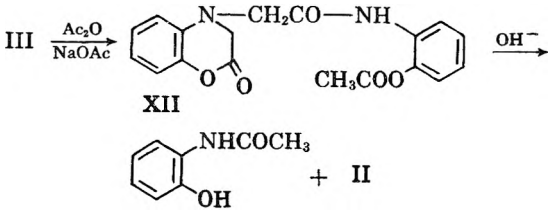
(9a) Subsequent to the completion of this work, a paper appeared by D. G. O'Sullivan and P. W. Sadler (*J. Chem. Soc.*, 2916 (1957)) in which VII was mentioned as having been prepared by Vater's[2] method from I. Drs. O'Sullivan and Sadler very kindly supplied a sample of their compound which we found to be identical to our compound III both from comparison of their infrared spectra and m.p.'s. Thus it appears that to date VII has not been successfully prepared.

(10) K. Shimo, *Bull. Chem. Soc. Japan*, **1**, 206 (1926).

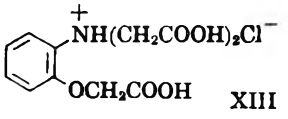
(11) The authors are grateful to B. M. Williams of the Edgar C. Britton Laboratory, The Dow Chemical Co., Midland, Mich., for a sample of II, submitted in the very early states of this work, and for his directions for preparing same.

(12) For example see, C. N. Webb, *Org. Syntheses*, **Coll. Vol. I**, 82 (1943).

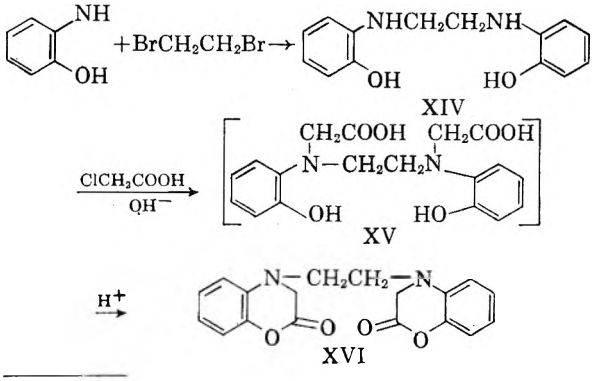
arrangements are common with the *o*-aminophenols and have been extensively investigated.[13]



The *O*-alkylated product V was isolated only as its disodium salt and it was not possible to convert the salt to the free tri- acid even by carefully controlled acidification or ion-exchange methods.[13a] However, no difficulty was experienced in obtaining the hydrochloride (XIII), though neutralization of XIII again gave impure material. The structures of V and XIII were confirmed by their ultraviolet and infrared spectra and by titration data, as well as by the usual elemental analyses.

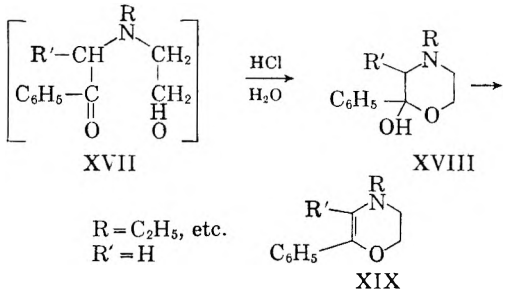


Formation of 2- and 3-phenmorpholones. Our interest in these compounds arose from the observation that *N*-(*o*-hydroxyphenyl)glycine (I) could not be induced to lactonize even by boiling in strong acid while the corresponding iminodiacetic acid (IIa) could be isolated only as the lactone (II).

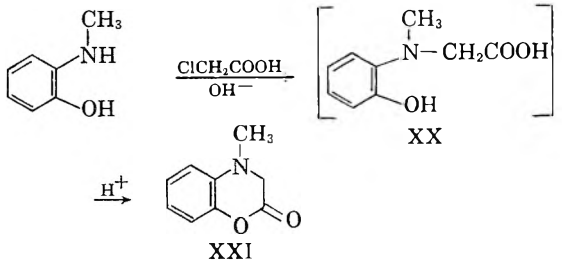


This same phenomenon was encountered in an attempted preparation of *N*,*N*′-ethylenebis(*N*-*o*-hydroxyphenyl)glycine (XV) by the action of chloroacetic acid on *o*,*o*′-ethylenediiminodiphenol (XIV). On acidification of the alkaline reaction mixture, only the dilactone, XVI, was obtained. Whereas neither II nor XVI were acid-soluble, the nonlactonizable I formed a stable hydrochloride.

Though the data presented above is far from conclusive, it strongly suggests that the formation of the morpholone ring is spontaneous when the nitrogen is tertiary but ring closure does not occur when the nitrogen is secondary. We were, therefore, interested to learn that this same phenomena has been observed with a related system. Thus, Lutz and co-workers[14,15] and Cromwell and Tsou[16] report that the α-(β-hydroxyethylamino)ketones exist in the chain form when the nitrogen is secondary (XVIII, R equals H) and in the ring form when the nitrogen is tertiary (XVIII and XIX, R equals alkyl). Further, a recent study[17] of the factors which control this cyclization reports that in the absence of secondary steric and electronic effects, the dominant factor in the equilibrium distribution of chain and cyclic forms is the presence or absence of an alkyl group on nitrogen.[18]



To obtain additional information about the spontaneous formation of *N*-alkyl-2-phenmorpholones, an attempt was made to isolate *N*-methyl-*N*-(*o*-hydroxyphenyl)glycine (XX) from the chloro,



(13) For the most recent work, see A. L. LeRosen and E. D. Smith, *J. Am. Chem. Soc.*, **70**, 2705 (1948); **71**, 2815 (1949).

(13a) Some time after the completion of this work, the authors received a private communication from L. F. Berhenke of the Edgar C. Britton Laboratory, The Dow Chemical Co., Midland, Mich., to the effect that the free acid (of V or XIII) had been successfully prepared in their laboratory. The isolation was accomplished in approximately 25% yield by repeated extraction of an aqueous solution of V (acidified to its isoelectric point) with methyl isobutyl ketone and repeated recrystallizations from this solvent. The product, which was estimated to be 99.3% pure by analysis and titration, had an indefinite m.p. and was found to readily decarboxylate with the loss of two moles of CO_2 when allowed to stand in aqueous solution. This latter observation undoubtedly explains our difficulties, inasmuch as we attempted purification from aqueous media.

(14) R. E. Lutz, J. A. Freek, and R. S. Murphey, *J. Am. Chem. Soc.*, **70**, 2015 (1948).

(15) R. E. Lutz and R. H. Jordan, *J. Am. Chem. Soc.*, **71**, 996 (1949).

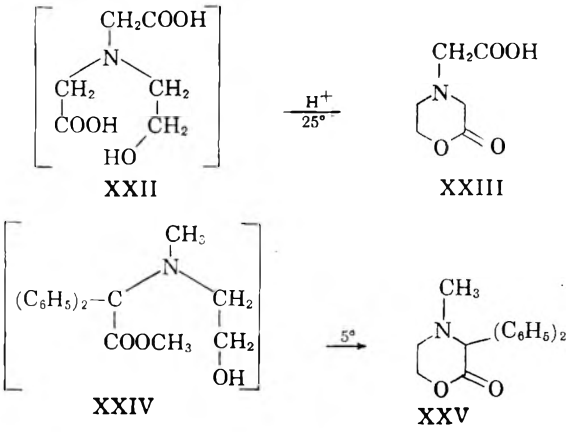
(16) N. J. Cromwell and Kwan-Chung Tsou, *J. Am. Chem. Soc.*, **71**, 993 (1949).

(17) C. E. Griffin and R. E. Lutz, *J. Org. Chem.*, **21**, 1131 (1956).

(18) The non-spontaneous lactonization of VIII must be attributed to the presence of a tertiary amide in place of a tertiary amine group.

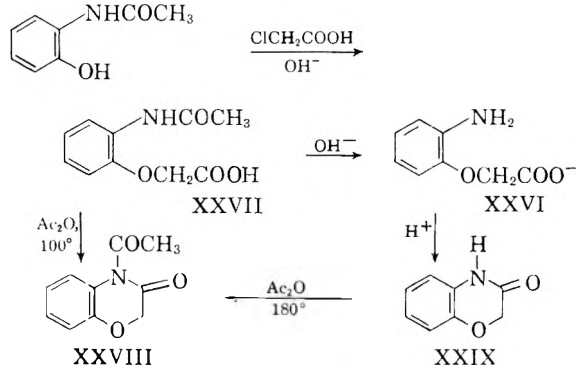
acetic acid alkylation of *N*-methyl-*o*-aminophenol.

As expected on the basis of the previous discussion, however, the sole product of the reaction was the lactone XXI. Other isolated examples have been previously reported, two of which are noted here. When an alkaline solution of *N*-(2-hydroxyethyl)iminodiacetic acid (XXII) is acidified, a quantitative yield of the lactone (XXIII) is obtained,[19] and *N*-methyl-3,3-diphenyl-2-morpholone (XXV) is obtained from the nonisolable ester

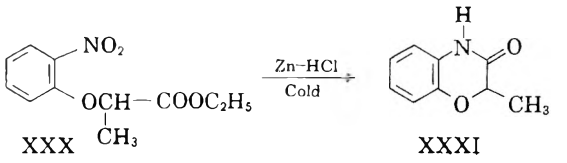


XXIV.[20] In this connection, it has been reported that the secondary amine, *N*-hydroxyethylglycine is not lactonized, but is converted to its hydrochloride on treatment with acid.[21]

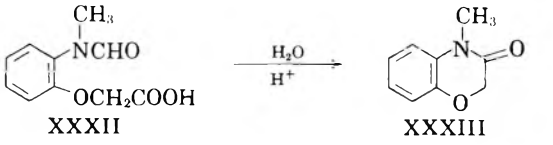
As a logical adjunct to the formation of the 2-morpholones, the analogous lactamization of *o*-aminophenoxyacetic acids to 3-phenmorpholones was briefly investigated. An attempt to prepare *o*-aminophenoxyacetic acid by the hydrolysis of *o*-acetylaminophenoxyacetic acid (XXVII) yielded the salt (XXVI) of the desired product, but acidification of XXVI gave only the lactam XXIX, in agreement with the work of Jacobs and Heidelberger.[22] Other workers[23,24] have attempted to prepare the free amino acid by the reduction of *o*-nitrophenoxyacetic but again obtained only the salt (XXVI) or the lactone (XXIX). Further, we have found that XXVII ring-closes to *N*-acetylphenmorpholone-3 (XXVIII) under the vigorous dehydrating conditions of hot acetic anhydride while Wheeler and Barnes[23] who prepared XXVIII by the action of acetyl chloride on the silver salt of XXIX, report that XXVIII could not be prepared by acetylation of XXIX with acetic anhydride even at 180°. We interpret these data as indicating that, although acetylation of the free amino group (as in XXVII) greatly reduces the tendency for lactamization, the tendency toward formation of the morpholone ring does exert some driving force toward acylation of the *N*, which is completely inhibited once the ring is formed (as in XXIX).



An additional example of the spontaneous lactonization of an *o*-aminophenoxyacetic acid derivative is available in the observation[25] that XXX on reduction affords only the phenmorpholone XXXI. However, no examples concerning the corresponding secondary amine compounds are available and



we, therefore, investigated the acid hydrolysis of the previously unreported *N*-methyl-*N*-formyl-*o*-phenoxyacetic acid (XXXII), which gave as the only isolatable product, *N*-methylphenmorpholone-3 (XXXIII).



In the light of the above, it would seem that in the case of the *o*-aminophenoxyacetic acids, spontaneous lactamization takes place with both primary and secondary amino groups. Further elucidation of the driving force in these and related ring closures must await additional data.

EXPERIMENTAL

General. All melting points are uncorrected. The analyses were carried out by Dr. C. K. Fitz, Needham Heights, Mass. Infrared spectra were obtained as split mulls in Fluorolube and Nujol on a Baird Associates Model 4-55 Recording Spectrophotometer equipped with sodium chloride optics and the ultraviolet spectra on a Cary Model 14 Spectrophotometer. Potentiometric titration curves were

(19) L. W. Ziemlak, J. L. Bullock, F. C. Bersworth, and A. E. Martell, *J. Org. Chem.*, **15**, 255 (1950).

(20) H. S. Mosher, M. B. Frankel, and M. Gregory, *J. Am. Chem. Soc.*, **75**, 5326 (1953).

(21) A. I. Kipriyanov and G. I. Kipriyanov, *J. Gen. Chem. (U.S.S.R.)* **2**, 585 (1932); *Chem. Abstr.*, **27**, 1319 (1933).

(22) W. A. Jacobs and M. Heidelberger, *J. Am. Chem. Soc.*, **39**, 2188 (1917).

(23) H. L. Wheeler and B. Barnes, *Amer. Chem. J.*, **20**, 560 (1898).

(24) A. Thate, *J. pract. Chem.*, [2], **29**, 146 (1884).

(25) C. A. Bischoff, *Ber.*, **33**, 1591 (1900).

obtained directly from the Precision-Dow Recording Titrator.

o-Aminophenol was Eastman or Fisher Practical grade, recrystallized from alcohol (charcoal). It was usually light tan in color and had m.p. 165–170° (subl. and dec.). Chloroacetic acid was Fisher Reagent grade, used as received.

o-Aminophenolchloracetate (IV). *o*-aminophenol (0.1 mol.) and chloroacetic acid (0.2 mol.) in 100 ml. of water was stirred at room temperature for 2 hr. The undissolved solid was collected, washed with cold water, dried, and washed with ether to remove traces of unreacted amine. The yield of white-tan powder, m.p. 148–149°, was 90%. IV may be obtained as large white crystals from hot water or from ether-benzene. $\lambda_{max.}^{Nujol}$ 3.62, 2.78ms (NH_3^+); 6.33vs (COO^-).

Anal. Calcd. for $C_8H_{10}NO_3Cl$: C, 47.2; H, 4.9; N, 6.9; Cl, 17.2. Found: C, 47.8; H, 5.0; N, 7.1; Cl, 17.1.

N-(o-Hydroxyphenyl)glycine (I). A mixture of 10.9 g. (0.1 mol.) of *o*-aminophenol and 4.7 g. (0.05 mol.) of chloroacetic acid in 50 ml. of water was neutralized with 0.05 mol. of 10% sodium hydroxide solution and the mixture brought to reflux under a nitrogen atmosphere. The *p*H was maintained at about 8 by dropwise addition of 10% base, and the reaction was discontinued when 0.1 mol. (total) base had been added. The average reaction time was 1 hr. The solution was chilled and the insoluble unreacted *o*-aminophenol was collected; 6 g. (55%). Acidification of the filtrate to *p*H 4 and prolonged chilling afforded 5.5 g. (60%) of tan-brown prisms, m.p. about 140°, with resolidification to yellowish plates and final m.p. of about 270° (dec.). An analytical sample was obtained as light tan crystals from water. It is readily subject to air oxidation and, in fact, a colorless, dry sample becomes brown in color after a few days in a tightly stoppered vial. $\lambda_{max.}^{Nujol}$ 3.18s (OH); 3.65, 3.82m (NH_2^+); 6.13s (COO^-).

Anal. Calcd. for $C_8H_9NO_3 \cdot H_2O$: C, 51.9; H, 6.0; N, 7.6. Found: C, 51.8; H, 6.1; N, 7.6.

The *hydrochloride* was obtained as a grey to white powder from concentrated hydrochloric acid; after washing with acetone and ether it melted at 162–165°. $\lambda_{max.}^{Nujol}$ 3.09s (OH); 3.63, 3.84w (NH_2^+); 5.74s (COOH).

Anal. Calcd. for $C_8H_9NO_3 \cdot HCl$: C, 47.2; H, 4.9; N, 6.9; Cl, 17.2. Found: C, 46.7; H, 5.0; N, 6.8; Cl, 16.9.

I was converted to *2,5-dioxo-1,4-di-(o-hydroxyphenyl)-piperazine* (VI) by dehydration at 140° under vacuum. The yellow solid was purified by washing with acetone and precipitating from an aqueous, basic solution by acidification; white powder, m.p. 273–274° (dec.). $\lambda_{max.}^{Nujol}$ 3.17m (OH); 6.08s (amide I), no amide II.

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.7; N, 9.2.

2-Phenmorpholone-4-acetic acid (II). The procedure given for I was repeated with 0.1 mol. *o*-aminophenol, 0.4 mol. chloroacetic acid and 0.6 mol. of base. When the clear solution was made strongly acid and warmed on the steam bath, it deposited a solid. After chilling there was obtained 16.5 g. (80%) of tan plates, m.p. 178–180°. An analytical sample was obtained as white plates from water (charcoal), m.p. 180–182°. $\lambda_{max.}^{Nujol}$ 5.65s (δ-lactone, γ,δ-unsatd.); 6.03s (amide I); 6.43s (amide II).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.6; N, 9.4.

2-Phenmorpholone-4-(2'-hydroxy)acetanilide (III). Nine g. (0.008 mol.) of *o*-aminophenol and 3.8 g. (0.045 mol.) of chloroacetic acid in 50 ml. of water were refluxed for 30 min. under nitrogen. The solid, which did not dissolve on prolonged reflux, was collected, washed with water, and dried; 3.0 g. (50%) of dark brown powder, m.p. 220–230°. Purification was effected by recrystallization from aqueous acetone (charcoal) and an analytical sample was obtained from alcohol as large, almost-white plates, m.p. 236–238°. $\lambda_{max.}^{Nujol}$ 3.01m (NH), 3.27s (OH), 5.67s (δ-lactone C=O, γ, δ-unsatd.), 6.07s, 6.45s (amide I and II).

Anal. Calcd. for $C_{16}H_{14}N_2O_4$: C, 64.4; H, 4.7; N, 9.4. Found: C, 64.5; H, 4.6; N, 9.4. Neutral. Equiv., 298.3. Found: 290, 305.

III was also prepared by refluxing a mixture of 1.04 g. (0.005 mol.) of II and 0.55 g. (0.005 mol.) of *o*-aminophenol in 40 ml. of water under a nitrogen atmosphere. The clear solution deposited a solid which was collected after 30 min. of reflux. There was obtained 1.2 g. (80%) of tan powder, whose infrared spectrum and melting point were identical to that of III, prepared as described above.

Acetylation of III: 2-phenmorpholone-4-(o-acetoxy)acetanilide (XII). A mixture of 1 g. of III, 1 g. of anhydrous sodium acetate, and 2 ml. of acetic anhydride was warmed until most of the solid had dissolved. Trituration with water followed by addition of alcohol gave 0.7 g. of white solid, m.p. 173–175°. Recrystallization from aqueous alcohol did not raise the m.p. but afforded fine white needles. $\lambda_{max.}^{Nujol}$ 3.02m (NH); no OH; 5.68s, br. (δ-lactone and acetoxy; γ,δ-unsatd.); 5.96s, 6.55s (amide I and II).

Anal. Calcd. for $C_{18}H_{16}N_2O_5$: C, 63.6; H, 4.7; N, 8.2. Found: C, 63.6; H, 4.6; N, 8.3.

[o-(Carboxymethoxy)-phenyl]imino-diacetic acid, disodium salt (V). The procedure given for II was repeated with the exception that the solution was allowed to occasionally reach a *p*H of 10. The cooled, clear solution was acidified to about *p*H 5 with 3*N* hydrochloric acid and the precipitated solid collected; 17 g. (50%) of tan powder which did not melt up to 285°. An analytical sample was obtained as white crystals from aqueous alcohol. $\lambda_{max.}^{Nujol}$ 2.92m, br (H_2O); 5.83m (COOH); 6.20s, br (COO^-).

Anal. Calcd. for $C_{12}H_{11}NO_7Na_2 \cdot H_2O$: C, 41.8; H, 3.8; N, 4.05; Na, 13.3. Found: C, 41.3; H, 4.3; N, 4.1; Na, 13.1.

V was converted to the free acid *hydrochloride* (XIII) by dissolving 1 g. in 3 ml. of concentrated hydrochloric acid, filtering the precipitated sodium chloride, and evaporating the filtrate to dryness.

Anal. Calcd. for $C_{12}H_{14}NO_7Cl \cdot H_2O$: C, 42.8; H, 4.8; N, 4.1; Cl, 10.6; neut. eq., 86.3. Found: C, 43.0; N, 4.6; N, 4.0; Cl, 11.0; neut. eq. 88.3.

A pure sample of the free amino acid was not obtained.[13a]

N-Acetyl-N-(o-hydroxyphenyl)glycine (VIII). One g. each of I, anhydrous sodium acetate, and acetic anhydride were warmed until a clear melt was obtained. After cooling, the mixture was dissolved in 20 ml. of hot water, charcoaled, and concentrated to one half its volume. At this point there may be isolated by chilling, the monosodium salt monohydrate of VIII as lustrous plates, m.p. 276–278°. On acidification the salt was converted to the free anhydrous acid which was recrystallized from boiling water to yield 0.8 g. of white, rod-like crystals, m.p. 190–192° (lit.[10] 201–202°) $\lambda_{max.}^{Nujol}$ 2.97s (OH); 5.84s (COOH); 6.22s (amide I); 6.30s (?).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7; neut. eq. 209.2. Found: C, 57.1; H, 5.2; N, 6.9; neut. eq. 212.1.

VIII gave no color with ferric chloride and was recovered unchanged after brief boiling in 6*N* hydrochloric acid.

N-Acetyl-phenmorpholone-2 (X). This was prepared by brief reflux of 0.1 g. of VIII in 2 ml. of acetic anhydride. Addition of 5 ml. of water gave 0.06 g. of a white powder, m.p. 171–3°. It was insoluble in water, ligroin and ether and was obtained as white prismatic rods, m.p. 176–7°, from alcohol. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.60 (δ-lactone; γ,δ-unsatd.); 6.02 (amide I).

Anal. Calcd. for $C_{10}H_9NO_3$: C, 62.9; H, 4.7; N, 7.3. Found: C, 62.6; H, 4.8; N, 7.4.

X was soluble in dilute bicarbonate and on acidification was quantitatively converted back to VIII.

o,o'-Ethylenediiminodiphenol (XIV). A mixture of 25 g. (0.23 mol.) of *o*-aminophenol and 50 g. (0.23 mol.) of ethylenebromide in 650 ml. of water was refluxed under nitrogen for 2 hr. The clear yellow solution was decanted and the dark oily solid converted to a tan solid by washing with ether. There was obtained 12 g. of product, m.p. 214–217° (dec.), soluble in hot alcohol, strong acid, and base, and insoluble in water, ether, benzene, and ligroin. It gave a dark brown color with ferric chloride. An analytical sample, obtained as fine white needles from alcohol, melted

at 215° (dec.) $\lambda_{max.}^{Nujol}$ 3.04w (NH); 3.75br (OH); 6.28s, 6.62s, 13.54vs (*o*-disubst. phenyl).

Anal. Calcd. for $C_{14}H_{16}N_2O_2$: C, 68.8; H, 6.6; N, 11.5. Found: C, 68.8; H, 6.2; N, 11.6.

XIV was converted to *N,N'-ethylenebis(2'-hydroxyacetanilide), diacetate,* by warming with an excess of acetate-acetic anhydride. The solid, obtained by extraction with water, was recrystallized from benzene to give colorless prisms, m.p. 171–173°.

Anal. Calcd. for $C_{22}H_{24}N_2O_6$: C, 64.1; H, 5.9; N, 6.8. Found: C, 63.9; H, 6.2; N, 6.9.

Treatment of XIV with 2 mols. of acetate-acetic anhydride gave *N,N'-ethylenebis-o-hydroxyacetanilide,* m.p. 242–243° (dec.), as tan crystals from alcohol. This same product could be obtained by careful alkaline hydrolysis of the diacetate.

Anal. Calcd. for $C_{18}H_{20}N_2O_4$: C, 65.8; H, 6.1; N, 8.5. Found: C, 65.5; H, 6.3; N, 8.6.

N,N'-Ethylenebis-(N-o-hydroxyphenyl)glycine, di-δ-lactone (XVI). An alkaline solution of 1 g. of XIV was refluxed with an excess of sodium chloroacetate under nitrogen for 2 hr. until the *p*H was about 7. The solution was cooled, the *p*H adjusted to 5 with hydrochloric acid, and the solid collected and combined with an additional crop obtained on concentrating the filtrate; total yield 1.2 g. of buff powder, m.p. 160–170°. An analytical sample, obtained as very fine white needles from alcohol, melted at 176–178°. It was insoluble in water and acid and slowly soluble in dilute base. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.66s (δ-lactone-γ,δ-unsatd.).

Anal. Calcd. for $C_{18}H_{16}N_2O_4$: C, 66.7; H, 5.0; N, 8.6. Found: C, 66.5; H, 5.2; N, 8.8.

N-Methyl-phenmorpholone-2 (XXI). A solution of 0.5 g. (0.004 mol.) of *N*-methyl-*o*-aminophenol (prepared by the method of Clark[26]) and 0.5 g. (0.005 mol.) of chloroacetic acid was maintained at *p*H 8 by the addition of 10% sodium hydroxide solution, while refluxed under nitrogen. After 1 hr. the clear solution was cooled, acidified, and refrigerated overnight. The precipitated tan plates weighed 0.2 g. and melted at 51–52°. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.62s (δ-lactone, γ,δ-unsatd.).

Anal. Calcd. for $C_9H_9NO_2$: N, 8.6. Found: N, 8.4.

N-Methyl-N-formyl-o-aminophenoxyacetic acid (XXXII). This was prepared by the usual procedure from 1.5 g. (0.01 mol.) of *N*-methyl-*o*-hydroxyformanilide (m.p. 108–109°, lit.,[26] 103–104°), 0.94 g. (0.01 mol.) of chloroacetic acid and 0.08 g. (0.02 mol.) of caustic in 20 ml. of water. Acidification yielded 0.8 g. of crude product, m.p. 157–163°, and 0.5 g. of starting material was isolated from the filtrate. Recrystallization from 25 ml. of boiling water (charcoal) gave 0.5 g. (*ca.* 30%) of white microcrystalline powder, m.p. 174–174.5°. $\lambda_{max.}^{Nujol}$ no NH or OH; 5.72s (COOH); 6.16s (amide I); 6.30s (?).

Anal. Calcd. for $C_{10}H_{11}NO_4$: C, 57.4; H, 5.3; N, 6.7. Found: C, 57.6; H, 5.4; N, 6.6.

XXXII was converted to *N-methyl-phenmorpholone-3* (XXXIII) by dissolving in warm 1*N* hydrochloric acid and allowing the product to crystallize. The white needles had m.p. 59.5–60° (lit.[23] 58–59°).

N-Acetyl-phenmorpholone-3 (XXVIII). One g. of *N*-acetyl-*o*-aminophenoxyacetic acid[24] (XXVII) was boiled briefly with 2 g. of acetic anhydride, cooled, and treated with 15 ml. of water. The oily product crystallized on standing and after recrystallization from 50 ml. of alcohol consisted of 0.7 g. (80%) of fine white needles, m.p. 79–79.5° (lit.[23] 77°).

Acknowledgments. The authors are indebted to A. A. Carlson of this laboratory for carrying out much of the experimental work, and to A. E. Martell, L. F. Berhenke, and B. M. Williams for helpful discussions. The assistance of F. W. McLafferty in commenting on the manuscript is gratefully acknowledged.

FRAMINGHAM, MASS.

(26) L. M. Clark, *J. Chem. Soc.*, 234 (1926).

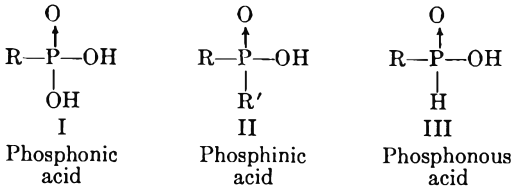
[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, OHIO UNIVERSITY]

Substituted Aryl Phosphonic and Phosphinic Acids[1,2]

JOSEPH M. DENHAM AND ROBERT K. INGHAM

A number of new, substituted arylphosphonic and phosphinic acids have been prepared from the corresponding anilines. These include the 2,5-dibromophenyl-, 2-bromo-3-nitrophenyl-, 2,3-dichlorophenyl-, 3,5-dichlorophenyl-, 2,3,6-trichlorophenyl-, and 2,4,5-trichlorophenylphosphonic and phosphinic acids. Ethyl esters of several such acids are also reported. These compounds are being tested for plant-growth activity.

Halogen-substituted benzoic acids have been examined in detail as plant growth substances and factors relating structure and growth activity have been suggested.[3–5] It was of interest to prepare and test the phosphonic and phosphinic acid analogs of the active benzoic acids; the present paper reports initial investigations of this problem.



To date, there has been no report of the testing of halogen-substituted arylphosphorus acids as plant growth substances. Maguire and Shaw have reported the preparation and testing of 2,4-dichloro-

(1) Taken in part from the M.S. thesis of Joseph M. Denham, Ohio University, 1956.

(2) This work was supported by a contract with the U. S. Army Chemical Corps., Fort Detrick, Frederick, Md.

(3) A. G. Norman and R. L. Weintraub, *First Symposium on Chemical-Biological Correlation,* National Research Council, Washington, D. C., 1951, pp. 45–72; C. E. Minarik, D. Ready, A. G. Norman, H. E. Thompson, and J. F. Owings, Jr., *Botan. Gaz.*, **113**, 135 (1951).

(4) H. Veldstra, *Annual Review of Plant Physiology,* Annual Reviews, Inc., Stanford, Calif., 1953, Vol. 4, pp. 151–198.

(5) R. M. Muir and C. Hansch, *Annual Review of Plant Physiology,* Annual Reviews, Inc., Stanford, Calif., 1955, Vol. 6, pp. 157–176.

phenoxymethylphosphonic acid[6] and of 2,4-dichlorophenoxymethylphosphonous acid[7] (phosphorus analogs of 2,4-D). Also, 3-indolemethylphosphonic acid,[8-10] and unsubstituted phenyl- and naphthyl-phosphorus acids[8,9] have been reported.

The substituted phosphonic acid phosphinic acids were prepared *via* the diazonium salts by the method of Doak and Freedman.[11] The use of a two-to-one ratio of diazonium salt to phosphorus tribromide, rather than the more usual one-to-one ratio, should be more favorable for the formation of the desired phosphinic acids. Both ratios were run for the preparation of the 2,5-dichlorophenyl derivatives; using a two-to-one ratio, the yield of phosphinic acid was nearly doubled and the yield of phosphonic acid increased approximately fifty per cent over the yields obtained with a one-to-one ratio. A similar change of ratio of reactants in the preparation of arsonic and arsinic acids has been stated to have no significant effect on the yields obtained.[12] The two-to-one ratio has been employed in the work herein reported with the hope of obtaining maximum amounts of the phosphinic acids.

All of the compounds reported here are new, with three exceptions. *m*-Tolylphosphonic acid[13] and 2,5-dichlorophenylphosphinic acid[14] have been previously reported but are included in the tables because of a significant difference in melting point. *m*-Iodophenylphosphonic acid was prepared earlier by a less direct method.[15]

It is of interest that, contrary to expectation, the 2,4,5-trichlorophenylphosphonic acid has a higher melting point than the bis(2,4,5-trichlorophenyl)-phosphinic acid.

Preliminary tests indicate that there is no correlation between growth activities of the phosphorus acids and of the corresponding benzoic acids. For example, the phosphorous analog of the markedly active 2,3,6-trichlorobenzoic acid is inactive; also, bis(*m*-bromophenyl)phosphinic acid shows considerable activity while the *m*-halobenzoic acids are inactive. Detailed biological results will be published elsewhere by Dr. R. L. Weintraub, U. S. Army Chemical Corps, Fort Detrick, Frederick, Md.

(6) M. H. Maguire and G. Shaw, *J. Chem. Soc.*, 1756 (1955).

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EXPERIMENTAL[16]

Typical procedures for each of the general types of reactions are described below.

3,5-Dichlorobenzenediazonium fluoborate. A method similar to that of Roe[17] was used for the preparation of all diazonium compounds. To a cold mixture (0–10°) of 62 ml. of concentrated hydrochloric acid, 120 ml. of water, 41.5 g. (0.38 mole) of sodium fluoborate, and 48.6 g. (0.30 mole) of 3,5-dichloroaniline in a 1-liter beaker was added, dropwise, a solution of 20.7 g. (0.30 mole) of sodium nitrite in 40 ml. of water. A broad-bladed stirrer was used to ensure effective stirring of the continually-thickening mixture. The precipitate was collected on a filter and washed with 50 ml. of cold 5% fluoboric acid, 50 ml. of cold methanol, and several 60-ml. portions of ethyl ether to give, when dry, 45 g. (58%) of the diazonium salt. The product was dried by spreading it thinly over filter paper supported on a wire screen and allowing it to stand overnight; it was used in the next reaction without further purification.

3,5-Dichlorophenylphosphonic acid (Table I). The following method[11] was used for the preparation of all derivatives in Tables I and II; modifications were introduced when necessary.

A mixture of 250 ml. of absolute ethyl acetate and 45.0 g. (0.17 mole) of 3,5-dichlorobenzenediazonium fluoborate was placed in a 2-liter, 3-necked flask. The flask was fitted with a mechanical stirrer and a reflux condenser containing a wide-bore delivery tube leading to a gas trap. With stirring, 23.3 g. (0.086 mole) of phosphorus tribromide was added, followed by 2.0 g. of cuprous bromide. The mixture changed from a red to a violet color and foamed vigorously for a brief period. The foaming was held under control by application of an ice bath and soon subsided. Stirring for an additional 30 min. at room temperature and heating to 50° for 5 min. failed to produce evidence of further reaction. The mixture was cooled to room temperature and hydrolyzed by the dropwise addition of 25 ml. of water.

The ethyl acetate was removed by steam distillation; when a separate water layer began forming, the receiver was changed and the steam distillation was continued until all steam-volatile, water-insoluble material ceased collecting in the distillate (approximately one liter). Filtration of the distillate yielded 6.0 g. of yellow solid melting at 74–75.5°. One recrystallization from ethanol raised the melting point to 75–76.5°. No depression of melting point occurred when this sample was mixed with authentic 3,5-dichlorobromobenzene.

A red oil had separated in the residual steam distillation mixture. The hot water layer was decanted through a filter and allowed to cool to give a pink precipitate of crude phosphonic acid. The precipitate was collected on a filter. The red oil, composed principally of phosphinic acid, hardened somewhat on cooling and solidified on extraction with 150 ml. of boiling 6*N* hydrochloric acid. The crude phosphinic acid was collected by filtration and this filtrate was added to the main filtrate. The combined filtrates were evaporated to approximately 50 ml. on a steam bath to obtain a second portion of crude phosphonic acid.

The pure phosphonic acid was isolated in two portions. The first was obtained by treating the pink solid obtained

(16) All melting points are uncorrected.

(17) A. Roe, *Org. Reactions*, **V**, 205 (1949). A brief previous mention of the 3,5-dichlorobenzenediazonium fluoborate appears in the literature (see Roe, *loc. cit.*, p. 217); a detailed procedure is included as typical of the fluoborates used in this work.

TABLE I

SUBSTITUTED PHENYLPHOSPHONIC ACIDS[a]

I, R =	Yield, %	M.P., °C.	Formula	Analysis: Halogen, % Calcd.	Halogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
m-Tolyl-[b]	8.7	125–126	$C_7H_9O_3P$	—	—	18.0	17.38
m-Iodo-[c]	20	183–184	$C_6H_6IO_3P$	—	—	—	—
2,5-Dibromophenyl-	25	204–208	$C_6H_6Br_2O_3 \cdot H_2O$	47.86	47.6	9.28	9.1
2-Bromo-3-nitrophenyl-[d,e]	12	224 (dec.)	$C_6H_5BrNO_5P$	28.35	28.0	10.99	10.8
2,3-Dichlorophenyl-[f]	14	200–202	$C_6H_6Cl_2O_3P \cdot H_2O$	28.94	29.5	12.64	12.4
3,5-Dichlorophenyl-	19[g]	188–190	$C_6H_5Cl_2O_3P$	31.24	31.69	13.65	13.80
2,3,6-Trichlorophenyl-[e]	[h]	203–204	$C_6H_4Cl_3O_3P$	40.69	40.24	11.85	11.5
2,4,5-Trichlorophenyl-	19[i]	252–254	$C_6H_4Cl_3O_3P$	40.69	40.36	11.85	11.64

[a] All of these acids were recrystallized from 6*N* hydrochloric acid; the *m*-tolylphosphonic acid was also recrystallized from benzene. [b] Reported m.p. 121° (see ref. 13) and 116–117° [see A. Michaelis, *Ann.*, 293, 261 (1896)]. [c] Prepared previously *via* nitration of phenylphosphonic acid (see ref. 15). [d] Calcd. for N: 4.97; found: 4.95. [e] The required aniline was prepared from the corresponding benzoic acid *via* the Hofmann reaction. [f] Also dried to constant weight for analysis. Calcd. for $C_6H_5Cl_2O_3P$: Cl, 31.24; P, 13.65. Found: Cl, 31.28; P, 13.41. [g] Yield based on product melting at 186.5–190°. [h] Only 0.25 g. was obtained, with a theoretical yield of 0.064 mole. [i] The initial reaction was very vigorous, resulting in some loss of product; yield based on product melting at 250–252°.

TABLE II

SUBSTITUTED PHENYLPHOSPHINIC ACIDS

II, R = R′ =	Yield, %	M.P., °C.	Solvent for Recrystn.	Formula	Analysis: Halogen, % Calcd.	Halogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
m-Tolyl-	5.5	166–168	EtOH-H_2O	$C_{14}H_{15}O_2P$	—	—	12.58	12.33
m-Iodophenyl-	8.0	212.5–213.5	EtOH-H_2O	$C_{12}H_9I_2O_2P$	54.01	53.51	6.59	6.61
2,5-Dibromophenyl-	1.6	277–279	EtOAc	$C_{12}H_7Br_4O_2P$	59.88	60.2	5.80	5.8
2-Bromo-3-nitrophenyl-[a]	5.4	296–297 (dec.)	AcOH	$C_{12}H_7Br_2N_2O_6P$	34.30	34.22	6.65	6.11
2,3-Dichlorophenyl-	9.3	278–280	EtOH-H_2O	$C_{12}H_7Cl_4O_2P$	39.84	39.82	8.70	8.66
2,5-Dichlorophenyl-[b]	16	221–222	EtOH-H_2O	$C_{12}H_7Cl_4O_2P$	39.84	39.56	8.70	8.6
3,5-Dichlorophenyl-	13[c]	243–244.5	EtOH-H_2O	$C_{12}H_7Cl_4O_2P$	39.84	39.81	8.70	8.76
2,3,6-Trichlorophenyl-	6.4	287–288.5	EtOH	$C_{12}H_5Cl_6O_2P$	50.07	49.57	7.29	7.25
2,4,5-Trichlorophenyl-	11[d]	244.5–246	EtOH-H_2O; EtOAc	$C_{12}H_5Cl_6O_2P$	50.07	49.97	7.29	7.35
R = Phenyl- / R′ = *m*-Bromophenyl-[e]	50	161.5–162	EtOH-H_2O	$C_{12}H_{10}BrO_2P$	26.90	27.04	10.43	10.35

[a] Dried to constant weight for analysis. Calcd. for N: 6.01; found: 5.92. [b] This compound, m.p. 232–233°, has been prepared by Freedman and co-workers (see ref. 14); additional recrystallization did not change the melting point. [c] Yield based on product recrystallized from aqueous ethanol, m.p. 241–243°. [d] Yield based on product m.p. 240–242°, recrystallized from aqueous ethanol. [e] Phenylphosphine dichloride used in place of phosphorus tribromide; yield based on product melting at 160–161°.

from the cooled water layer of the steam distillation mixture with 20% sodium hydroxide and isolation of the hemi-sodium salt. The salt was precipitated by acidifying the alkaline solution to the Congo Red point with concentrated hydrochloric acid. The alkaline solution was filtered prior to acidification and, if necessary, was decolorized with charcoal. Two recrystallizations from 6*N* hydrochloric acid gave 1.5 g. of 3,5-dichlorophenylphosphonic acid as pink needles melting at 186.5–190°.

The base treatment separated a tan oil which solidified on standing. Recrystallization from aqueous ethanol gave 1.4 g. of white needles melting at 50–51°; no depression of melting point occurred when the solid was mixed with an authentic sample of 3,5-dichloroaniline.

The second portion of pure phosphonic acid was isolated by treating in a similar manner the residue obtained from the evaporated filtrates. Two recrystallizations gave 2.15 g. of pink needles melting at 186.5–190°. The combined yield was 3.65 g. (19%, based on a theoretical yield of 0.086 mole).

Two additional recrystallizations from 6*N* hydrochloric acid produced an analytical sample as colorless needles melting at 188–190°.

Bis(3,5-dichlorophenyl)phosphinic acid (Table II). The crude phosphinic acid from the above preparation was dissolved in dilute sodium hydroxide solution. The alkaline solution was decolorized with charcoal and filtered, and the filtrate was acidified with concentrated hydrochloric acid to isolate the free acid; the acid was then recrystallized from aqueous ethanol. The first two treatments with water produced a trace of amorphous solid; the third gave 5.2 g. of pink-to-red crystals melting at 239–240.5°. Extraction with 30 ml. of warm ethyl acetate left 4.0 g. (13%, based on a theoretical yield of 0.086 mole) of bis(3,5-dichlorophenyl)phosphinic acid melting at 241–243°. An additional recrystallization from aqueous ethanol and a final recrystallization from absolute ethanol produced an analytical sample as pink, hexagonal platelets melting at 243–244.5°.

Several other phosphonic and phosphinic acids were prepared in this manner and the results are listed in Tables I and II. Variations in the above procedure were necessary with two of the acids and these modifications are given below. In most cases only a single run was made and, therefore, the yields probably are not optimum.

2,3,6-Trichlorophenylphosphonic acid (Table I). A very small quantity of crude phosphonic acid was isolated as

TABLE III

ETHYL ESTERS OF SUBSTITUTED PHENYLPHOSPHONIC AND PHENYLPHOSPHINIC ACIDS

	Yield, %	B.P., °C.	Pressure, Mm.	n_D^{25}	Formula	Analysis: Halogen, % Calcd.	Halogen, % Found	Phosphorus, % Calcd.	Phosphorus, % Found
Phosphonate Esters									
m-Chlorophenyl-	41	101	0.25	1.5005	$C_{10}H_{14}ClO_3P$	14.26	14.74	12.46	12.12
m-Bromophenyl-	30	109–113	0.22	1.5200	$C_{10}H_{14}BrO_3P$	27.26	27.19	10.57	10.42
2,5-Dibromophenyl-	26	134–139	0.30	1.5475	$C_{10}H_{13}Br_2O_3P$	42.97	42.38	8.33	8.19
Phosphinate Esters									
Bis(*m*-chlorophenyl)-	48	183–187	0.70	1.5794	$C_{14}H_{13}Cl_2O_2P$	22.50	22.66	9.83	9.51
Phenyl-*m*-chlorophenyl-	58	170–174	0.60	1.5701	$C_{14}H_{14}ClO_2P$	12.63	12.04	11.03	11.14

above from the steam distillation mixture. Attempts to prepare the hemi-sodium salt gave only a green colored, gummy mass; thus, excess hydrochloric acid was added to effect solution of the product. The solution was evaporated to dryness and the residue then extracted with acetone. Removal of the acetone left a residue that gave, after recrystallization from 6*N* hydrochloric acid, 0.25 g. of 2,3,6-trichlorophenylphosphonic acid as white needles.

Bis(2,4,5-trichlorophenyl)phosphinic acid (Table II). The residue containing the phosphinic acid, isolated in the usual manner from the steam distillation mixture, failed to dissolve appreciably in 100 ml. of 10% sodium hydroxide solution. The mixture was diluted with one liter of water and heated to reflux. The boiling mixture was treated with charcoal and filtered through a heated funnel to prevent crystallization of the salt. The free acid was isolated by acidification with concentrated hydrochloric acid.

m-Chlorophenylphosphonyl dichloride.[18] To 10.0 g. (0.052 mole) of *m*-chlorophenylphosphonic acid in a 200-ml. flask fitted with condenser and drying tube, was added 24.1 g. (0.10 mole plus 10% excess) of phosphorus pentachloride. The solids fused after a period of 15 min. and rapid refluxing followed. When the reaction subsided, the mixture was warmed to maintain refluxing for 30 min. and then allowed to stand at room temperature overnight. The phosphorus oxychloride and excess phosphorus pentachloride were removed at water pump pressure and a water bath temperature of 60°. The residue was vacuum distilled to give 10.1 g. (84%) of colorless liquid, boiling at 86–89° (0.4 mm.). The acid chloride was used in the ester preparation without further purification.

m-Bromophenylphosphonyl dichloride (b.p. 94–100°/0.25 mm.) and 2,5-dibromophenylphosphonyl dichloride (m.p. 107–114°, without purification) were prepared in a similar manner in yields of 92% and 85%, respectively. Bis-(*m*-chlorophenyl)phosphinyl chloride and phenyl-*m*-chlorophenylphosphinyl chloride were prepared using a one-molar ratio of phosphorus pentachloride plus 10% excess. The application of heat was required in some cases to initiate the reaction of the acid with phosphorus pentachloride. The phosphinyl chlorides were used directly after removal of the phosphorus oxychloride and excess phosphorus pentachloride.

(18) Method of L. D. Freedman, *et al.*; see reference 14.

Diethyl m-chlorophenylphosphonate (Table III).[19] A mixture of 2.0 g. (0.044 mole) of absolute ethanol, 3.9 g. (0.049 mole) of dry pyridine, and 20 ml. of absolute ethyl ether was added, in 3 portions, to a cooled solution of 5.0 g. (0.022 mole) of *m*-chlorophenylphosphonyl dichloride and 30 ml. of dry ether in a 100-ml. flask fitted with condenser and drying tube. Refluxing occurred after each portion was added and pyridinium chloride precipitated. The mixture was allowed to stand overnight and then filtered. The solvent was removed by distillation and the residue was vacuum distilled. A small amount of pyridinium chloride sublimed initially; this was removed from the column and the distillation continued to give 2.25 g. (41%) of diethyl *m*-chlorophenylphosphonate as a colorless liquid, b.p. 100–101° (0.30 mm.), n_D^{25} 1.5005.

The *m*-bromo-, 2,5-dibromo-, and phenyl-*m*-bromophenyl- derivatives were also prepared by this procedure; results may be found in Table III.

Ethyl bis(m-chlorophenyl)phosphinate (Table III). Bis(*m*-chlorophenyl)phosphinyl chloride, prepared from 5.0 g. (0.017 mole) of the phosphinic acid, was dissolved in 9 ml. of carbon tetrachloride. To this solution was added 1.5 ml. of absolute ethanol; some warming occurred on adding the ethanol. The mixture was refluxed for 2 hr. (hydrogen chloride was evolved) and the solvent and excess ethanol were removed by distillation at water-pump pressure. The residue was vacuum-distilled to give 1.75 g. of ethyl phosphate, b.p. 47–50° (0.7 mm.) and 1.45 g. (48%, based on amount of acid not recovered) of ethyl bis(*m*-chlorophenyl)phosphinate, b.p. 183–187° (0.7 mm.), n_D^{25} 1.5794.

The dark brown residue from the distillation was dissolved in 50 ml. of hot ethanol and decolorized with charcoal; dilution with water and cooling gave 2.1 g. (42% recovery) of white solid melting at 133–152°. Recrystallization from petroleum ether (b.p. 90–120°) brought the melting point to 162–165°; a mixture melting point with the starting acid showed no depression.

ATHENS, OHIO

(19) Method of M. I. Kabachnik, P. A. Rossiĭskaya, and N. N. Novikova, *Bull. acad. sci., U.R.S.S., Classe sci. chim.*, 97 (1947) [*Chem. Abstr.*, **42**, 4132 (1948)].

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

Reaction of Trialkyl Phosphites with Methanol[1]

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At 210–215° in a sealed glass tube, *n*-butyl alcohol reacts with triethyl phosphite to give only transesterification; ethyl alcohol reacts slowly to give phosphonates; and methyl alcohol reacts more rapidly to give phosphonates. Under the most favorable conditions found, there was obtained an 85% yield of a phosphonate mixture which consisted of about 60% diethyl methylphosphonate, 25% diethyl phosphonate, and 15% triethyl phosphate. Evidence is presented that the latter two compounds do not arise by simple hydrolysis and oxidation of a part of the triethyl phosphite by moisture and air. Significant amounts of ethylphosphonates or mixed esters such as methyl ethyl methylphosphonate were shown to be absent. Transesterification is the most rapid reaction between methyl alcohol and triethyl phosphite; subsequent rearrangement may proceed in a manner analogous to the Arbuzov reaction. Reaction of trimethyl phosphite with less than 0.1 mole equivalent of methyl alcohol gave a 92% yield of pure dimethyl methylphosphonate. In pentavalent phosphorus compounds, such as dialkyl methylphosphonates, absorption in the infrared for the CH_3—P structure was found to occur at 7.65 ± 0.02μ, in contrast with the trivalent phosphorus compounds where absorption for this structure was observed at about 7.75μ, as has been previously reported.

In a recent investigation,[3] it has been found that heating of trialkyl phosphites with aliphatic alcohols results in transesterification to yield mixed trialkyl phosphites. It had been reported earlier[4] that heating of triaryl phosphites with alcohols boiling above 100° results in transesterification with replacement of one or more aryl groups; however, there is a single older report[5] that heating of triphenyl phosphite at 225° with an excess of methyl or *n*-propyl alcohol results not only in transesterification but also in formation of an alkylphosphonate. The net conversion to form alkylphosphonate was represented as in the following equation. Since

$$P(OPh)_3 + 3\ CH_3OH \xrightarrow{225^\circ} CH_3{-}P(O)(OCH_3)_2 + 3\ PhOH$$

such a rearrangement represents a potential synthesis of alkylphosphonic esters, the present investigation has been devoted to examination of similar conversions of triethyl phosphite and trimethyl phosphite.

In preliminary experiments, it was observed that heating of triethyl phosphite in a sealed glass tube with about 1.1 mole equivalent of *n*-butyl alcohol at 210° for 15 hr. resulted only in transesterification; no product was obtained which exhibited infrared absorption at 8μ, characteristic[6] of the P → O bond in phosphates and phosphonates. In contrast, similar heating of triethyl phosphite with ethanol resulted in only about 60% recovery of the triethyl phosphite, and there was obtained about 35% yield of a higher boiling product which exhibited absorption in the infrared for the P → O bond. When methanol was used in the reaction, little phosphite was recovered, and yields of 50–70% of pentavalent phosphorus compounds were observed. The latter material was found to consist in part of triethyl phosphate. The amount of phosphate was increased when 10 mole % of water was added to the methanol, but its amount could not be reduced below about 5% when the sealed tube was filled with nitrogen, and methanol dried over magnesium was employed. Since methanol exhibits such a facile reaction with triethyl phosphite, the principal investigations have been concerned with reactions of this alcohol.

The best conditions found for conversion of triethyl phosphite to diethyl methylphosphonate involved heating the phosphite with 1.15 mole equivalents of methanol in a sealed glass tube[7] at 210–215° for 5 hr. Ethyl alcohol was a product of the reaction; about 10% of the phosphite was recovered; and about 85% yield of the "phosphonate fraction," b.p. 103–108°/48 mm., was received. Analysis of the latter fraction by gas phase chromatography and infrared spectroscopy showed it to consist almost entirely of three compounds: about 60% diethyl methylphosphonate, about 25% diethyl phosphonate [$(C_2H_5O)_2P(O)H$], and about 15% triethyl phosphate. One is tempted to rationalize appearance of the latter two compounds on the basis of simple hydrolysis and oxidation of a part of the triethyl phosphite; however, present evidence indicates that these compounds arise by more devious routes.

When a reaction was carried out in a tube filled with nitrogen before sealing, utilizing freshly dis-

(1) This work was done on a subcontract with the University of Chicago in fulfillment of a contract with the Chemical Corps.

(2) Member of the Armed Forces assigned to the Army Chemical Corps.

(3) F. W. Hoffmann, R. J. Ess, and R. P. Usinger, Jr., *J. Am. Chem. Soc.*, **78**, 5817 (1956).

(4) R. Reuter, U.S. Patent 2,175,509 (1939); S. R. Laudaner and H. N. Rydon, *J. Chem. Soc.*, 2224 (1953).

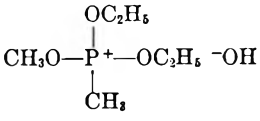
(5) T. Milobenzki and K. Szulgin, *Chemik Polski*, **15**, 66 (1917); *Chem. Abstr.*, **13**, 2867 (1919).

(6) For comparison purposes in the present investigation, infrared spectra were recorded for appropriate known compounds; however, extensive use was made of the valuable source material in L. J. Bellamy, *The Infra-red Spectra of Complex Molecules*, Methuen and Co. Ltd., London, 1954, Chap. 18.

(7) When the reaction mixture was heated in a steel bomb, no volatile liquid products were obtained.

tilled triethyl phosphite and methanol dried over magnesium, there was no significant effect on the composition of the phosphonate fraction. Further, the reaction appears not to be catalyzed by traces of acid, for it proceeded about as well in a run in which 0.015 mole equivalent of magnesium metal had been allowed to react with the methanol before the phosphite was added. When the phosphite was heated similarly without addition of methanol, even for periods of 15 hr., 93% of it was recovered, and there was only 4% of the phosphonate fraction. Mixed methyl ethyl phosphites were also essentially unaltered (as determined by infrared analysis) by heating alone or in presence of 5% by weight of ethanol. When the heating period in presence of methanol was extended to 15 hr., the yield of phosphonate fraction was reduced to about 50%, but the composition of the fraction was the same as that observed after the 5 hr. heating period. After the longer heating period, a quantity of diethyl ether was recovered, and there was about 22% yield of a nonvolatile residue; so conversion of the initial products to compounds of the pyrophosphate type is indicated. Further, if only one molar equivalent of methanol is heated with triethyl phosphite, conversion to phosphonate is much slower, and the product contains less diethyl phosphonate and more triethyl phosphate.

Although we are unable to suggest a mechanism which will correlate the observations concerning all the products detected in the phosphonate fraction, it is possible that the major product, diethyl methylphosphonate, is formed *via* an intermediate of the type shown in the formula, analogous to the presumed intermediate in the widely investigated Ar-



buzov[8] reaction for preparation of alkylphosphonates from phosphites and alkyl halides. Although the Arbuzov reaction has been utilized with a great variety of halides (including acid chlorides) and is usually regarded as applying specifically to halides, numerous similar reactions have been reported with other types of compounds. These methods include substitution of gramine for a halide,[9] synthesis of a monothiophosphate (phosphorothioate) by use of ethyl thiocyanate[10] or diethyl disulfide,[11] and preparation of carbethoxyalkylphosphonates from α,β-unsaturated acids[12] or from β- or γ-lactones.[13] It has also been claimed[14] that a trialkyl phosphite may be converted to a dialkyl alkylphosphonate by heating at 150° with catalytic amounts of sodium iodide. An intermediate such as proposed would be expected to form more readily with methanol than with higher alcohols, as is observed; and if this type of intermediate is involved, it must also be the case that methyl is abstracted from oxygen considerably more readily than is ethyl. If this were not the case, mixed esters such as methyl ethyl methylphosphonate would be formed, and these would have shorter retention times in gas phase chromatography than diethyl methylphosphonate. One or two minor bands of shorter retention times were frequently observed in the chromatograms, but the sum of these never exceeded 3% of the total. In addition, there was observed no absorption in the infrared at 8.4μ, the region of P—O—CH_3 absorption.[6] Presence of significant amounts of ethylphosphonate is also contraindicated by the infrared spectrum of the acid obtained on hydrolysis of the phosphonate fraction; there was no significant absorption at 7.2μ, the region of CH_3—C absorption.

The facility of methyl groups in this reaction was also demonstrated by heating at 210–215° for 5 hr. a mixed methyl ethyl phosphite with about 0.1 mole equivalent of methanol. As judged by infrared analysis for the P → O bond, there was about 55% conversion to phosphonate. Further, when trimethyl phosphite was heated similarly with 0.08 mole equivalent of methanol, there was realized a 92% yield of dimethyl methylphosphonate, in which no other compounds could be detected by either infrared spectroscopy or gas phase chromatography. These observations, as well as certain of those previously mentioned, strongly suggest that the first reaction between triethyl phosphite and methanol is transesterification; and indeed this reaction occurs readily when the mixture is simply heated under reflux, with the equilibrium highly favorable to methyl ester.

During the course of the present work, it was noted that in pentavalent phosphorus compounds the CH_3—P structure gives absorption at 7.65 ± 0.02μ. Absorption in this region was noted not only for diethyl methylphosphonate and dimethyl methylphosphonate, but also in other compounds including methylphosphonic dichloride [CH_3—$P(O)Cl_2$] and bistetrahydrofurfuryl methylphosphonate. The tentative assignment by Bellamy[6] for absorption by the CH_3—P structure at about 7.75μ has been observed by us only in trivalent phospho-

(8) The Arbuzov reaction is discussed by G. M. Kosolapoff, *Organophosphorus Compounds*, John Wiley & Sons, Inc., New York, 1950, pp. 121–3. Numerous applications of the reaction have been reported since 1950; one critical examination is by A. E. Arbuzov and L. V. Nesterov, *Izvest. Akad. Nauk S.S.S.R., Odtel. Khim. Nauk*, 361 (1954); *Chem. Abstr.*, 49, 9541 (1955).

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(11) H. I. Jacobson, R. G. Harvey, and E. V. Jensen, *J. Am. Chem. Soc.*, 77, 6064 (1955).

(12) G. Kamai and V. A. Kukhtin, *Doklady Akad. Nauk S.S.S.R.*, 109, 91 (1956); *Chem. Abstr.*, 51, 1827 (1957).

(13) R. L. McConnell and H. W. Coover, *J. Am. Chem. Soc.*, 78, 4553 (1956).

(14) H. Coates and P. C. Crofts, British Patent 713,669, Aug. 18, 1954.

rus compounds such as trimethylphosphine and methyldichlorophosphine.

EXPERIMENTAL[15]

Materials. Triethyl phosphate and triethyl phosphite were redistilled commercial grades. Triethyl phosphite must be distilled just before use or else protected from air, for it slowly oxidizes to triethyl phosphate. *Trimethyl phosphite*, b.p. 113°, was prepared from phosphorus trichloride and methanol in presence of dimethylaniline. According to a published procedure,[16] *diethyl methylphosphonate* was prepared by heating under reflux for 15 hr. a mixture of 20 g. (0.12 mole) of triethyl phosphite and 100 g. (0.70 mole) of methyl iodide; yield 13.5 g. (62.5%), b.p. 83°/13 mm., n_D^{25} 1.4118 (lit.,[17] b.p. 56.5°/3.5 mm., n_D^{20} 1.4140).

Anal. Calcd. for $C_5H_{13}O_3P$: C, 39.47; H, 8.61. Found: C, 39.86; H, 8.62.

Diethyl phosphonate was prepared by a published procedure[18] from phosphorus trichloride and anhydrous ethanol; yield 62%, b.p. 72–73°/11 mm., n_D^{25} 1.4061 (lit.,[17,19] b.p. 75°/15 mm., n_D^{20} 1.4080).

Anal. Calcd. for $C_4H_{11}O_3P$: C, 34.78; H, 8.03. Found: C, 34.94; H, 8.05.

Transesterification of triethyl phosphite with methanol. A mixture of 11.06 g. (0.067 mole) of triethyl phosphite and 4.28 g. (0.134 mole) of anhydrous methanol was heated under reflux for 16 hr., then distilled to yield 5.27 g. of ethanol containing a little methanol, b.p. 69–80°; 4.89 g. of mixed phosphite of b.p. 128–145°; and 3.60 g. of mixed phosphite of b.p. 145–154°. Boiling points of the mixed phosphites have not been reported, but trimethyl phosphite has b.p. 111–112°, and triethyl phosphite has b.p. of 154.5–155.5°.

In a similar run, except that there was used 0.062 mole of methanol, distillation yielded 2.81 g. (theory, 2.85 g.) of ethanol, b.p. 75–80°; 0.05 g. of intermediate fraction; 4.69 g. of mixed phosphite, b.p. 142–148°; and 3.34 g. of mixed phosphite of b.p. 148–155°.

Heat stability of phosphites. A sample of mixed phosphite, b.p. 128–154°, also a sample of pure triethyl phosphite, were heated for 5 hr. at 210–215° in sealed glass tubes. This treatment caused no significant change in the infrared spectra, in particular there was no evidence of P → O absorption at about 8μ. A 10-g. sample of triethyl phosphite heated similarly for 15 hr. yielded on distillation 9.3 g. of triethyl phosphite, b.p. 57–58°/18 mm., and 0.4 g. of material distilling principally at 45°/0.5 mm. and giving infrared absorption characteristic of the P → O bond.

High temperature reaction of phosphites with methanol. Results of the more significant runs are described in this section, and criteria for identification of the components of the phosphonate fractions are described in the next section.

A. Trimethyl phosphite. A mixture of 5.0 g. (0.040 mole) of freshly distilled trimethyl phosphite and 0.10 g. (0.003 mole) of anhydrous methanol was heated in a sealed tube at 210–215° for 5 hr. Distillation of the reaction product yielded two drops of methanol and a single fraction of b.p. 87.5–88.0°/28 mm., n_D^{25} 1.4111, weight 4.6 g. (92%); lit.,[20] for dimethyl methylphosphonate, b.p. 67°/12 mm., n_D^{20} 1.4105. Only one component was observed in gas phase chromatography. The infrared spectrum showed no absorption at 4.15μ (P—H bond), but showed strong bands at 7.65μ (CH_3—P), 8.0μ (P → O), and 8.4μ (CH_3—O—P).

B. Mixed phosphite. A 500-mg. sample of phosphite of b.p. 128–145° was heated with 10 mg. of anhydrous methanol as described in (A). Infrared absorption at 8μ indicated 50–60% conversion to products containing the P → O grouping.

C. Triethyl phosphite. In the procedure giving most satisfactory conversion to phosphonates, a mixture of 11.06 g. (0.067 mole) of freshly distilled triethyl phosphite and 2.50 g. (0.077 mole) of anhydrous methanol was heated in a sealed glass tube (flushed with nitrogen before filling) at 210–215° for 5 hr. When the cooled tube was opened a small amount of gas (not investigated) escaped; distillation of the contents of the tube yielded three principal fractions: (1) 2.5 g., b.p. 64–80°, ethanol containing a trace of methanol; (2) 1.1 g., b.p. 74–80°/48 mm., mixed phosphites, as judged by the characteristic infrared spectrum[6] and its rapid exothermic reaction with sulfur; (3) 9.3 g. (84%), b.p. 102–108°/48 mm., phosphonate fraction determined as described below to consist of about 15% triethyl phosphate, 25% diethyl phosphonate, and 60% diethyl methylphosphonate.

Results of certain of the variations of this procedure are described below.

(*a*) When the heating period was extended to 15 hr., considerably more gas was evolved on opening the cooled reaction tube. Distillation yielded three principal fractions: (1) 1.6 g., b.p. 27–35°, diethyl ether; (2) 5.3 g. (48%), b.p. 67–69°/9 mm., phosphonate fraction consisting of 10% triethyl phosphate, 26% diethyl phosphonate, 61% diethyl methylphosphonate, and 3% minor components more volatile than diethyl methylphosphonate; (3) 2.4 g. of nonvolatile residue.

(*b*) When the heating period was reduced to 4 hr., fractions obtained on distillation were: (1) 0.65 g., b.p. 61–77°; (2) 1.75 g., b.p. 77–79°; (3) 3.80 g., b.p. 64–80°/50 mm., phosphite fraction; (4) 6.00 g., b.p. 70–80°/8 mm., phosphonate fraction.

(*c*) When the heating period was 5 hr. and the methanol was reduced to 0.067 mole (equimolar with phosphite), distillation yielded: (1) 1.9 g., b.p. 74–80°; (2) 9.1 g. (82% recovery), b.p. 64–80°/48 mm., phosphite fraction; (3) 1.6 g. (14%), b.p. 105–108°/48 mm., phosphonate fraction consisting of 24% triethyl phosphate, 15% diethyl phosphonate, and 61% diethyl methylphosphonate.

(*d*) When heating was in a steel bomb, rather than a glass tube, the only products were considerable gas and an amorphous nonfusible solid.

(*e*) In a run made as first described except that 1.0 g. of alumina was added, products (in addition to considerable gas) were 4.3 g. of diethyl ether, b.p. 27–35°, and 3.6 g. of a nonvolatile liquid.

(*f*) In a run as first described except that 25 mg. of magnesium metal was allowed to react with the methanol before addition of phosphite to the tube, no significant phosphite fraction was recovered; principal products obtained on distillation were: (1) 0.5 g., b.p. 27–37°; (2) 0.4 g., b.p. 37–77°; (3) 1.0 g., b.p. 77–79°; (4) 8.4 g., b.p. 102–105°/41 mm., phosphonate fraction.

(15) Boiling points are uncorrected; distillations were through a half-meter simple Podbielniak column of the type which has been described in detail (J. Cason and H. Rapoport, *Laboratory Text in Organic Chemistry*, Prentice-Hall, Inc., New York, 1950, pp. 237–43). Microanalyses were by the Microanalytical Division, Department of Chemistry, University of California, Berkeley. Infrared spectra were taken in carbon disulfide or carbon tetrachloride solution and recorded on a Baird double-beam recording spectrophotometer. Gas phase chromatography was in a 2 m. × 9 mm. tube, packed with −30 +60 mesh Celite firebrick impregnated with Dow-Corning High-Vacuum Silicone grease (10 parts firebrick: 4 parts grease). All sealed glass tubes were heated in steel pressure bombs.

(16) A. H. Ford-Moore and J. H. Williams, *J. Chem. Soc.*, 1465 (1947).

(17) C. I. Meyrick and H. W. Thompson, *J. Chem. Soc.*, 225 (1950). The values for index of refraction given by Kosolapoff (*cf.* ref. 8, p. 149), which includes that given in ref. 16, appear to be in error.

(18) H. McCombie, B. C. Saunders, and G. J. Stacey, *J. Chem. Soc.*, 380 (1945).

(19) B. A. Arbuzov and V. S. Vinogradova, *Doklady Akad. Nauk S.S.S.R.*, 55, 31 (1947).

(20) B. A. Arbuzov and V. S. Vinogradova, *Izvest. Akad. Nauk S.S.S.R. Odtel. Khim. Nauk*, 459 (1947).

Identification of components of phosphonate fractions. Gas phase chromatography[15] in the 2-m. tube at 143° resolved the peaks for the three major components, and the retention times were the same as those of authentic samples. With a pressure of 4 cm. of mercury applied to the tube, retention times were 4′ 05″ (min., sec.) for diethyl phosphonate, 4′ 30″ for diethyl methylphosphonate, and 6′ 00″ for diethyl phosphate. Triethyl phosphite has essentially the same retention time as diethyl phosphonate; however, this component is readily separated from the mixture by distillation, as indicated in the results described in the preceding section. The two phosphonates lie too close together for determination of areas under the peaks. Although a 4-m. column would probably supply sufficient resolution, it was deemed expedient to determine total phosphonate from area under the combined peaks, then determine diethyl phosphonate from the intensity of the 4.15-μ band in the infrared (the spectra of the methylphosphonate and phosphate are entirely clear in this region). In runs on pure components, areas under the peaks were found to be approximately proportional to weights of components. In runs on known mixtures, values within 5% of the true values were obtained.

In some runs, such as variation (*a*) under section *C* above, two small peaks were observed with lower retention times than diethyl phosphonate; these were usually barely detectable, never more than 3% of the total area of all bands. No other peaks were observed.

Although excellent coincidence with known compounds was obtained in gas phase chromatography of the reaction products, and the infrared spectra showed absorption at all expected places,[6] additional verification of the identity of the components was obtained. A solution of 10 g. of phosphonate fraction in 50 ml. of benzene was allowed to stand overnight with 5 g. of sodium cut in small pieces; hydrogen was evolved. Filtration of the resultant mixture and recovery of material from the benzene solution yielded 3.9 g. of product distilling chiefly at 94–95°/21 mm. Gas phase chromatography of this product showed the peaks characteristic of triethyl phosphate and diethyl methylphosphonate, and absence of that attributed to diethyl phosphonate.

One sample of phosphonate fraction was carefully distilled in the half-meter column and separated into 8 fractions. Of these, the second, b.p. 103–104°/58 mm., showed the 4.15-μ infrared absorption characteristic of diethyl phosphonate; however, fraction 7, b.p. 114°/58 mm., showed no absorption at 4.15μ. Gas phase chromatography of the latter fraction showed no diethyl phosphonate, and indicated about two parts of diethyl phosphate to one of diethyl methylphosphonate. Analysis was in agreement with the composition of these compounds.

Anal. Calcd. for $C_5H_{13}O_3P$ (methylphosphonate): C, 39.47; H, 8.61. Calcd. for $C_6H_{15}O_4P$ (phosphate): C, 39.56; H, 8.30. Found: C, 39.97; H, 8.47.

Analysis of fraction 3 from this distillation, b.p. 104–106°/58 mm., gave values of C, 37.64; H, 8.27. Similar values to these latter ones were obtained on analysis of several of the total phosphonate fractions.

Reaction of phosphites with ethanol. When a 500 mg. sample of mixed phosphite, b.p. 128–145°, was heated with 50 mg. of anhydrous ethanol at 210–215° for 5 hr., there was no significant change in the infrared spectrum of the phosphite, in particular no absorption in the 8-μ region.

When a mixture of 11.06 g. (0.067 mole) of triethyl phosphite and 3.06 g. (0.067 mole) of anhydrous ethanol was heated in a sealed glass tube at 210–215° for 15 hr., there was recovered by distillation 2.35 g. of ethanol, 6.45 g. (58%) of triethyl phosphite, and 3.85 g. (35%) of phosphonate fraction (infrared absorption at 8μ).

Reaction of triethyl phosphite with n-butyl alcohol. A mixture of 11.06 g. (0.067 mole) of triethyl phosphite and 4.93 g. (0.067 mole) of *n*-butyl alcohol was heated at 210–215° in a sealed glass tube for 15 hr. Distillation of the product yielded: (1) 2.8 g., b.p. 78–79°, n_D^{25} 1.3610, infrared spectrum that of ethyl alcohol; (2) 13 g. in a series of fractions of b.p. in the range from 64°/23 mm. to 70°/1 mm.; all fractions gave the phosphite infrared spectrum, reacted rapidly and exothermally with sulfur, and showed no significant absorption at 8μ.

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Di(*p*-chlorophenyl)trichloromethylcarbinol and Related Compounds

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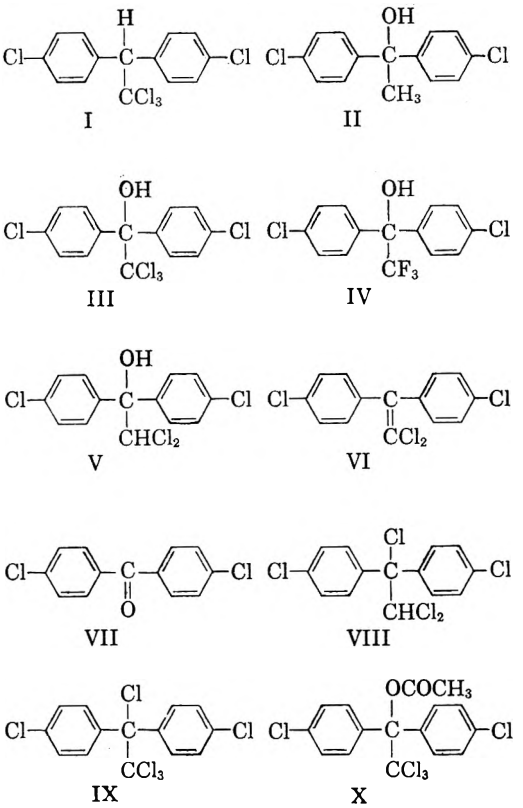
Three diaryltrichloromethylcarbinols have been prepared by reaction of the corresponding 1,1-diaryl-1,2,2,2-tetrachloroethanes with silver acetate and subsequent acid hydrolysis. The high temperature (117°) chlorination of di(*p*-chlorophenyl)-methylcarbinol introduces, broadly speaking, only two chlorine atoms into the methyl group.

If the hypothesis[1] is correct that synergists for DDT (I) of the type of di(*p*-chlorophenyl)methylcarbinol (DMC) (II) are active because of their structural similarity to the insecticide, one would expect di(*p*-chlorophenyl)trichloromethylcarbinol (III) to be more active than II. An indication to this effect may be seen in the fact that di(*p*-chlorophenyl)trifluoromethylcarbinol (IV)[2] is, indeed, a more potent synergist for DDT than II. Curiously enough III has not been described in the scientific literature, although it is sold commercially as a powerful acaricide and its effects have been studied by various workers.[3] The reported method for its preparation is the high-temperature chlorination of II. When this reaction was carried out in glacial acetic acid under the conditions specified in the experimental part, three main constituents could be isolated from the product : di(*p*-chlorophenyl)-dichloromethylcarbinol(V), 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene (VI) and 4,4′-dichlorobenzophenone (VII).[4] In addition, an oil was formed, from which by dehydrohalogenation VI was obtained. It probably contains, therefore, 1,1-di(*p*-chlorophenyl)-1,2,2-trichloroethane (VIII),[5] which could owe its formation to the interaction of V or VI with the gaseous hydrogen chloride. The compound III was present under these conditions only in minute amounts.[6,7] In this connection, it



may be recalled that also the reaction of ethyl trichloroacetate or 4,ω,ω,ω-tetrachloroacetophenone with aromatic Grignard compounds did not lead to compound III.[8,9]

The method finally employed used as starting material the olefin (VI), which adds halogen to yield IX. The latter exchanges the chlorine in the 1-position for the acetoxy group, when it is treated

(1) S. Tahori, *J. Econ. Entomol.*, **48**, 638 (1955). *Cf.* F. A. Gunther, R. C. Blinn, G. E. Carman, and R. L. Metcalf, *Arch. Biochem. Biophys.*, **50**, 504 (1954).

(2) (*a*) E. D. Bergmann, S. Tahori, A. Kaluszyner, and S. Reuter, *Nature*, **176**, 266 (1955). (*b*) A. Kaluszyner, S. Reuter, and E. D. Bergmann, *J. Am. Chem. Soc.*, **77**, 4164 (1955). (c) S. Reuter, S. Cohen, R. Mechoulam, A. Kaluszyner, and S. Tahori, *Riv. parassitol.*, **17**, 125 (1956). (*d*) S. Cohen and S. Tahori, *J. Agr. Food Chem.*, **5**, 519 (1957). See also S. Tahori, ref. 1.

(3) (a) D. Asquith, *J. Econ. Entomol.*, **48**, 329 (1955). (b) J. S. Barker and F. B. Maugham, *J. Econ. Entomol.*, **49**, 458 (1956). (c) F. A. Gunther, R. C. Blinn, and R. L. Metcalf, *J. Agr. Food Chem.*, **4**, 338 (1956). (d) R. D. Garmus and V. H. Unger, *Agr. Chem.*, **11**, No. 7, 41 (1956). (e) I. Rosenthal, G. J. Firsone, and F. A. Gunther, *J. Agr. Food Chem.*, **5**, 514 (1957). (f) F. A. Gunther and R. C. Blinn, *J. Agr. Food Chem.*, **5**, 517 (1957). (g) L. R. Jeppson, H. S. Elmer, M. J. Jesser, and J. O. Complin, *J. Agr. Food Chem.*, **5**, 592 (1957). (h) F. A. Gunther, R. C. Blinn, L. R. Jeppson, J. H. Barkley, G. L. Frisone, and R. D. Garmus, *J. Agr. Food Chem.*, **5**, 597 (1957). (i) Two patents (U. S. **2,812,280** and **2,812,362**) have recently been published which describe the preparation of III.

(4) It is possible that 4,4′-dichlorobenzophenone is formed by disproportionation of III, a reaction which occurs generally under the influence of alkali.

(5) S. Cohen, A. Kaluszyner, and R. Mechoulam, *J. Am. Chem. Soc.*, **79**, 5979 (1957).

(6) According to a private communication from Dr. A. H. M. Kirby, East Malling Research Station (Maidstone, Kent), he has isolated small amounts of the carbinol (III) from a commercial product.

(7) The bromination of II gave exclusively 1,1-di(*p*-chlorophenyl)-2,2-dibromoethylene, the analog of (VI).

(8) A. Kaluszyner and S. Reuter, *J. Am. Chem. Soc.*, **75**, 5176 (1953). *Cf.* K. R. Dishart and R. Levine, *J. Am. Chem. Soc.*, **78**, 2268 (1956).

(9) J. M. Pepper and M. Kulka, *J. Am. Chem. Soc.*, **72**, 1417 (1950).

with silver acetate in boiling glacial acetic acid; potassium or lead acetate were without effect. Hydrolysis of the ester (X) so obtained in acidic medium (sulfuric acid in acetic acid) gave III. All attempts to carry out the conversion of IX to III in a single step failed. Furthermore, the alkaline hydrolysis of X only leads to decomposition to 4,4′-dichlorobenzophenone (VII) according to the scheme:

$$Ar_2C(OCOCH_3)CCl_3 \xrightarrow{H_2O} Ar_2CO + CHCl_3 + CH_3COOH$$

a reaction which is not without analogies.[3e, 3f]

In the same way, diphenyltrichloromethylcarbinol and di(*p*-fluoromethyl)trichloromethylcarbinol were obtained from 1,1-diphenyl- and 1,1-di(*p*-fluorophenyl)1,2,2,2 - tetrachloroethane, respectively.

The reaction of IX with silver propionate gave in smooth reaction the propionate, corresponding to X.

The diaryltrichloromethylcarbinols give halochromic solutions in concentrated sulfuric acid; however, the color fades quickly. A similar observation has been made and the reaction occurring elucidated in the case of the di(*p*-halogenophenyl)-trifluoromethylcarbinols (such as IV).[10] The reaction taking place in the present case, will form the subject of a forthcoming publication.

The insecticidal activity, for resistant houseflies, of diphenyl-, di(*p*-chlorophenyl)-, and di-(*p*-fluorophenyl)trichloromethylcarbinol is LD_{50} 300, 33, and 12γ per fly, respectively. The acetates of these carbinols are inactive. At a ratio of DDT: synergist = 10:1, the synergistic effect of both III and di(*p*-fluorophenyl)trichloromethylcarbinol is 140, while that of the corresponding di(*p*-chlorophenyl)-trifluoromethyl-carbinol (IV) is 30. Here, too, the acetates of the trichloromethylcarbinols had no effect.

EXPERIMENTAL

1,1-Diphenyl-1,2,2,2-tetrachloroethane. Thirty-nine g. of 1,1-diphenyl-2,2-dichloroethylene (m.p. 77–78°), prepared from 1,1-diphenyl-2,2,2-trichloroethane[11] and alcoholic potassium hydroxide solution, was added to a solution of 11.2 g. of chlorine in 200 ml. of glacial acetic acid and the mixture kept for 2 days in a closed flask. The solid was filtered and the mother liquid treated at 100° with a current of dry chlorine gas for 2 hr. Then the solvent was evaporated and the residue, together with the first crop, recrystallized from methanol. M.p. 87–88° (lit.[12]: 87–88°); yield, 41.1 g. (82%).

1,1-Diphenyl-1-acetoxy-2,2,2-trichloroethane. A mixture of 16.0 g. of the preceding compound, 8.4 g. of silver acetate, and 110 ml. of glacial acetic acid was refluxed for 90 min., cooled, and filtered, and the solution concentrated to half its volume and diluted with water. The oily product crystallized, when the excess of the acid was neutralized with sodium bicarbonate. Successive recrystallizations from methanol and petroleum ether (40–60°) gave 12.8 g. (74%) of m.p. 83–85°. λ_{max}^{EtOH} 261 mμ (2.76); 266 mμ (2.81); 272 mμ (2.68).

Anal. Calcd. for $C_{16}H_{13}Cl_3O_2$: C, 55.9; H, 3.8. Found: C, 56.1; H, 4.1.

Ethanolic potassium hydroxide (1.2 g.) transformed the compound (1.7 g.) (heating for 5 min.) into benzophenone (0.7 g.), which was characterized by its 2,4-dinitrophenylhydrazone, m.p. 238°.

Diphenyltrichloromethylcarbinol. A mixture of 3.4 g. of the foregoing ester, 20 ml. of glacial acetic acid, 15 ml. of water, and 2 ml. of concentrated sulfuric acid was refluxed for 90 min. and poured into ice. Upon addition of 25 g. of sodium hydroxide in 100 ml. of water, a solid separated which was dried and recrystallized from petroleum ether (60–90°). Crystals, of m.p. 67–68.5; yield, 1.7 g. (56%). λ_{max}^{EtOH} 230 mμ (3.85); 250 mμ (3.00); 254 mμ (3.04); 258 mμ (3.04); 264 mμ (3.00); 270 mμ (2.85).

Anal. Calcd. for $C_{14}H_{11}Cl_3O$: C, 55.8; H, 3.7. Found: C, 55.6; H, 3.6.

1,1-Di(p-fluorophenyl)-1,2,2,2-tetrachloroethane. A solution of 8.5 g. of chlorine and 35.7 g. of 1,1-di(*p*-fluorophenyl)-2,2-dichloroethylene[13] in 200 ml. of glacial acetic acid was exposed for 6 hr. to direct sunlight, a slightly exothermic reaction taking place. The solvent was removed *in vacuo* and the remaining oil distilled; b.p. 160–162° (2 mm.); yield, 28.3 g. (88%); n_D^{28} 1.5855. Upon prolonged standing, the oil crystallized; m.p. 55–56°. The compound is mentioned briefly in the literature,[14] but without physical constants.

Anal. Calcd. for $C_{14}H_8Cl_4F_2$: C, 47.2; H, 2.3. Found: C, 47.4; H, 2.4.

1,1-Di(p-fluorophenyl)-1-acetoxy-1,2,2-trichloroethane. The reaction between 17.8 g. of the foregoing compound and 8.35 g. of silver acetate in 200 ml. of glacial acetic acid was carried out as above. From methanol, then from petroleum ether long rods of m.p. 135–136°; yield, 16.7 g. (88%). λ_{max}^{EtOH} 266 mμ (2.81); 271 mμ (2.70).

Anal. Calcd. for $C_{16}H_{11}Cl_3FO_2$: C, 50.6; H, 2.8. Found: C, 51.1; H, 3.0.

Di(p-fluorophenyl)trichloromethylcarbinol. In the manner described before 7.6 g. of the foregoing ester, 80 ml. of glacial acetic acid, 25 ml. of water, and 5 ml. of concentrated sulfuric acid, gave 4.7 g. (70%) of the desired compound; after recrystallization from petroleum ether (60–90°) it melted at 78.5–80°. λ_{max}^{EtOH} 230 mμ (3.76) (inflection); 258 mμ (2.93); 265 mμ (3.00); 271 mμ (3.00).

Anal. Calcd. for $C_{14}H_9Cl_3F_2O$: C, 49.8; H, 2.7. Found: C, 50.3; H, 3.0.

1,1-Di(p-chlorophenyl)-1-acetoxy-2,2,2-trichloroethane (X). From 29.2 g. of 1,1-di(*p*-chlorophenyl)-1,2,2,2-tetrachloroethane (IX)[15] and 13.7 g. of silver acetate in 300 ml. of boiling glacial acetic acid (90 min.), 22.1 g. (71%) of the desired product, m.p. 127.5–128.5° was obtained after recrystallization from methanol and petroleum ether (40–60°). λ_{max}^{EtOH} 230 mμ (4.48); 255 mμ (2.70); 266 mμ (2.76).

Anal. Calcd. for $C_{16}H_{11}Cl_5O_2$: C, 46.6; H, 2.7. Found: C, 46.9; H, 2.9.

1,1-Di(p-chlorophenyl)-1-propionoxy-2,2,2-trichloromethane. A mixture of 7.8 g. of (IX), 2.3 g. of silver oxide, and 100 ml. of propionic acid was refluxed for 90 min., filtered, poured into water, and almost completely neutralized by addition of sodium hydroxide solution. The precipitate was filtered, dried, and recrystallized first from methanol, then from low-

(10) S. Cohen and A. Kaluszyner, *Experientia*, **13**, 236 (1957). S. Cohen, *J. Am. Chem. Soc.*, **79**, 1499 (1957).

(11) A. v. Baeyer, *Ber.*, **5**, 1094 (1872).

(12) O. G. Backeberg and J. L. Marais, *J. Chem. Soc.*, 803 (1945). For another method, see H. Bader, W. A. Edmiston, and H. H. Rosen, *J. Am. Chem. Soc.*, **78**, 2590 (1956).

(13) H. L. Bradlow and C. A. Vander Werf, *J. Am. Chem. Soc.*, **69**, 662 (1947).

(14) W. Voegtli and P. Laeuger, *Helv. Chim. Acta*, **38**, 46 (1955).

(15) O. Grummit, A. Buck, and A. Jenkins, *J. Am. Chem. Soc.*, **67**, 155 (1945).

boiling (40–60°) petroleum ether. M.p. 86.5–87°; yield, 3.9 g. (46%).

Anal. Calcd. for $C_{17}H_{13}Cl_5O_2$: C, 47.9; H, 3.1. Found: C, 47.6; H, 3.1.

Di(p-chlorophenyl)trichloromethylcarbinol (III). The hydrolysis of the ester (X) (12.4 g.) with concentrated sulfuric acid (5 ml.) and 75% acetic acid (160 ml.) was carried out as described above. The oily product was dissolved in chloroform, washed with sodium bicarbonate solution, and recovered by evaporation of the solvent. From petroleum ether (40–60°), m.p. 77–78°.[16] λ_{max}^{EtOH} 226 mμ (4.43); 258 mμ (2.82), 266 mμ (2.85), 276 mμ (2.60).

Anal. Calcd. for $C_{14}H_9Cl_5O$: C, 45.4, H, 2.5. Found: C, 45.6; H, 2.7.

Chlorination of di(p-chlorophenyl)methylcarbinol [*DMC* (II)]. A current of chlorine was passed through a solution of 26.7 g. of (II) in 250 ml. of glacial acetic acid. The initial reaction was fairly exothermic. When it had somewhat subsided, chlorination was continued for 2.5 hr. at 65–75° and for 8 hr. at the boiling temperature of the solvent. About 200 ml. of glacial acetic acid was then distilled off and the residue diluted with water and cautiously neutralized with sodium bicarbonate. The product was dissolved in ether, dried, concentrated, and taken up in 20 ml. of petroleum ether (60–90°). Thus, 3.2 g. of a crystalline product was obtained; two recrystallizations from methanol gave 1 g. of 4,4′-dichlorobenzophenone, m.p. and mixed m.p. with an authentic specimen, m.p. 146–147°.

The petroleum ether solution was distilled under 2-mm. pressure, two fractions being secured:

(a) 150–180°, 8.6 g., and (b) 180–205°, 12.0 g.

Fraction (a). From the solution in 15 ml. of petroleum ether (40–60°) there crystallized first 0.8 g. of 4,4′-dichlorobenzophenone, then 2.1 g., which crystallized from methanol, had m.p. 84–86° and were identified as 1,1-di(*p*-chlorophenyl)-2,2-dichloroethylene (VI), and 2.0 g. of unsharp m.p. 78–84° which were not identical with (VI), but were not further investigated. *Fraction (b).* From the solution in 20 ml. of petroleum ether (40–60°), there crystallized upon cooling 4.8 g. of m.p. 95–104° and, after recrystallization from petroleum ether (70–90°), 107–109°. This is di(*p*-chlorophenyl)dichloromethyl-carbinol (V), for which the literature gives m.p. 108–109°;[9] b.p. 200–210° (1 mm.), and m.p. 105–106°.[17,18]

Anal. Calcd. for $C_{14}H_{10}Cl_4O$: C, 50.0; H, 3.0. Found: C, 49.0; H, 2.9. Ultraviolet spectrum (in ethanol): 231 mμ (4.45); 260 mμ (2.87); 266 mμ (2.85). Infrared spectrum (KBr disk): ν(OH) 3570 cm.$^{-1}$; ν(CCl_2) 770–780 cm.$^{-1}$

No further crystalline material could be obtained upon concentration of the petroleum ether solution of fraction (b). Treatment of the remaining oil with alcoholic potassium hydroxide gave only (VI).

Bromination of di(p-chlorophenyl)methylcarbinol (II). To a solution of 13.4 g. of II in 100 ml. of glacial acetic acid, 24 g. of bromine in 50 ml. of the same solvent was added with stirring. When the color of the bromine had disappeared, the solution was diluted with water and the solid filtered and recrystallized from ethanol. Thus 12.3 g. (41%) of 1,1-di(*p*-chlorophenyl)-2,2-dibromoethylene was obtained, m.p. 102–104° (lit.,[19] 104–105°).

Anal. Calcd. for $C_{14}H_8Cl_2Br_2$: C, 41.3; H, 2.0. Found: 41.1; H, 2.4.

Acknowledgment. Thanks are due to Mr. Sasson Cohen for his advice in this investigation, and to Dr. S. Tahori for the biological evaluation of the compounds.

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(16) The compound showed no depression of the melting point upon admixture of a sample kindly supplied by Dr. Kirby, see ref. 5.

(17) *Cf.* W. E. Craig, E. Y. Shropshire, and H. F. Wilson, U. S. Patent **2,720,548** (*Chem. Abstr.*, **50**, 8735 (1956)). In this patent, V was formed by hydrolysis of VIII, which in turn was obtained from 1,1-di(*p*-chlorophenyl)-2-chloroethylene.

(18) The solution in concentrated sulfuric acid is reddish, but the color fades quickly, due to formation of VI.

(19) S. J. Cristol and H. L. Haller, *J. Am. Chem. Soc.*, **68**, 140 (1946).

[CONTRIBUTION FROM THE NATIONAL BUREAU OF STANDARDS]

Mutarotation, Hydrolysis, and Rearrangement Reactions of Glycosylamines[1]

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The mutarotation, hydrolysis, and rearrangement reactions of D-glucosylamine, D-mannosylamine, and D-xylosylamine have been studied, and rationalized on the basis of the formation of an intermediate, acyclic imonium ion. Rate constants are given for the hydrolysis reaction under various conditions. The formation of diglycosylamines is explained as a type of transamination in which a second molecule of the glycosylamine reacts with the first (in the imonium ion form) with the subsequent elimination of ammonia. Unsubstituted D-glucosylamine has been found to undergo an Amadori rearrangement in glacial acetic acid or in some of the methylenic compounds found by Hodge and Rist to be effective in the rearrangement of *N*-substituted glycosylamines. Intramolecular mechanisms are suggested to account for the effectiveness of carboxylic acids and methylenic compounds in promoting the Amadori rearrangement. By these mechanisms an enolic structure can be transferred from a catalyst to the amine.

The following new compounds are reported: β-D-mannopyranosylamine monohydrate; *N*-acetyl-tetra-*O*-acetyl-β-D-mannopyranosylamine; *N*-acetyl-β-D-mannopyranosylamine monohydrate; octa-*O*-acetyl-di-D-mannosylamine; *N*-acetyl-tri-*O*-acetyl-β-D-xylopyranosylamine; *N*-acetyl-β-D-xylopyranosylamine; di-D-xylosylamine; hexa-*O*-acetyl-di-D-xylosylamine; di-L-arabinosylamine. On the basis of periodate oxidation data and comparisons of optical rotation, ring structures and anomeric configurations have been assigned to the above glycosylamines and their acetates (except the diglycosylamines) and also to β-D-glucopyranosylamine, β-D-xylopyranosylamine, and their acetates.

In connection with the development of methods for the synthesis of C^{14}-labeled carbohydrates,[2] a study of some reactions of the glycosylamines was undertaken because these materials can be used as intermediates for the production of labeled amino sugars. Glycosylamines, or *N*-glycosides, formed by the condensation of reducing sugars with ammonia or amino compounds, are of major biological importance.[3] They include nucleic acids, certain coenzymes, some vitamins and other natural products. The reactions of the glycosylamines are also of interest, in relation to the formation and properties of osazones,[4] mucoproteins,[5] riboflavin,[6,7] and other substances.

The importance of the glycosylamine structure lies not only in its widespread occurrence in natural products, but also in its ability to rearrange and to participate in a variety of reactions.[8,9] The versatility of the structure arises from its capacity to supply or remove electrons, or to aid in moving them from one part of the molecule to another. This concept, suggested in 1943,[10] was subsequently applied to the interpretation of the hydrolysis and mutarotation of the aldosylamines.[11-13] It was shown that, in suitable solvents, the glycosylamines, like the sugars, establish equilibrium states involving cyclic and acyclic forms, and it was postulated that the conversion of one modification to another takes place through an imonium ion $[R-\overset{H}{C}=\overset{+}{N}RR']$ formed by acid catalysis. C-1 of the ion tends to acquire electrons in various ways. In the mutarotation reaction, the incipient electron deficiency at C-1 is satisfied by a pair of electrons drawn from a hydroxyl group within the molecule, thus generating a cyclic modification of the glycosylamine. The reaction is reversible and ultimately leads to an equilibrium state which includes all modifications of the glycosylamine. In other reactions, the deficiency is satisfied by addition, to the imonium ion, of a nucleophilic group from the environment. The addition is usually followed by elimination of the amine (or ammonia) as, for example, in hydrolysis and transglycosylation. Furthermore, the imonium ion can acquire electrons from the adjacent carbon atom by enolization. The resulting enolic amine is in some respects analogous to the enediols of the sugars, and undergoes a variety of rearrangement, cleavage, and condensation reactions.

In this paper, it is pointed out that the mutarotation, hydrolysis, and rearrangement reactions of

(1) Part of a project on the development of methods for the synthesis of radioactive carbohydrates sponsored by the Division of Research, Atomic Energy Commission.

(2) H. S. Isbell, J. V. Karabinos, H. L. Frush, N. B. Holt, A. Schwebel, and T. T. Galkowski, *J. Research Natl. Bur. Standards*, **48**, 163 (1952); H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **50**, 133 (1953); R. Schaffer and H. S. Isbell, *J. Research Natl. Bur. Standards*, **56**, 191 (1956); H. S. Isbell and R. Schaffer, *J. Am. Chem. Soc.*, **78**, 1887 (1956).

(3) R. Kuhn, *Angew. Chem.*, **69**, 23 (1957).

(4) F. Weygand, *Ber.*, **73**, 1284 (1940).

(5) A. Gottschalk, *Nature*, **167**, 845 (1951); *Biochem. J.*, **52**, 455 (1952).

(6) F. Weygand, *Ber.*, **73**, 1259 (1940).

(7) F. Weygand, *Ber.*, **73**, 1278 (1940); German Patent **727,402** (Oct. 1, 1942); U. S. Patent **2,354,846** (Aug. 1, 1944).

(8) G. P. Ellis and J. Honeyman, *Advances in Carbohydrate Chem.*, **10**, 95 (1955).

(9) J. E. Hodge, *Advances in Carbohydrate Chem.*, **10**, 169 (1955).

(10) H. S. Isbell, *Ann. Rev. Biochem.*, 12, 205 (1943).

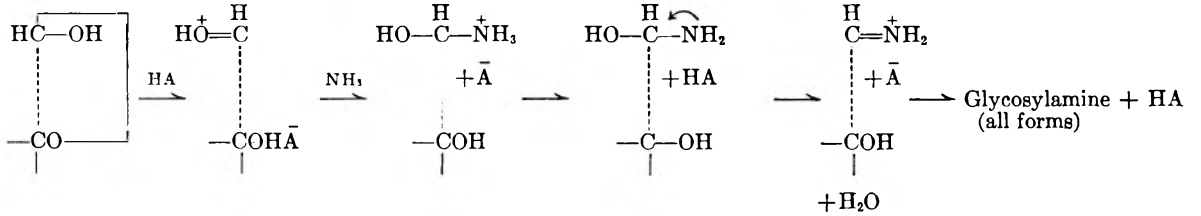
(11) H. S. Isbell and H. L. Frush, *J. Am. Chem. Soc.*, **72**, 1043 (1950).

(12) H. S. Isbell and H. L. Frush, *J. Research Natl. Bur. Standards*, **46**, 132 (1951).

(13) H. L. Frush and H. S. Isbell, *J. Research Natl. Bur. Standards*, **47**, 239 (1951).

the glycosylamines take place concurrently and that the formation of products can be rationalized on the basis of the intermediate imonium ion. It is shown that the mutarotation and hydrolysis of D-glucosylamine, D-mannosylamine and D-xylosylamine, like those of D-galactosylamine and L-arabinosylamine, studied previously, are extremely sensitive to changes in acidity; rate constants are given for the hydrolysis reactions of several glycosylamines under various conditions. An intramolecular mechanism is suggested to account for the effectiveness of certain methylenic compounds and of carboxylic acids in promoting the Amadori rearrangement; evidence is presented for the effectiveness of these reagents in promoting the Amadori rearrangement of unsubstituted D-glucosylamine. Directions are given for the preparation, from D-glucose, D-mannose, and D-xylose, of the free glycosylamines, fully acetylated glycosylamines, *N*-acetylglycosylamines, and diglycosylamines. Some of these are new crystalline compounds. Structures are assigned to the products on the basis of periodate oxidation studies and optical rotation measurements.

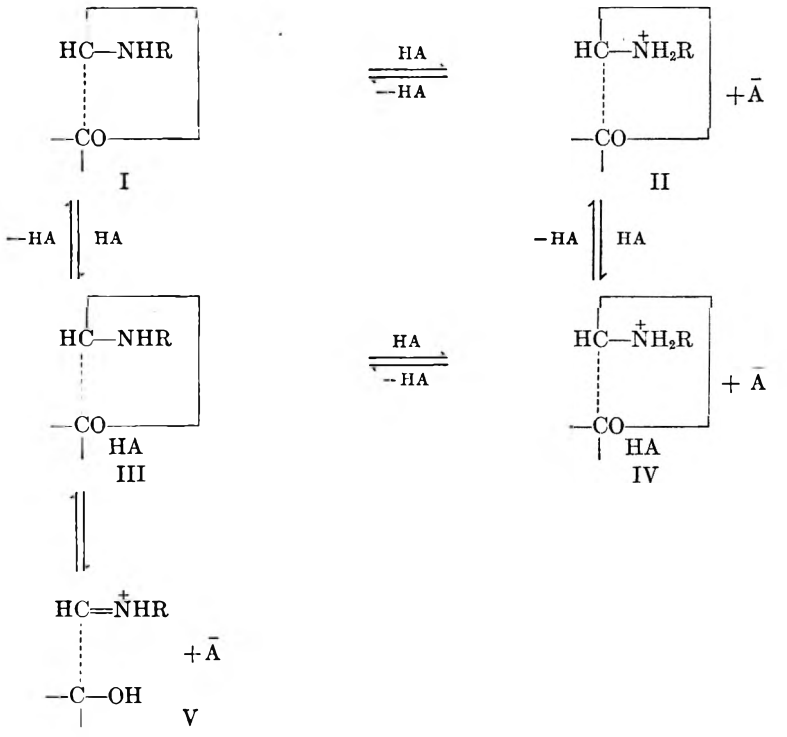
Discussion of the reaction mechanisms. Formation of the glycosylamine from the sugar plus ammonia, represented by Equation 1, involves the initial addition of ammonia to one of the acyclic modifications formed from the sugar by the mutarotation reaction.[12] The addition compound decomposes, with elimination of a hydroxyl ion, to form the imonium ion of the glycosylamine. Condensation of the sugar with ammonia can presumably take place either through the neutral, carbonyl modification of the sugar or through the acyclic cation $[R—\overset{H}{C}=OH]^+$ formed by acid catalysis, but the acyclic cation is far more reactive. This hypothesis accounts for the effectiveness of general acid catalysts in promoting formation of glycosylamines. Condensation of the acyclic cation with ammonia does not take place in strongly acidic solution, because, under these conditions, the nucleophilic character of the ammonia is satisfied by combination with hydrogen ion (ammonium salt formation).



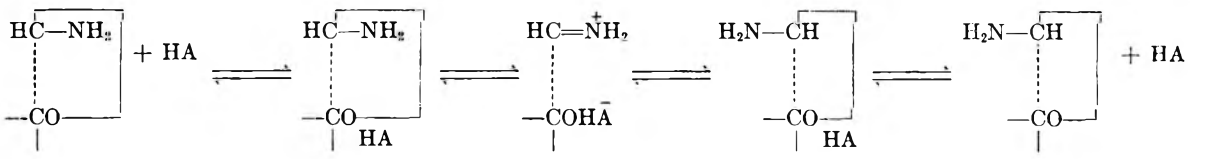
Equation 1. Formation of glycosylamine

Formation of the imonium ion from the glycosylamine I, shown in Equation 2, depends on the presence of an acid catalyst, but the situation is complicated by a side reaction yielding the unreactive ammonium salt II. The extent of the side reaction depends on the *p*H of the solution and on the basicity of the amino component of the glycosylamine. At a low *p*H substantially all of the glycosylamine exists in the form of ammonium salts II and IV; this accounts for the stability of the glycosylamine in strongly acidic solution.[11–13] When the amino component is strongly basic, the glycosylamine readily forms the ammonium salt II; on the other hand, when the amino component is weakly basic, the glycosylamine yields more of the intermediate III. In the formation of the imonium ion V from III, electrons must move from the nitrogen atom to the glycosidic carbon atom. Strongly basic amino components supply electrons more readily than do weakly basic. Thus, strong basicity of the amino component is favorable for the last step in the production of the imonium ion but unfavorable for the existence of the glycosylamine I under acid conditions. For this reason, the concentration of the imonium ion V is dependent on both the acidity of the environment and the basicity of the amino component of the glycosylamine. The equilibria given in Equation 2 may be present.

According to the hypothesis previously presented,[12] the mutarotation reaction of a glycosylamine (Equation 3) involves addition of an acid catalyst to the ring oxygen atom, accompanied by a shift of electrons to give the open-chain imonium ion; the anomeric furanoses and pyranoses are then derived by intramolecular condensation with a hydroxyl group of C-4 or C-5, respectively. In this process, the electrophilic property of the carbon atom attached to nitrogen is satisfied by electrons from the oxygen atom of the hydroxyl group. In the present study, it was found that the mutarotation reactions of D-glucosylamine, D-mannosylamine, and D-xylosylamine, like those of D-galactosylamine and L-arabinosylamine, are extremely rapid in neutral and acid solutions but slow in alkaline solutions. The extent of the mutarotation reaction can be estimated from the difference in the optical rotations of freshly prepared solutions of the glycosylamine in aqueous ammonia (in which mutarotation and hydrolysis are slow) and in aqueous acid (in which mutarotation is nearly instantaneous and hydrolysis is slow). The changes in specific rotation for β-D-glucopyranosylamine (+20.9° to +20.6°) and for β-D-xylopyranosylamine (−19.5° to −17.6°) are small. This is evidence that D-glucosylamine and D-xylosylamine establish equilibrium mixtures consisting almost entirely of the



Equation 2. Formation of imonium ion



Equation 3. Mutarotation of glycosylamine

beta pyranose modification. The stability of the *beta* pyranose forms of D-glucosylamine and D-xylosylamine presumably arises from their assuming the normal chair conformation, C'1, in which all of the groups attached to the ring, except the hydrogen atoms, lie in equatorial positions.[14–16] The large change in rotation for β-D-mannosylamine (−11.7° to −2.9° for the monohydrate) is evidence that the *beta* form is less stable than β-D-glucosylamine, and that the equilibrium solution contains other, presumably *alpha*, modifications. The difference in behavior of the two glycosylamines may be attributed to the presence of an additional instability factor in the C'1 conformation of the mannose derivative, namely, the axial hydroxyl group at C-2. Since one of the boat forms (B1)[14] for α-D-mannopyranosylamine has an exceptionally stable arrangement (eeeee), it may possibly exist in equilibrium with the β-C'1 form. This would account for the greater mutarotation of β-D-mannopyranosylamine, as well as for the anomalous rotational differences in the mannose series which were previously ascribed to differences in ring conformation.[17]

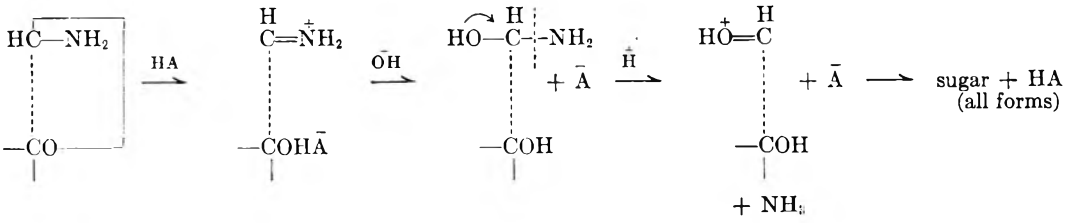
The rate of hydrolysis of glycosylamines was previously found to have a striking and unique dependence on the *p*H of the solution; it attains a maximum in *weakly* acid solution. This marked dependence on *p*H was ascribed to the fact that the reaction requires both an acid catalyst and a hydroxyl ion (Equation 4). As in the other reactions considered here, the hydrolysis mechanism we propose includes the imonium ion intermediate. Addition of a hydroxyl ion forms an aldehyde-ammonia which decomposes to yield ammonia plus the acyclic cation of the sugar. Removal of the ammonia or amine by volatilization or by combination with an acid drives the reaction to completion. As shown in Table II, the rates of hydrolysis for the glycosylamines of D-glucose, D-mannose, and D-xylose reach a maximum in the region of *p*H 5; in strongly acidic or in basic solution the rates are very low. The maximum rate found for D-glucosylamine (0.0081) was only one seventh that for D-mannosylamine (0.060) and one fifth that previously found

(14) R. E. Reeves, *Advances in Carbohydrate Chem.*, 6, 108 (1951).

(15) H. S. Isbell, *J. Research Natl. Bur. Standards*, 57, 171 (1956).

(16) H. S. Isbell, F. A. Smith, E. C. Creitz, H. L. Frush, J. D. Moyer, and J. E. Stewart, *J. Research Natl. Bur. Standards*, 59, 41 (1957).

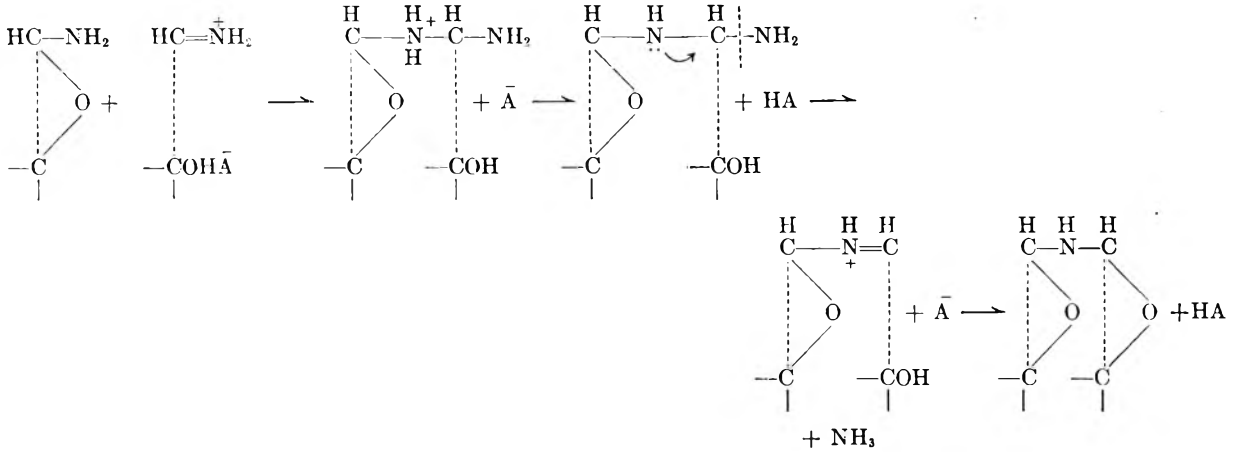
(17) H. S. Isbell, *J. Research Natl. Bur. Standards*, 18, 505 (1937); 24, 125 (1940).



Equation 4. Hydrolysis of glycosylamine

for D-galactosylamine (0.043). The maximum rate for D-xylosylamine (0.112) does not differ widely from that previously found for L-arabinosylamine (0.108).

Transglycosylation reactions[18-20] and the formation of diglycosylamines may also be interpreted in terms of the imonium ion. In transglycosylation reactions, a second amino compound adds to the imonium ion of the first (Equation 5). The resulting diamino compound decomposes with formation of a new glycosylamine and liberation of the amino group originally present (as the free amine or ammonia). When an unsubstituted glycosylamine is heated in a suitable solvent, two molecules condense to form one of a diglycosylamine. This is a type of transglycosylation in which one molecule of the glycosylamine adds to the imonium ion of another molecule. The addition product, like the aldehyde-ammonia formed in the hydrolysis reaction, is unstable and decomposes with the elimination of ammonia. In the absence of an acid catalyst, the reaction is slow for lack of the imonium ion, and in acid solution it is slow for lack of the free amine. Each of the glycosyl groups of the diglycosylamine might have a pyranose or a furanose structure and an *alpha* or a *beta* configuration for the glycosidic carbon atom. Various combinations of these structural features make a number of isomers possible for each glycosylamine, and, in fact, two modifications of di-D-glucosylamine have been isolated.[21] In the present study, it was found that the reaction in methanol or in methyl Cellosolve (ethylene glycol monomethyl ether) is accelerated by the addition of phenol. This catalyst provides some imonium ion without converting the major part of the glycosylamine to the ammonium salt. The conditions do not differ widely from those used for the Amadori rearrangement, except that volatilization of ammonia tends to drive the transglycosylation to completion.



Equation 5. Formation of diglycosylamine

The character of the Amadori rearrangement,[22] the conversion of a *N*-substituted aldosylamine to a *N*-substituted 1-amino-1-deoxyketose, was first recognized by Kuhn and Weygand[23] who clarified the mechanism[6,23] and showed the general application of the reaction. Until fairly recently, the Amadori rearrangement was believed to take place only with *N*-arylglycosylamines. However, Hodge and Rist[24] greatly extended the scope of the reaction by the discovery that members of all classes of *N*-substituted glycosylamines can be rearranged by treatment with a compound having an activated methylene group, in the presence of a

(18) R. Kuhn and A. Dansi, *Ber.*, 69, 1745 (1936).

(19) Y. Inoue and K. Onodera, *J. Agr. Chem. Soc. Japan*, 22, 119 (1948).

(20) R. Bognar and P. Nanasi, *J. Chem. Soc.*, 189, 193 (1955).

(21) P. Brigl and H. Keppler, *Z. physiol. Chem.*, 180, 38 (1929).

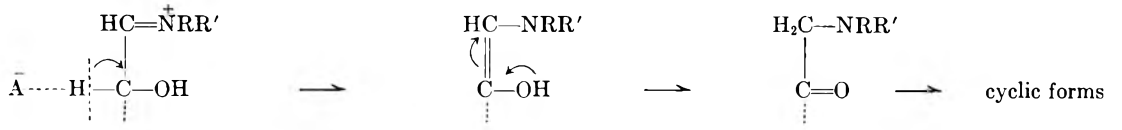
(22) M. Amadori, *Atti. reale accad. nazl. Lincei*, [6] 2, 337 (1925); [6] 9, 68, 226 (1929); [6] 13, 72 (1931).

(23) R. Kuhn and F. Weygand, *Ber.*, 70, 769 (1937).

(24) (a) J. E. Hodge and C. E. Rist, *J. Am. Chem. Soc.*, 74, 1494 (1952); (b) J. E. Hodge and C. E. Rist, *J. Am. Chem. Soc.*, 75, 316 (1953).

catalytic quantity of a secondary amine. More recently, it has been found that *N*-alkyl-4,6-*O*-benzylidene-D-glucosylamines can be readily rearranged,[25] presumably because substitution on carbon 6 stabilizes the reactive carbonyl form of the ketose. We have found that rearrangement of unsubstituted glycosylamines can be effected by some of the methylenic compounds of Hodge and Rist, as well as by glacial acetic acid.[26]

Weygand's interpretation of the mechanism of the Amadori rearrangement[6] involves the addition of a proton from an acid catalyst to the nitrogen atom of the glycosylamine. The resulting ammonium salt II is converted to the open-chain, imonium ion V. Subsequent release of a hydrogen atom from the adjacent carbon atom to a base catalyst yields a 1,2-enolic amine. This, on deenolization, presumably gives the two epimeric aldosylamines and the corresponding 1-amino-1-deoxyketose. We consider that the rearrangement of the glycosylamine involves addition of the acid catalyst to the ring oxygen atom rather than to the nitrogen atom[12,13] (see Equation 2) and thus avoids the stable ammonium salt II as a reaction intermediate.[27] As shown in Equation 6, enolization of



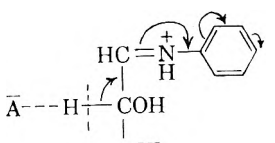
Equation 6. Amadori rearrangement

the resulting imonium ion then takes place by removal of the hydrogen atom of C-2. This hydrogen atom is susceptible to elimination, because a flow of electrons toward the positive nitrogen atom leaves C-1 transiently positive, and a secondary flow of electrons from C-2 to C-1 weakens the C—H bond of C-2. Elimination of the hydrogen atom, with a shift of electrons, yields the enolic amine of Kuhn and Weygand. By tautomeric shift, the enolic glycosylamine is then converted to the 1-amino-1-deoxyketose and presumably to the corresponding epimeric aldosylamines.

Removal of the hydrogen atom of C-2 requires a proton acceptor (base catalyst). Heretofore, this has been considered to derive from the environment. However, the exceptionally strong catalytic effect of methylenic compounds[24] and of the carboxylic acids[28] suggests that more than simple acid-base catalysis is involved, in some cases. Intramolecular mechanisms seem possible for these reactions. Rearrangements effected by methylenic compounds may take place through the addition of the enolic form of the methylenic compound to the imonium ion (Equation 7). The transitory intermediate would then decompose intramolecularly, with regeneration of the methylenic compound in the keto form and formation of the enolic form of the glycosylamine. The process is a type of transenolization, whereby an enolic structure is transferred from one substance to another. It may be considered a model for certain biological enolizations.

In rearrangements effected by carboxylic acids there may be condensation of the imonium ion with the carboxylate ion, followed by intramolecular decomposition of the intermediate and liberation of the carboxylic acid.[29] The process is illustrated in Equation 8.

The facility with which *N*-substituted glycosylamines undergo the Amadori rearrangement is strikingly dependent on the character of the amino component. *N*-Arylglycosylamines, in particular, show a wide variation in reactivity. As shown in Equation 9, both imonium ion formation and subsequent enolization are affected by the nature of the *N*-substituent. It was pointed out in a previous paragraph that strongly basic amino compounds (although tending in acid solution to enter into a side reaction, ammonium ion formation) supply electrons for the formation of the imonium ion more readily than do weakly basic amino components. In this step, the electron shift is away from the aromatic nucleus. However, in the next step (enolization) the electron shift is toward the aromatic nucleus as shown in VI. The electron shift is facilitated by the tendency of the ring (particularly



VI

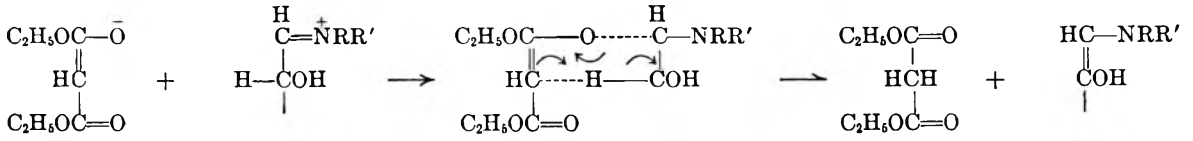
(25) F. Micheel and A. Frowein, *Chem. Ber.*, **90**, 1599 (1957).

(26) See W. Pigman, E. A. Cleveland, D. H. Couch, and J. H. Cleveland, *J. Am. Chem. Soc.*, **73**, 1976 (1951). These workers found that *N*-substituted D-glucosylamines, when dissolved in glacial acetic acid, develop a brown color, and that D-glucosylamine and *N*-butyl-D-glucosylamine show changes in optical rotation from positive to negative values. They suggested that an Amadori-type rearrangement is involved.

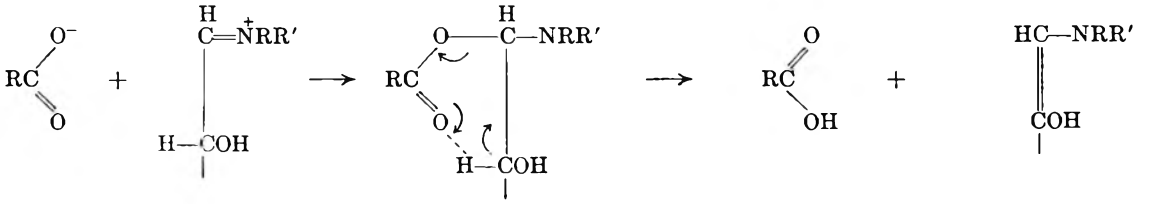
(27) The stability of the salt is evidenced by the inertness of the glycosylamine in strongly acidic solution. The ammonium salt, in the equilibrium, is therefore considered to be only a collateral product.

(28) L. Rosen, J. W. Woods, and W. Pigman, *Chem. Ber.*, **90**, 1038 (1957).

(29) Presumably the transitory intermediate can also be formed by the addition of the carboxylic acid, followed by elimination of a proton. This accounts for the effectiveness of glacial acetic acid in the rearrangement.



Equation 7. Suggested mechanism for effect of methylenic compounds in promoting Amadori rearrangement

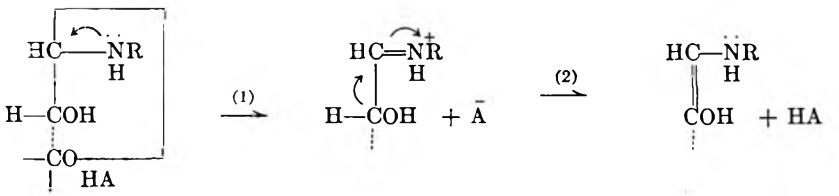


Equation 8. Suggested mechanism for effect of carboxylic acids in promoting Amadori rearrangement

in weakly basic arylamino components) to take up electrons, thus enhancing the electron deficiency at carbon 1. The opposite requirements involved in these two steps are not mutually exclusive, but they do limit the conditions under which the Amadori rearrangement can most favorably occur. Thus, when the attraction of R in Equation 9 for the electrons of the nitrogen atom is too great (as in *N*-acetylglucosylamine[30] and *N*-glycosides of *p*-nitroaniline[28,31]) step 1, namely imonium ion formation, is inhibited; when the attraction of R for these electrons is too small (as in the more strongly basic alkylamines), there is little or no tendency for the enolization, step 2, to occur by the mechanism given. However, the intramolecular mechanisms suggested in Equations 7 and 8 depend upon decomposition of an intermediate formed from the imonium ion, and not upon an electron shift toward R, as given in step 2 of Equation 9. It seems significant that the methylenic compounds of Hodge and Rist are effective in promoting rearrangement of strongly basic alkylamines, compounds for which the substituent R does not promote step 2.

Amadori rearrangement proceeds more or less completely from the *N*-substituted glycosylamine to the corresponding substituted 1-amino-1-deoxyketose. The process is complicated by side reactions arising from the tendency of the intermediate enolic amine to decompose in a variety of ways as summarized by Hodge.[9] Some of these may involve migration of electrons from points of higher electron-density to points of lower electron-density, together with the addition and elimination of ions by steps analogous to those described for the formation of 2-furaldehyde and reductic acid from pentoses.[33]

It was mentioned above that the original concept of the Amadori rearrangement has been broadened to include rearrangement of both *N*-aryl- and *N*-alkylaldosylamines to the corresponding substituted 1-amino-1-deoxyketoses. It is suggested here that the name should also be applied to the so-called "reverse Amadori rearrangement" of ketosylamines to the corresponding 2-amino-2-deoxyaldoses, a type of rearrangement that has received relatively little attention. Such use of the term, Amadori rearrangement, would recognize the simi-



Equation 9. Effect of basicity of amino component on imonium ion formation and subsequent enolization

The labile, enolic amine obtained by these mechanisms should yield an equilibrium mixture of the two epimeric aldosylamines plus the corresponding 1-amino-1-deoxyketose, but this equilibrium condition has not been realized experimentally.[32] The larity of the intermediates and of the reaction mechanisms. The similarity is shown by the conversion of D-fructosylamine to 2-amino-2-deoxy-D-glucose (D-glucosamine) in liquid ammonia containing ammonium hydroxide.[34] Here, the ammonium

(30) E. Mitts and R. M. Hixon, *J. Am. Chem. Soc.*, 66, 483 (1944).

(31) F. Weygand, W. Perkow, and P. Kuhner, *Chem. Ber.*, 84, 594 (1951).

(32) See K. Heyns, H. Breuer, and H. Paulsen, *Chem. Ber.*, 90, 1374 (1957). These authors recently reported that, in an Amadori-type rearrangement of D-fructosyl compounds of certain amino acids, the 2-amino acid derivatives of both D-glucose and D-mannose were obtained.

(33) H. S. Isbell, *J. Research Natl. Bur. Standards*, 32, 45 (1944).

(34) K. Heyns and K. H. Meinecke, *Chem. Ber.*, 86, 1453 (1953).

ion presumably serves as acid catalyst to form the imonium ion, and either the hydroxyl ion or the ammonia molecule serves as base catalyst. Several *N*-substituted D-fructosylamines prepared from aliphatic amines or amino acids have also been found to undergo rearrangement to the corresponding D-glucosamine derivatives.[32,35–37]

Assignment of Ring Structure. The structures for the *N*-acetylglycosylamines were assigned from the changes in optical rotation found on oxidation of the material with sodium metaperiodate (Table IV). Niemann and Hays[38] had previously reported that one mole of *N*-acetyl-D-glucosylamine reacts with 2 moles of sodium metaperiodate to yield a product characteristic of a pyranose structure. On the basis of the specific rotation (−22°) they assigned the *beta* pyranose structure to *N*-acetyl-D-glucosylamine. The later preparation of an anomeric pair of *N*-acetyl-D-galactopyranosylamines by Frush and Isbell[13] made possible a comparison of the optical rotations of the dialdehydes formed by periodate oxidation, and hence an assignment of ring structure for other *N*-acetylglycosylamines. Thus, the *alpha* and *beta* *N*-acetyl-D-aldohexopyranosylamines, on periodate oxidation, give products having specific optical rotations, respectively, of about +60° and −96°, based on the weight of the glycosylamine; all *N*-acetyl-pentopyranosylamines having the same absolute configuration for C-1 as *N*-acetyl-α-L-arabinopyranosylamine give a product with an optical rotation of about −49°. The ring structures and anomeric configurations of the *N*-acetylglycosylamines listed in Table I were assigned on the basis of these values. Three of these assignments were made from the data of Table IV; the others had been made previously.

The structures for the fully acetylated glycosylamines of Table I are based on the structures of the corresponding *N*-acetyl derivatives, which were obtained by their deacetylation with barium methylate. This mild treatment would presumably not lead to a change in structure or configuration; hence, the fully acetylated glycosylamines have been assigned the same structures as the corresponding *N*-acetyl derivatives.

The structures for the free glycosylamines (Table III) were assigned by application of Hudson's principle of isorotation.[39a,39b] According to this principle, the approximate rotation of the *alpha* pyranose is given by B + A and that of the *beta* pyranose by B − A, where A is the rotational contribution of C-1, and B is that of the rest of the molecule. The molecular rotations of the glycosylamines were calculated on the assumption that the values of B for the glycosylamines and the sugars are alike, and that the value of A, obtained from the rotations of the *alpha* and *beta* D-galactopyranosylamines, is applicable to all of the glycosylamines listed, except D-mannosylamine. Because the values of A in the mannose series are anomalous, the molecular rotation of β-D-mannosylamine was calculated from that of β-D-glucosylamine by application of Hudson's rule for epimeric difference.[40] The agreement of the calculated molecular rotations with the observed values supports the structures listed. The marked similarity in the optical rotations of the sugars and the corresponding glycosylamines is noteworthy.

Several diglycosylamines are also listed in Table I. Although a detailed study of their structures is contemplated, this report is restricted to a description of their properties.

EXPERIMENTAL

β-D-Mannopyranosylamine monohydrate. To 50 ml. of methanol were added 20 g. of D-mannose and 0.5 g. of ammonium chloride, and the mixture was treated with ammonia gas at 0° until the sugar had dissolved. The solution was stored at 0° until satisfactory crystallization had occurred. The first crystallization was slow, and required storage of the solution for about a month. Subsequent crystallizations with the aid of seed crystals were more rapid, but maximum yields required storage for a week or two. The crystals were separated, washed with methanol, and dried over sodium hydroxide in a vacuum desiccator. The crude product, 17 g., was dissolved in 17 ml. of water and the solution was diluted with 170 ml. of methanol and sufficient ethanol to produce turbidity. After 48 hr., the crystalline material was separated, washed with methanol, and stored over sodium hydroxide in an atmosphere of ammonia for 2 days.

Anal. (after removal of excess ammonia by evacuation): Calcd. for $C_6H_{13}NO_5.H_2O$: C, 36.54; H, 7.67; N, 7.10. Found: C, 36.9; H, 7.7; N, 7.1. M.p. 93–94°; $[\alpha]_D^{20}$ −11.6° (H_2O, c = 2).

The new, crystalline D-mannosylamine can be kept for short periods in an atmosphere of ammonia. However, when stored for several weeks in a vacuum desiccator over phosphoric anhydride, it is converted to an amorphous material from which the previously known di-D-mannosylamine[41] can be crystallized.

N-Acetyl-tetra-O-acetyl-β-D-mannopyranosylamine. Finely powdered, crystalline β-D-mannopyranosylamine (10 g.) was added to a previously cooled mixture of 100 ml. of pyridine and 50 ml. of acetic anhydride in a flask that was equipped with a mechanical stirrer and immersed in a mixture of ice and salt. Stirring was continued in the ice-salt bath until the crystals had dissolved. After standing a few hours at room temperature, the solution was poured into a liter of ice and water; the mixture was stirred for 30 min. and then extracted with chloroform. Evaporation of the chloroform gave a crude product, 15.6 g., which was recrystallized twice from chloroform, with the addition of petroleum ether, to give pure *N*-acetyl-tetra-*O*-acetyl-β-D-manno-

(35) J. F. Carson, *J. Am. Chem. Soc.*, **77**, 1881, 5957 (1955); **78**, 3728 (1956).

(36) K. Heyns, R. Eichstedt, and K. H. Meinecke, *Chem. Ber.*, **88**, 1551 (1955).

(37) K. Heyns, H. Paulsen, and H. Breuer, *Angew. Chem.*, **68**, 334 (1956).

(38) C. Niemann and J. T. Hays, *J. Am. Chem. Soc.*, **62**, 2960 (1940).

(39) (a) C. S. Hudson, *J. Am. Chem. Soc.*, **31**, 66 (1909); (b) F. J. Bates and Associates, *Natl. Bur. Standards Circ.* **C440**, 428 (1942).

(40) C. S. Hudson, *J. Am. Chem. Soc.*, **48**, 1434 (1926).

(41) C. A. Lobry de Bruyn and F. H. Van Leent, *Rec. trav. chim.*, **15**, 81 (1896).

TABLE I

GLYCOSYLAMINES, DIGLYCOSYLAMINES, AND THEIR ACETATES INCLUDED IN THIS STUDY

Compound	Reference to Preparation	Formula	Molecular Weight	$[\alpha]_D^{20}$	Molecular Rotation	Melting[a] Point, °C.
α-L-Arabinopyranosylamine	b,c	$C_5H_{11}NO_4$	149.15	+ 86.3° (H_2O)	+12,870	124–125
β-D-Xylopyranosylamine	b	$C_5H_{11}NO_4$	149.15	− 19.6° (H_2O)	− 2,920	128–129
α-D-Galactopyranosylamine ammonia complex	d,b	$C_6H_{16}N_2O_5$	196.21	+138° (H_2O)	+27,080	107–109
β-D-Galactopyranosylamine	d,b	$C_6H_{13}NO_5$	179.18	+ 62.2° (H_2O)	+11,140	134–136
β-D-Glucopyranosylamine	e,f	$C_6H_{13}NO_5$	179.18	+ 20.8° (H_2O)	+ 3,730	125–127
β-D-Mannopyranosylamine monohydrate	New	$C_6H_{15}NO_6$	197.20	− 11.6° (H_2O)	− 2,290	93–94
N-Acetyl-tri-*O*-acetyl-α-L-arabinopyranosylamine	c	$C_{13}H_{19}NO_8$	317.30	+ 89.6° ($CHCl_3$)	+28,430	177–178
N-Acetyl-tri-*O*-acetyl-β-D-xylopyranosylamine	New	$C_{13}H_{19}NO_8$	317.30	+ 28.5° ($CHCl_3$)	+ 9,040	172–173
N-Acetyl-tetra-*O*-acetyl-α-D-galactopyranosylamine	d	$C_{16}H_{23}NO_{10}$	389.36	+117.4° ($CHCl_3$)	+45,710	172–173
N-Acetyl-tetra-*O*-acetyl-β-D-galactopyranosylamine	d	$C_{16}H_{23}NO_{10}$	389.36	+ 34.7° ($CHCl_3$)	+13,510	173–174
N-Acetyl-tetra-*O*-acetyl-β-D-glucopyranosylamine	f	$C_{16}H_{23}NO_{10}$	389.36	+ 17.4° ($CHCl_3$)	+ 6,770	163–164
N-Acetyl-tetra-*O*-acetyl-β-D-mannopyranosylamine	New	$C_{16}H_{23}NO_{10}$	389.36	− 16.5° ($CHCl_3$)	− 6,420	188–189
N-Acetyl-α-L-arabino-pyranosylamine	c	$C_7H_{13}NO_5$	191.18	+ 69.7° (H_2O)	+13,330	222–224
N-Acetyl-β-D-xylo-pyranosylamine	New	$C_7H_{13}NO_5$	191.18	− 0.7° (H_2O)	− 130	213–214
N-Acetyl-α-D-galacto-pyranosylamine	d	$C_8H_{15}NO_6$	221.21	+194.9° (H_2O)	+43,110	179–180
N-Acetyl-β-D-galacto-pyranosylamine	d	$C_8H_{15}NO_6$	221.21	+ 9.8° (H_2O)	+ 2,170	233
N-Acetyl-β-D-gluco-pyranosylamine	f	$C_8H_{15}NO_6$	221.21	− 22.8° (H_2O)	− 5,040	260[g]
N-Acetyl-β-D-mannopyranosyl-amine monohydrate	New	$C_8H_{17}NO_7$	239.23	− 47.4° (H_2O)	−11,340	203–204
Di-L-arabinosylamine	New	$C_{10}H_{19}NO_8$	281.27	+ 50.6° (H_2O)	+14,230	145
Di-D-xylosylamine	New	$C_{10}H_{19}NO_8$	281.27	− 44.3° (H_2O)	−12,460	159–161
"β"-Di-D-glucosylamine dihydrate	f	$C_{12}H_{27}NO_{12}$	359.49	− 21.1° (H_2O)	− 7,590	106–109[h]
Di-D-mannosylamine	i	$C_{12}H_{23}NO_{10}$	341.33	− 36.8° (H_2O)	−12,560	157–158
Hexa-*O*-acetyl-di-D-xylosyl-amine	New	$C_{22}H_{31}NO_{14}$	533.48	+ 16.8° ($CHCl_3$)	+ 8,960	218–219
Octa-*O*-acetyl-di-D-mannosyl-amine	New	$C_{28}H_{39}NO_{18}$	677.60	− 68.0° ($CHCl_3$)	−46,080	146–147

[a] In some cases the specific rotations and melting points given differ somewhat from those reported in the literature cited. [b] Ref. 44. [c] Ref. 12. [d] Ref. 13. [e] Ref. 43. [f] Ref. 21. [g] Gradual decomposition from about 230°. [h] Brigl and Keppler[21] reported 125–126°. [i] Ref. 41.

Pyranosylamine. M.p. 188–189°; $[\alpha]_D^{20}$ −16.5° ($CHCl_3$, $c = 2$).

Anal. Calcd. for $C_{16}H_{23}NO_{10}$: C, 49.35; H, 5.95; N, 3.60. Found: C, 49.3; H, 5.9; N, 3.6.

N-Acetyl-β-D-mannopyranosylamine monohydrate. *N*-Acetyl-tetra-*O*-acetyl-β-D-mannopyranosylamine (10 g.) was dissolved in 100 ml. of anhydrous methanol containing 10 ml. of 0.2*M* barium methylate. After the solution had stood for 1 hr. at room temperature, dilute sulfuric acid, exactly equivalent to the barium methylate, was added. The barium sulfate was removed by filtration and the filtrate was concentrated under reduced pressure to a sirup from which *N*-acetyl-β-D-mannopyranosylamine was separated by crystallization. The crude product weighed 6 g. and had a specific rotation of −44.9° in water. It was recrystallized several times by dissolving in 2 parts of warm water, and adding 12 parts of methanol and 3 parts of ethanol. The properties of the new *N*-acetyl-β-D-mannopyranosylamine were not altered by further recrystallization. M.p. 203–204°; $[\alpha]_D^{20}$ −47.4° (H_2O, $c = 2$).

Anal. Calcd. for $C_8H_{15}NO_6.H_2O$: C, 40.16; H, 7.16; N, 5.86. Found: C, 40.2; H, 7.2; N, 5.8.

Di-D-mannosylamine and octa-O-acetyl-di-D-mannosylamine. A sample of the new D-mannosylamine hydrate, when recrystallized after long storage over phosphorus pentoxide, was found to have been converted to the previously known di-D-mannosylamine.[41] The latter substance was also prepared by heating crude D-mannosylamine hydrate in methanol. The material was recrystallized several times from 1 part of aqueous ammonia by the addition of 5 parts of methanol. M.p. 157–158°; $[\alpha]_D^{20}$ −36.8° (5 min.) (H_2O, $c = 5$). This value is somewhat higher than that (−28.3°) reported by Lobry de Bruyn and Van Leent.[41] When di-D-mannosylamine was hydrolyzed in a hydrochloric acid–sodium acetate buffer (*p*H 5) the optical rotation, $[\alpha]_D^{20}$, reached a constant value of +13.8°, based on the weight of the D-mannose formed. This is in approximate agreement with the accepted value for D-mannose (+14.2°).

Di-D-mannosylamine (4.0 g.) was acetylated in a mixture of 60 ml. of pyridine and 30 ml. of acetic anhydride by the

TABLE II

MUTAROTATION AND HYDROLYSIS OF GLYCOSYLAMINES[a]

Composition of Solvent	pH	Optical Rotation: First reading Time (min.)	Optical Rotation: First reading $[\alpha]_D^{20}$	Optical Rotation: Last reading Time (min.)	Optical Rotation: Last reading $[\alpha]_D^{20}$	pH of Mixture	$k_{hydrol.}$[b]
β-D-Glucosylamine							
Concd. NH_4OH + water (1:9)	11.4	4.0	+20.9°	4,320	+23.9°[c]	11.6	0.00001
Water (CO_2 free)	7.0	3.0	+20.8°	5,760	+23.0°[c]	10.0	0.00002
1*M* KH_2PO_4 + 1*N* NaOH (5:1)	5.9	6.4	+23.8°	1,440	+51.1°	6.4	0.0017
1*N* Acetic acid + 0.4*N* NaOH (1:1)	4.3	4.8	+24.7°	300	+52.8°	4.8	0.0081
1*N* Acetic acid + 0.2*N* NaOH (1:1)	4.0	4.4	+23.0°	300	+52.7°	4.4	0.0080
1*N* Acetic acid	2.2	3.7	+22.2°	1,400	+52.8°	3.7	0.0032
2.5*N* HCl	—	—	+20.6°	7,200	+22.7°[c]	—	0.00001
β-D-Mannosylamine							
Concd. NH_4OH + water (1:9)	11.4	2.0	−11.7°	1,110	− 9.7°[c]	11.4	0.00003
Water (CO_2 free)	7.0	4.0	−11.6°	1,140	−10.7°[c]	10.5	0.00002
1*M* KH_2PO_4 + 1*N* NaOH (5:1)	5.9	2.3	− 5.1°	36	+ 9.0°[c]	6.3	0.040
1*N* Acetic acid + 0.4*N* NaOH (1:1)	4.3	2.1	− 0.7°	30	+12.4°	4.9	0.060
1*N* Acetic acid + 0.2*N* NaOH (1:1)	4.0	2.0	+ 0.8°	160	+12.4°	4.6	0.032
1*N* Acetic acid	2.2	2.2	− 2.5°	1,180	+12.5°	4.3	0.025
2.5*N* HCl	—	9.0	− 2.9°	1,180	− 2.4°[c]	—	0.00001
β-D-Xylosylamine							
Concd. NH_4OH + water (1:9)	11.4	3.4	−19.5°	15,840	− 8.7°[c]	11.6	0.00004
Water (CO_2 free)	7.0	1.9	−19.6°	5,760	−10.5°[c]	10.0	0.00003
1*M* KH_2PO_4 + 1*N* NaOH (5:1)	5.9	1.9	− 1.3°	240	+18.0°	6.4	0.020
1*N* Acetic acid + 0.4*N* NaOH (1:1)	4.3	1.6	− 6.0°	40	+19.0°	4.8	0.112
1*N* Acetic acid + 0.2*N* NaOH (1:1)	4.0	1.5	− 7.9°	60	+18.9°	4.5	0.110
1*N* Acetic acid	2.2	1.9	− 9.9°	180	+19.1°	3.7	0.070
2.5*N* HCl	—	4.0	−17.6°	7,200	−11.8°[c]	—	0.00001

[a] The glycosylamine (0.5 g.) was dissolved in a sufficient quantity of the solvent to give a volume of 25 ml. [b] The rate constant was calculated from a series of readings taken between the first and last readings given. The following equation was used:

$$k_{hydrol.} = \frac{1}{t_2 - t_1} \log \frac{r_{t_1} - r_\infty}{r_{t_2} - r_\infty}$$

where t_2 and t_1 are points in time after a steady state has been obtained for the modifications of the amine in solution, r_{t_1} and r_{t_2} are the optical rotations observed at times t_1 and t_2, respectively, and r_∞ is the optical rotation of the solution after hydrolysis was complete. [c] When the hydrolysis reaction was not complete at the last reading, the optical rotation for the completely hydrolyzed material was used in the calculation.

TABLE III

CALCULATED AND OBSERVED OPTICAL ROTATIONS OF THE GLYCOSYLAMINES

Structure	Glycosylamine: Observed values $[\alpha]_D^{20}$	Glycosylamine: Observed values [M]	Glycosylamine: Calculated value[a] [M]	Sugar: Observed values[b] $[\alpha]_D^{20}$	Sugar: Observed values[b] [M]	2B
α-L-Arabinopyranose	+ 86.3°	+12,870	+12,200	+ 77.0°[c]	+11,560	+40,170
β-D-Xylopyranose	− 19.6°	− 2,920	− 2,360	− 20°	− 3,060	+11,050
α-D-Galactopyranose	+151°[d]	+27,080	+26,210	+150.7°	+27,150	+36,660
β-D-Galactopyranose	+ 62.2°	+11,140	+10,450	+ 52.8°	+ 9,510	+36,660
β-D-Glucopyranose	+ 20.8°	+ 3,730	+ 3,910	+ 18.7°	+ 3,370	+23,580
β-D-Mannopyranose	− 12.8°[e]	− 2,290	− 2,860	− 17.0°	− 3,060	—

[a] Molecular rotation M = B ± A, where A (obtained from the anomeric galactosylamines) is +7,880, and B is assumed to be the same as for the corresponding sugar. [b] Values are from Table 55 of Ref. 39b except the indirect value for β-D-xylose; for this, see C. S. Hudson and E. Yanovsky, *J. Am. Chem. Soc.*, **39**, 1013 (1917). [c] α-L-Arabinose crystallizes as a calcium chloride complex $C_5H_{10}O_5.CaCl_2.4H_2O$. The optical rotation is given on the basis of the sugar only. [d] α-D-Galactopyranosylamine crystallizes as a complex with one molecule of ammonia. The optical rotation is given here on the ammonia-free basis. See also Table I. [e] β-D-Mannopyranosylamine crystallizes with one molecule of water. The optical rotation is given here on the water-free basis. See also Table I.

procedure previously described. The crude crystalline product (4.1 g.), on repeated crystallization from hot ethanol, yielded 3.5 g. of a new octa-*O*-acetyl-di-D-mannosylamine. M.p. 146–147°; $[\alpha]_D^{20}$ −68.0° ($CHCl_3$, *c* = 2).

Anal. Calcd. for $C_{28}H_{39}NO_{18}$: C, 49.63; H, 5.80; N, 2.07. Found: C, 49.8; H, 5.9; N, 2.0.

β-D-Glucopyranosylamine. D-Glucose (40 g.) was converted to D-glucosylamine by the procedure described for the preparation of β-D-mannosylamine. The product was

TABLE IV

PERIODATE OXIDATION OF *N*-ACETYLGLYCOSYLAMINES

Reaction Time (min.)	Optical Rotation[a] $[\alpha]_D^{20}$	Moles Periodate per Mole Amine
N-Acetyl-β-D-glucosylamine		
2.8	−52.2°	—
15.9	−89.3°	—
30.	−94.8°	2.05
60.	−95.6°	2.06
N-Acetyl-β-D-mannosylamine		
2.5	−90.°	—
20.	−101.°	—
60.	−99.9°	2.05
120.	−98.9°	2.06
N-Acetyl-β-D-xylosylamine		
2.5	−16.2°	—
20.6	−43.6°	1.93
60.	−44.4°	2.03
120.	−39.3°	2.05

[a] The *N*-acetylglycosylamine (1 g.) was dissolved in sufficient 0.3*M* sodium metaperiodate to give a volume of 50 ml.; the solution was read in a 2-dm. tube, and $[\alpha]_D^{20}$ was based on the weight of the original *N*-acetylglycosylamine.

recrystallized from an equal weight of a 1:10 mixture of concentrated ammonium hydroxide and water, by the successive addition of 2 volumes of methanol and 2 volumes of ethanol. The yield was 25 g. The properties of the compound, given in Table I, are in substantial agreement with those previously described.[42]

N-Acetyl-tetra-O-acetyl-β-D-glucopyranosylamine. β-D-Glucopyranosylamine was acetylated by the method described above. The crude product was recrystallized from ethanol, and then from chloroform with the addition of heptane. M.p. 163–164°; $[\alpha]_D^{20}$ +17.4° ($CHCl_3$, $c = 2$) in substantial agreement with the values of Niemann and Hays.[38]

N-Acetyl-β-D-glucopyranosylamine. N-Acetyl-tetra-*O*-acetyl-β-D-glucopyranosylamine was *O*-deacetylated with barium methylate, and the crude crystalline product was recrystallized several times from aqueous acetone. Brigl and Keppler[21] reported a mutarotation from −22° to −23° in the course of 5 hr. Our product failed to show this mutarotation, but had a constant specific rotation (−22.8°) in substantial agreement with the final value previously reported.

β-Di-D-glucosylamine. This compound was prepared by the method of Sjollema[43] as described fully by Brigl and Keppler.[21] After recrystallization of the material from a concentrated water solution, by the addition of methanol, $[\alpha]_D^{20}$ was −21.1° (H_2O, $c = 2$). This value is in approximate agreement with that previously reported, but the melting point (106–109°) is considerably lower than that of Brigl and Keppler (125–126°). The compound will be investigated further.

β-D-Xylopyranosylamine and N-acetyltri-O-acetyl-β-D-xylopyranosylamine. D-Xylosylamine, previously reported by Lobry de Bruyn and Van Leent,[44] was prepared from D-xylose, and purified by the procedure described for D-mannosylamine. The specific rotation, $[\alpha]_D^{20}$, of the pure β-D-xylosylamine (−19.6°, 2 min., H_2O, $c = 2$) is somewhat higher than that previously reported (−18.1°). Acetylation of 10 g. of this material by the procedure previously described yielded 1.4 g. of silky needles, $[\alpha]_D^{20}$ +13.7°, which proved to be the new hexa-*O*-acetyl-di-D-xylosylamine described in a later paragraph. From the mother liquors, 12 g. of prismatic crystals were obtained, which, after several recrystallizations from chloroform with the addition of petroleum ether, gave a pure new *N*-acetyl-tri-*O*-acetyl-β-D-xylopyranosylamine. M.p. 172–173°; $[\alpha]_D^{20}$ +28.5° ($CHCl_3$, $c = 2$).

Anal. Calcd. for $C_{13}H_{19}NO_8$: C, 49.21; H, 6.04; N, 4.41. Found: C, 48.9; H, 6.0; N, 4.3.

N-Acetyl-β-D-xylopyranosylamine. N-Acetyl-tri-*O*-acetyl-β-D-xylopyranosylamine (10 g.), when *O*-deacetylated by barium methylate, yielded a crude, crystalline product that weighed 5.8 g. and had a specific rotation of −0.6° in water. After several recrystallizations from water, with the addition of methanol, a pure new, *N*-acetyl-β-D-xylopyranosylamine was obtained. M.p. 213–214°; $[\alpha]_D^{20}$ −0.7° (H_2O, $c = 2$).

Anal. Calcd. for $C_7H_{13}NO_5$: C, 43.97; H, 6.85; N, 7.33. Found: C, 44.1; H, 6.9; N, 7.4.

Di-D-xylosylamine and hexa-O-acetyl-di-D-xylosylamine. D-Xylosylamine (10 g.) was refluxed in 20 ml. of methyl cellosolve until evolution of ammonia had ceased (about 1 hr.). After the straw-colored solution had stood for several hours at room temperature, 2.3 g. of crystals were separated and then recrystallized from water with the addition of methanol. In a separate experiment, di-D-xylosylamine was obtained in approximately the same yield by refluxing a solution of β-D-xylosylamine in methanol containing a small amount of phenol, as described later for the preparation of di-L-arabinosylamine. The new di-D-xylosylamine melts at 154–155°; $[\alpha]_D^{20}$ −44.3° (10 min.), −40.2° (20 min.), −38.0° (90 min.) (H_2O, $c = 1.4$).

Anal. Calcd. for $C_{10}H_{19}NO_8$: C, 42.7; H, 6.45; N, 4.98. Found: C, 43.0; H, 6.9; N, 5.0.

When di-D-xylosylamine was hydrolyzed by bubbling carbon dioxide through the solution, the specific rotation, $[\alpha]_D^{20}$, became +18.4°, based on the weight of D-xylose formed. This is in good agreement with the equilibrium value, +18.8°, for pure D-xylose.

The di-D-xylosylamine was acetylated with pyridine and acetic anhydride as previously described. The product crystallized as a mixture of long, hair-like crystals that formed gelatinous clumps, and fine needles that separated in brush-like clusters. The substances were fractionally separated by successive recrystallizations from hot ethanol and then from chloroform with the addition of petroleum ether. The hair-like product is a new hexa-*O*-acetyl-di-D-xylosylamine. M.p. 218–219°; $[\alpha]_D^{20}$ +16.8° ($CHCl_3$, $c = 2$).

Anal. Calcd. for $C_{22}H_{31}NO_{14}$: C, 49.52; H, 5.86; N, 2.63. Found: C, 49.6; H, 5.8; N, 2.7.

The second product has not yet been identified.

Di-L-arabinosylamine. A mixture consisting of 5 g. of β-L-arabinopyranosylamine,[12,44] 25 ml. of methanol, and 1 ml. of phenol was heated and stirred under a reflux condenser. When the evolution of ammonia had subsided (about 1 hr.), the mixture was cooled to room temperature and set aside for crystallization. Two types of crystals formed, bipyramids and needles. By repeated recrystallization of the crude product from aqueous ammonia, with the addition of methanol, 3.1 g. of the pure bipyramid product, a new di-L-arabinosylamine, was obtained. M.p. 145° (dec.); $[\alpha]_D^{20}$ +50.6° (H_2O, $c = 1.6$).

Anal. Calcd. for $C_{10}H_{19}NO_8$: C, 42.70; H, 6.45; N, 4.98. Found: C, 42.3; H, 6.9; N, 4.9.

On treatment of di-L-arabinosylamine with 0.1*N* hydrochloric acid, the specific rotation, $[\alpha]_D^{20}$ ($c = 2$), of the substance reached a maximum of +94.2° in 6 min., decreased to +90.4° in 21 min., and finally increased to +109.3° in 60 hr. It seems probable that the initial rapid change arises from establishment of an equilibrium state for the di-L-arabinopyranosylamine; the decrease in rotation results

(42) C. A. Lobry de Bruyn, *Rec. trav. chim.*, 14, 98 (1895).

(43) B. Sjollema, *Rec. trav. chim.*, 18, 292 (1899).

(44) C. A. Lobry de Bruyn and F. H. Van Leent, *Rec. trav. chim.*, 14, 134 (1895).

from cleavage of the diglycosylamine, thus forming L-arabinosylamine and L-arabinose; and the final slow increase indicates hydrolysis of L-arabinosylamine to L-arabinose.

The substance that separated in needle-like crystals has not yet been isolated in the pure state.

Amadori rearrangement of D-*glucopyranosylamine in acetic acid.* β-D-Glucopyranosylamine (0.5 g.) was dissolved in 10 ml. of glacial acetic acid and the solution was kept at 20°. The optical rotation, $[\alpha]_D^{20}$, changed from a positive value to −18° in 1 hr. and −65° in 18 hr.; the solution had then become amber-colored. The acetic acid was removed by the repeated addition of toluene and evaporation in a rotary vacuum still. The residue, containing a small amount of acetic acid, was dissolved in 10 ml. of water, and the solution, after standing for several hours for hydrolysis to take place, was again concentrated; this treatment caused decomposition of any remaining D-glucosylamine. The residue was dissolved in 10 ml. of water and passed through a column containing 20 ml. of cation exchange resin (Amberlite IR120-H. Rohm & Haas Co., Philadelphia, Pa.); the resin was then washed with water and the wash liquor discarded. The basic materials held on the resin were eluted with 20 ml. of *N* hydrochloric acid. The eluate and wash liquor were combined, concentrated and then adjusted to a volume of 10 ml. The specific rotation, $[\alpha]_D^{20}$, was −58° on the basis of the original D-glucosylamine. Production of the stable basic substance having a levorotation indicates the presence of 1-amino-1-deoxy-D-fructose. The material is being investigated further.

Amadori rearrangement by a modification of the Hodge and Rist method. D-Glucosylamine (0.2 g.) was dissolved in 5 ml. of dimethylsulfoxide[45] and 5 ml. of diethyl malonate was added. The mixture was heated for 90 min. at 80° and kept at room temperature overnight. The brown solution was diluted with water and allowed to stand for several hours to effect hydrolysis of the remaining D-glycosylamines. The solution was then extracted several times with chloroform, and the aqueous portion was filtered through decolorizing carbon, concentrated in a rotary still, and adjusted to a volume of 10 ml. The optical rotation, $[\alpha]_D^{20}$, was −43.5°, based on the weight of the original D-glucosylamine. The levorotatory product, presumably containing 1-amino-1-deoxy-D-fructose, is being studied further.

WASHINGTON 25, D. C.

(45) Dimethyl sulfoxide has been found to be an exceptionally useful solvent for glycosylamines.

[CONTRIBUTION FROM THE LABORATORY OF ORGANIC ELECTROCHEMISTRY, DEPARTMENT OF CHEMICAL ENGINEERING, TOKYO INSTITUTE OF TECHNOLOGY]

Guanidination of D-Glucosamine*

KEIJIRO ODO, KENTARO KONO, AND KIICHIRO SUGINO

Received October 22, 1957

Since 1942, quantitative studies on the preparation of several naturally occurring guanidine compounds have been carried out and reported by K. Sugino, K. Odo, and their collaborators.

Both the *S*-methylisothiourea method and improved cyanamide condensation methods were applied for this purpose. The latter involves the following two methods which were newly established by the same authors as the result of researches made on the mechanism of the guanidination of amines with cyanamide. (1) The reaction of amine salt with cyanamide in the fused state.[1,2] (2) The reaction of an amine salt with cyanamide in aqueous solution in the presence of a small amount of free amine.[3]

As of this writing, quantitative studies on the preparation of diguanidines [ethylene-,[2] tetramethylene-(arcain),[2] hexamethylene-,[4] decamethylene-[4]], aminoalkyleneguanidine (agmatine),[5] guanidino amino acid or diguanidino acid [arginine and diguanidino valerianic acid,[6] homoarginine and diguanidino caproic acid[7]), and creatine[8] were completed successfully using one of these methods selectively. The detailed description of each special procedure suitable to each compound has been given in the preceding papers.

In the present work, the synthesis of 2-deoxy-2-guanidino-D-glucose from D-glucosamine has been studied. In regard to this problem, only one paper which turned out to be erroneous has been reported.[9]

Among the three methods of guanidine preparation described above, the cyanamide condensation in the fused state appeared to be out of the question in view of the thermal stability of D-glucosamine. Therefore, the *S*-methylisothiourea method and the cyanamide condensation in aqueous solution were both tried. The condensations of D-glucosamine with S-methylisothiourea were unsuccessful. Instead of a guanidino compound, a resinous product was obtained due to the effect of alkali on D-glucos-

* Cyanamide Derivatives, XLVII.

(1) K. Sugino, *J. Chem. Soc. Japan*, **60**, 421 (1939).

(2) K. Sugino, K. Shirai, and K. Aoyagi, *Bull. Chem. Soc. Japan*, **17**, 126 (1942).

(3) K. Odo, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **71**, 394 (1950).

(4) K. Odo and K. Sugino, *J. Chem. Soc. Japan*, **63**, 336 (1942).

(5) K. Odo, *J. Chem. Soc. Japan*, **67**, 132 (1946).

(6) K. Odo, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **74**, 1, 774 (1953).

(7) K. Odo and E. Ichikawa, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **76**, 228 (1955).

(8) K. Odo and E. Ichikawa, *J. Chem. Soc. Japan, Pure Chem. Sect.*, **77**, 1413 (1956).

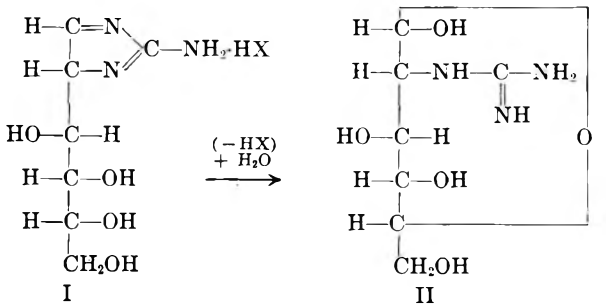
(9) J. Miller, *J. Chem. Soc.*, 2722 (1949).

TABLE I

Run No.	D-Glucosamine HCl, G.	Cyanamide, G.	NaOH Solution N	NaOH Solution Cc.	Water, Cc.	pH	Temp., °C.	Time, Hr.	Yield of I Picrate G.	Yield of I Picrate %	Cyanamide Unconverted, %
1	5.40	2.30	5.6	4.46	15	...	30	72	0	0	0
2	4.30	0.90	...	...	16	...	30	792	0.30	3.5	86
3	21.50	4.50	...	...	60	...	80	5	5.50	12.7	44
4	21.50	4.50	1.0	6.00	54	5.8	80	5	7.90	18.3	54
5	5.40	2.47	5.6	0.75	15	8.3	60	5	2.95	27.3	Trace
6	5.40	1.71	5.6	0.55	20	7.0	60	7	4.10	38.0	0

amine. The reaction of cyanamide with D-glucosamine, therefore, was the only method remaining for this purpose. Fortunately, after many trials, it was found that this condensation occurred most effectively when an aqueous solution of D-glucosamine hydrochloride was treated with cyanamide at *p*H 7 at 60° until the cyanamide disappeared. The condensation product was isolated first as the picrate, which was then converted to the hydrochloride and the nitrate. The analytical values of these salts coincided with the formula $C_7H_{13}O_4N_3 \cdot HX$. The aqueous solution of these salts showed the following characteristic properties. (1) It gave a very weak Sakaguchi's test[10] for guanidine compound. However, after treating with an equivalent amount of alkali, the solution turned to give the distinct positive test indicating the presence of guanidine group. (2) It reduced Fehling's solution when it was heated with the latter as usual.

These facts indicate that these salts may have structure I in the crystalline state but change to formula II when their aqueous solution is treated with alkali to form a free base.



I II

From these results, the compound was characterized as 2-amino-D-*arabino*-tetrahydroxybutyl-4-isoimidazole (I), anhydro-2-guanidino-D-glucose.

In order to ascertain the optimum conditions for this reaction, a set of experiments was made in which the amount of water, alkali, temperature, and time were varied. The results are shown in Table I.

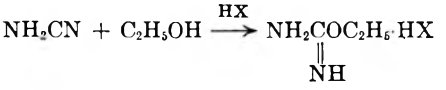
In run 1, when free D-glucosamine was used, condensation did not proceed at all. This is unusual in the reactions of amines with cyanamide and may be due to the instability of D-glucosamine in alkaline medium.

In runs 2–3, when an aqueous solution of D-glucosamine hydrochloride was used, condensation occurred to some extent even below 60°. This is also an exceptional phenomenon for this kind of reaction and may be explained by the existence of free amino groups[3] due to hydrolysis of the hydrochloride.

In runs 4–6, when the solution of D-glucosamine hydrochloride was neutralized with alkali so as to keep the *p*H at 6–8, condensation proceeded at an increased rate. At *p*H 7, a maximum yield of 38% was obtained.

It was noticed that increased alkalinity or high temperature have a tendency to cause resinification.

In 1949, J. Miller[9] carried out the same reaction, in which D-glucosamine hydrochloride was treated with cyanamide in 60% aqueous-ethanolic solution by boiling it for several hours. After the reaction, a picrate was obtained by adding an ethanolic solution of picric acid to the resulting solution. This picrate melted at 189–190° and was identified as *N'*-D-glucosylbiguanide monopicrate, based solely on the results of elemental analysis. In order to confirm this result and to clarify the difference between Miller's and our results, the authors carried out the same experiment, following precisely the description in his paper. A picrate which had almost the same melting point as that obtained by Miller was obtained. However, it was found that the picrate thus obtained was not *N'*-D-glucosylbiguanide monopicrate, but *O*-ethylisourea picrate by comparing it with an authentic sample. It may be formed by the following reaction.



It is well known that this reaction proceeds well in the presence of acid at elevated temperature. *O*-ethylisourea picrate has almost the same elemental composition (C, 34.1; H, 3.50; N, 22.1) as *N'*-D-glucosylbiguanide picrate (C, 34.2; H, 4.1; N, 22.8). It is supposed, therefore, that Miller's result was erroneous and that he did not obtain a definite condensation product of D-glucosamine with cyanamide.

Two other picrates were also obtained in this experiment, one of which melted at 180° and was the picrate of I though the yield was very poor. Neither was reported by Miller.

(10) S. Sakaguchi, *J. Biochem. Tokyo*, **5**, 25, 133 (1925).

EXPERIMENTAL

Preparation of 2-amino-D-arabino-tetrahydroxybutyl-4-isoimidazole (I) *picrate.* A 5.40-g. sample of D-glucosamine hydrochloride (Anal. Calcd. for $C_6H_{14}O_5NCl$: N, 6.49, Found: N, 6.50) and 1.71 g. of cyanamide (purity 95%) were dissolved in 20 ml. of water and the *p*H was adjusted to 7 by adding 0.55 cc. of 5.6*N* NaOH. The solution was stirred and heated with reflux at about 60° for 7 hr., until the cyanamide disappeared. After the reaction, a methanolic solution of picric acid (11.5 g./150 cc.) was added to the reaction mixture.[11] After leaving it for two days, the precipitate was filtered and recrystallized from water as long needles, m.p. 180°. A further crop of the same picrate was collected from each filtrate. The total yield was 4.10 g. The compound was slightly soluble in cold water, soluble in hot water, slightly soluble in methanol.

Anal. Calcd. for $C_{13}H_{16}O_{11}N_6$: C, 36.1; H, 3.73; N, 19.4. Found: C, 36.6; H, 3.93; N, 19.1.

Preparation of the hydrochloride, the nitrate, and the sulfate of I. Crude sirup of the hydrochloride was prepared by treating 4.40 g. of the picrate dissolved in 100 cc. water with 30 cc. of 10% HCl and working up as usual. A small amount of ethanol was added to the resulting sirup and the mixture was allowed to stand in an ice box to obtain crude crystals which melted at 173°. The yield was 2.20 g. This was again dissolved in a small amount of water, decolorized, and concentrated, and a small amount of ethanol was added to it for crystallization. The product was finally purified by washing with ethanol to give 2.0 g. of pure hydrochloride in the form of white needles, m.p. 178° $[\alpha]_D^{12.5}$ (C, 2.392, water), −26.49. The compound was very soluble in water, very slightly soluble in methanol and ethanol, insoluble in ether.

Anal. Calcd. for $C_7H_{14}O_4N_3Cl$: C, 35.1; H, 5.89; N, 17.5; Cl, 14.8. Found: C, 35.3; H, 6.19; N, 17.4; Cl, 14.5.

Crude sirup of the nitrate was prepared by treating 4.50 g. of the picrate dissolved in 100 cc. water with 25 cc. of 10% nitric acid. In the resulting sirup, a small amount of ethanol was added to form a clear solution. After adding enough ether to cause a white turbidity, this solution was allowed to stand in a desiccator to obtain crude crystals of nitrate. Recrystallization from methanol gave 2.31 g. of pure nitrate melting at 137° $[\alpha]_D^{17.0}$ (C, 9.283, water) −29.23, very soluble in water, slightly soluble in methanol and ethanol, insoluble in ether.

The sulfate was prepared by treating 9.5 g. of the picrate dissolved in 140 cc. water with 70 cc. 10% sulfuric acid, but the attempt to crystallize it proved unsuccessful.

Sakaguchi's test (and Nessler's test) for I *and* II. A solution of 0.24 g. of I hydrochloride in 10 cc. *N* NaOH was allowed to stand for 3 hr. at room temperature. A few drops of the solution were placed in a test tube and diluted to 2 cc. with water. To it, a few drops of 0.1% α-naphthol solution in 70% ethanol and 5% aqueous sodium hypochlorite solution were added. A distinctly red color appeared which indicated a strongly positive Sakaguchi's test.

The same test was then carried out for a solution of I hydrochloride itself. A light pink color appeared, indicating a very weak Sakaguchi's test.

Neither solution gave the Nessler's test for ammonia. The former gave a black mercury precipitate, indicating the occurrence of reduction. The latter gave a white precipitate which turned gradually to black.

Reaction of D-glucosamine hydrochloride with cyanamide in aqueous ethanolic solution at high temperature (J. Miller's experiment). A 21.5-g. sample of D-glucosamine hydrochloride and 8.8 g. of cyanamide were dissolved in 250 ml. of 60% ethanol and the solution was refluxed for 5 hr. The resulting solution, after decolorizing, was concentrated to 100 ml. at reduced pressure and a solution of 46 g. of picric acid in 200 ml. of methanol was added to it, and heated once to form a clear solution and then allowed to cool in order to separate crude picrate. This picrate was collected by filtration and extracted with 200 ml. of hot water to obtain the picrate solution and the crystal residue. The latter was subjected to fractional crystallization in 200 ml. of water to yield 2.50 g. of picrate A of m.p. 186°. Concentration of the filtrate and recrystallization of the residue afforded 1.16 g. of picrate B, m.p. 192°. The picrate solution was also concentrated to give 0.66 g. of another picrate C, m.p. 180° which was recrystallized from water. The methanolic filtrate was evaporated to dryness at reduced pressure and the residue, after removing picric acid with ether, was extracted with 100 cc. methanol. The final residue was unreacted D-glucosamine hydrochloride and weighed 6.60 g. Evaporation of the methanolic solution and recrystallization of the residue gave 0.05 g. picrate C, m.p. 180°.

Anal. Picrate A. Calcd. for $C_9H_{11}O_8N_5$: C, 34.1; H, 3.50; N, 22.1. Found: C, 34.2; H, 3.52; N, 22.7. Picrate B. Calcd. for $C_8H_9O_8N_5$: C, 31.7; H, 2.99; N, 23.1. Found: C, 31.6; H, 2.88; N, 23.7.

Picrate C was, evidently, the picrate of I since it had an undepressed melting point on admixture with the authentic sample obtained by the former experiment.

These picrates were then converted to sulfates and hydrochlorides, respectively. *Hydrochloride* from picrate A, m.p. 121°. *Sulfate* from picrate A, m.p. 166°.

Anal. Calcd. for $C_5H_{18}O_6N_4S$: C, 26.3; H, 6.61; N, 20.4; S, 11.7. Found: C, 26.1; H, 6.44; N, 20.7; S, 11.8.

Hydrochloride from picrate B, m.p. 127°. *Sulfate* from picrate B, m.p. 168°.

Anal. Calcd. for $C_4H_{14}O_6N_4S$: C, 19.5; H, 5.73; N, 22.8; S, 13.0. Found: C, 20.3; H, 5.96; N, 23.8; S, 13.1.

Hydrochloride from picrate C, m.p. 178°.

The hydrochlorides and the sulfates derived from picrate A and B were identified as those of *O*-ethylisourea and *O*-methylisourea based on the melting point and the elemental analysis. They were also confirmed by reacting them with methylamine hydrochloride to give methylguanidine picrate. M.p. 198–200°.

The hydrochloride from picrate C was identical with that obtained by the former experiment.

Acknowledgment. The authors wish to express their appreciation to Prof. W. L. Wolfrom of Ohio State University for the nomenclature of *anhydro*-2-guanidino-D-glucose. Our gratitude also goes to Prof. Kimiko Anno of Ochanomizu Women's University for help to one of the authors (K.S.). Microanalyses for C and H were carried out in the research laboratory of Shionogi Pharmaceutical Co. at Osaka by Dr. H. Hirayama and staff. Our thanks are also due to them.

OOKAYAMA, MEGURO-KU, TOKYO, JAPAN

(11) It was noticed that *O*-methylisourea picrate was obtained together with the picrate of I when unreacted cyanamide remained in the solution as in runs 2, 3, 4, and 5 in Table 1. In these cases, it was necessary to separate the two picrates.

[CONTRIBUTION FROM THE INSTITUTE OF ORGANIC CHEMISTRY, THE UNIVERSITY OF CHICAGO]

Structure of Peroxides Derived from Cyclohexanone and Hydrogen Peroxide[1]

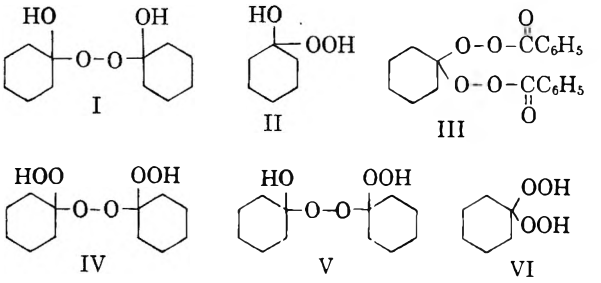
M. S. KHARASCH[2] AND GEORGE SOSNOVSKY

Received February 26, 1958

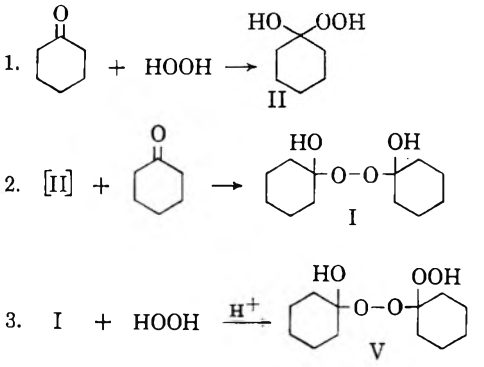
Cyclohexanone and aqueous hydrogen peroxide react in the absence of a mineral acid catalyst to form 1,1′-dihydroxydicyclohexyl peroxide (I). In the presence of traces of mineral acids, however, the only product is 1-hydroxy-1′ hydroperoxydicyclohexyl peroxide (V). Since I can be converted to V by the action of hydrogen peroxide and traces of mineral acids, I appears to be an intermediate in the formation of V. That 1-hydroxy-1-hydroperoxycyclohexane (II) is also an intermediate in these reactions is suggested by the fact that the 2-chloro and 2-bromo analogs of II certainly are products of the reactions between hydrogen peroxide with the corresponding 2-halocyclohexanones. The decompositions of I and V by ferrous ion have been reinvestigated. Several related peroxides have been prepared, and their infrared spectra recorded.

A number of investigators have described the reaction of cyclohexanone with hydrogen peroxide. In 1930 Stoll and Scherrer[3] reported that cyclohexanone and aqueous hydrogen peroxide reacted to form 1,1′-dihydroxydicyclohexyl peroxide (I). The same starting materials in the presence of mineral acid gave a mixture which they believed to consist of I and 1-hydroxy-1-hydroperoxycyclohexane (II). Milas and his co-workers,[4,5] using anhydrous ethereal solutions of cyclohexanone and hydrogen peroxide in the molar ratios of 2:1 and 1:1, obtained two products to which Structures I and II were assigned. Criegee,[6] re-examining this last work, found that, although I reacted with benzoyl chloride (in pyridine) to form benzoyl peroxide, compound II formed III. Oxidation of either I or II with concentrated hydrogen peroxide (84%) gave IV. Guided by these results, as well as by molecular weight determinations and analyses, Criegee concluded that compound I has the indicated structure. For the other product, however, he proposed structure V instead of structure II. More recently, Roedel and his co-workers[7,8] have studied the composition of the "cyclohexanone peroxides"—both the laboratory preparation and the commercial product (Lucidol). They conclude that these peroxides are a mixture of I and V with V as the major constituent. They believe that, in solution, these substances are in a complex equilibrium with their hydrolysis products, one of which is probably VI. This equilibrium product had already been suggested by Criegee[6] and by Cooper.[9]

In spite of the foregoing investigations the conditions leading to formation of either compound I or V remained uncertain; in particular neither I nor II had been established as an intermediate in the formation of V. The present investigation was undertaken in an attempt to settle these questions.



When cyclohexanone is treated with acid-free, aqueous hydrogen peroxide, compound I is the only product, regardless of the ratio of the starting materials. The identity and purity of the products have been established by infrared and active oxygen analysis. The same starting materials in the presence of small amounts of a mineral acid give compound V as the sole product. The infrared spectrum of the crude material thus obtained is indistinguishable from that of the purified product. The following reaction scheme is proposed to account for these observations.



Although intermediate II could not be isolated, the corresponding compounds (VII) derived from 2-chloro- and 2-bromo-cyclohexanone were prepared and characterized. In either the presence or the absence of mineral acid, the 2-halocyclohexa-

(1) This investigation was supported by the Office of Naval Research, Project NR 055-319.

(2) Deceased.

(3) M. Stoll and W. Scherrer, *Helv. Chim. Acta*, **13**, 142 (1930).

(4) N. A. Milas, S. A. Harris, and P. C. Panagiotakos, *J. Am. Chem. Soc.*, 61, 2430 (1939).

(5) N. A. Milas, U. S. Patent **2,298,405** (1942).

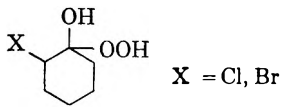
(6) R. Criegee, *Ann.*, **565**, 7, (1949).

(7) M. J. Roedel and co-workers, *J. Am. Chem. Soc.*, **77**, 1756 (1955).

(8) M. J. Roedel, U. S. Patent, **2,601,223** (1952).

(9) W. Cooper and W. H. T. Davison, *J. Chem. Soc.*, 1180 (1952).

nones react to form only the monomeric hydroxy hydroperoxides. Although these peroxides are too insoluble in benzene to allow their molecular weights to be determined, other analytical data agree well

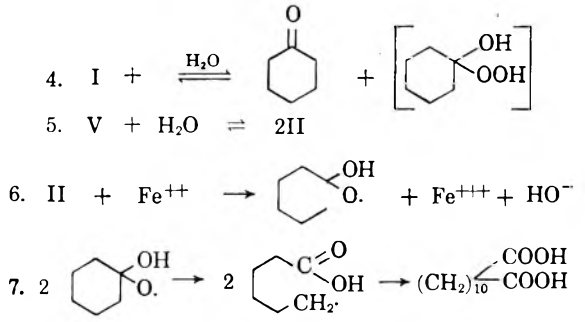


VII

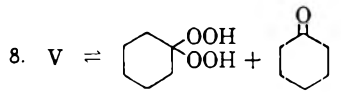
with the proposed structure. The fact that further reaction to form a dimeric peroxide does not occur may be attributed to: (1) the stabilization of VII by the α-halo substituent (analogous to the stabilization of carbonyl hydrates by electronegative α-substituents) and (2) the steric hindrance offered by the bulky halogen atoms in the dimeric structure. Molecular models suggest that the latter effect, although not large, may be significant.

A simple method for the preparation of 2-bromocyclohexanone has been developed. All previous preparations of this compound are based on the original procedure of Koetz and Grethe[10]; a slurry of cyclohexanone and calcium carbonate is treated with a stream of carbon dioxide saturated with bromine. This method can however be greatly simplified. When emulsion of cyclohexanone in water is brominated directly, a good yield of bromocyclohexanone is obtained.

The decomposition of compounds I and V by ferrous ion gave 1,12-dodecanedioic acid and cyclohexanone as major products in both cases.[11] However, the yield of acid from compound I was about half of that from compound V. To explain these results it may be assumed that compounds I and V are hydrolyzed prior to the attack by ferrous ions.



Compound V may be in an equilibrium with compound VI also, particularly, if dissociation occurs before hydrolysis:

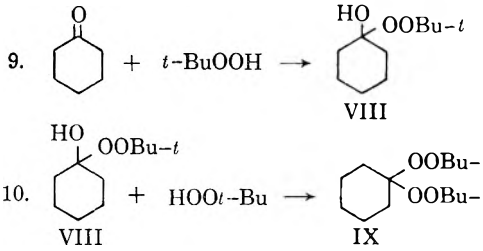


VI

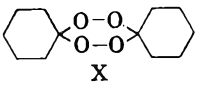
(10) A. Koetz and T. Grethe, *J. prakt. Chem.*, **80**, 473 (1909).

(11) Under similar conditions 1-hydroxy-2-chlorocyclohexyl hydroperoxide was decomposed to a dichloro-1,12-dodecanedioic acid. The position of the chlorine atoms has not yet been established with certainty.

The hypothetical *gem*-dihydroperoxide (VI) has never been isolated; Criegee, however, prepared its dibenzoyl derivative. Another derivative was prepared during the course of the present investigation. When *tert*-butyl hydroperoxide is stored with cyclohexanone or with compound I at room temperature for several months, a very explosive product is formed. On the basis of the molecular weight and infrared spectrum of this substance, structure IX is proposed for it.[12] Its formation may perhaps proceed through a hemiacetal intermediate (VIII):



Cyclohexanone peroxides when decomposed form a number of other products. Cooper[13] has shown that compound V gives 1,12-dodecanedioic acid, cyclohexanone, and hexanoic acid. Dilthey[14] isolated polymeric 6-hydroxyhexanoic acids from the products formed by the acid catalyzed decomposition of cyclohexanone peroxide. Stoll and Scherrer,[3] by treating a solution of cyclohexanone peroxide in alcohol with concentrated sulfuric acid, obtained the ester of 6-hydroxyhexanoic acid. In the present study it has been found that, in the presence of perchloric acid, V decomposes to give a mixture of high-boiling acids and dicyclohexylidene diperoxide (X).



X

The decomposition of cyclohexanone peroxides by ferrous ion gives, in addition to cyclohexanone and 1,12-dodecanedioic acid, a mixture of liquid products which appears to consist of hexanoic, hydroxyhexanoic, and polymerized hydroxyhexanoic acids. Small quantities of caprolactone were isolated from this mixture. Although the formation of these by-products in the absence of ferrous salts may be interpreted by an ionic mechanism,[15] a free radical mechanism is favored for this reaction in the presence of ferrous salts. In order to demonstrate that the liquid acids formed under the latter conditions are not derived from the acid-catalyzed decomposition of the peroxides, V was decomposed by dilute

(12) This compound was prepared by the acid-catalyzed condensation of *tert*-butyl hydroperoxide with cyclohexanone by F. H. Dicket, F. F. Rust, and W. E. Vaughan, *J. Am. Chem. Soc.*, **71**, 1432 (1949).

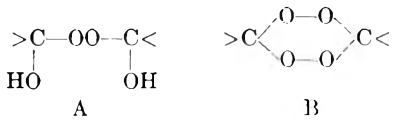
(13) W. Cocper, *J. Chem. Soc.*, 1341 (1951).

(14) W. Dilthey, M. Inckel, and H. Stephan, *J. prakt. Chem.*, **154**, 219 (1940).

(15) M. S. Kharasch and J. G. Burt, *J. Org. Chem.*, **16**, 150 (1951).

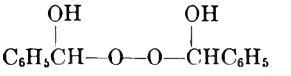
sulfuric acid at room temperature. Only cyclohexanone (75% yield) was identified.

In recent years a number of publications[16–20] dealing with the infrared spectra of various peroxides have appeared. However, as yet, very few spectra of compounds containing the groups A or B have been reported.

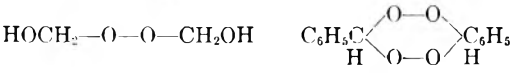


A B

In the present work, several representative compounds of these classes have been prepared and their spectra recorded. Because of the instability of these substances in solution, KBr disks were employed for the determination of their spectra. In spite of this precaution, the spectrum of bis(1-hydroxybenzyl) peroxide (XI) showed some carbonyl absorption. On account of the extreme sensitivity to heat and friction of bis(hydroxymethyl) peroxide (XII), its spectrum was determined in chloroform solution. The preparation of compounds XI and XII was reinvestigated. Benzaldehyde and 30% hydrogen peroxide gave a product (XI) melting at 86.5°; Nef's product[21] melted at 60–62°. A more detailed procedure (based on the method originally proposed by Wieland[22]) was developed for the preparation of XII.



XI



XII XIII

As other authors have found, no single infrared absorption band suitable for the identification of unknown peroxides can be chosen. However, the spectra of these substances can be used successfully to establish the identity and purity of known products. For future reference, the spectra of the more difficultly accessible peroxides are presented in Figure 1.

EXPERIMENTAL[23]

Analytical determination of ketone peroxides. Powdered sodium iodide (*ca.* 1 g.) was dissolved in glacial acetic acid (*ca.* 30 ml.) under an atmosphere of nitrogen gas. Whenever a small amount of iodine was liberated, the solution was carefully decolorized with the minimum amount of sodium thiosulfate solution. The peroxide (0.2–0.3 g.) was weighed on an analytical balance, dissolved in a minimum amount of isopropyl alcohol, and added to the iodide reagent. After a few minutes the liberated iodine was titrated with 0.1*N* sodium thiosulfate solution. This method is also applicable to the determination of hydroperoxides.

1,1′-Dihydroxydicyclohexyl peroxide (I). To stirred cyclohexanone (49 g., 0.5 mole) at room temperature, hydrogen peroxide (30%, 28 ml., 0.25 mole) was added. The mixture became slightly warm and homogeneous. After 1 hr. during which stirring was continued, an oil separated and slowly solidified. The solid (51 g., 90%) was crushed under water, collected on a filter, and thoroughly washed with water. Further purification was difficult since the compound decomposed partially during recrystallization, m.p. 69–71° (methanol-ether).

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63; active oxygen, 7.0%. Found: C, 62.50; H, 9.60; active oxygen, 6.7%.

1-Hydroxy-1′-hydroperoxydicyclohexyl peroxide (V). (*a*) *Criegee's procedure.*[6] A mixture of cyclohexanone (19.6 g., 0.2 mole) and 2*N* hydrochloric acid (2 ml.) was treated with hydrogen peroxide (30%, 22.6 ml., 0.2 mole) as described above. The crystalline mass was recrystallized from glacial acetic acid at 50–60°, washed with 50% acetic acid, and dried at 0.1 mm. Hg for 12 hr. The product (15. g., 62%) melted at 76–77°.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51, H, 9.00; molecular weight, 246; active oxygen, 13.0%. Found: C, 58.67; H, 8.85; molecular weight, 250 (cryoscopic in benzene); active oxygen, 12.7%.

(*b*) *From commercial cyclohexanone peroxide* (Luperco JDB-85). Commercial cyclohexanone peroxide (50 g.) was dissolved in methanol (500 ml.), and water (300 ml.) was immediately added to this solution. After a few minutes, crystallization commenced. The solid (27 g., 54%) was collected on a filter, washed with water (200 ml.), and dried in a vacuum desiccator over sodium hydroxide at 2 mm. Hg, m.p. 76–77°.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.51; H, 9.00. Found: C, 58.43; H, 8.70.

Infrared spectrum: identical with that of an authentic sample of 1-hydroxy-1′-hydroperoxy dicyclohexylperoxide (preparation described above).

(*c*) *From 1,1′-dihydroxydicyclohexyl peroxide* (I). 1,1′-Dihydroxy dicyclohexylperoxide (11.5 g., 0.05 mole) was mixed with 30% hydrogen peroxide (12 ml., 0.1 mole) in the presence of 2*N* hydrochloric acid (*ca.* 3 ml.). After a few minutes the slurry solidified. The product (8.5 g., 69%) was filtered and thoroughly washed with water. A small portion (1 g.) was recrystallized from a mixture of glacial acetic acid (2 ml.) and water (1 ml.), m.p. 76°.

Anal. Calcd. for $C_{12}H_{22}O_5$: C, 58.58; H, 9.00; molecular weight, 246; active oxygen, 13.0%. Found: C, 59.00; H, 9.18; molecular weight, 250; active oxygen, 13.5%.

1-Hydroxy-2-chlorocyclohexyl hydroperoxide (VII, X = Cl). A mixture of 2-chlorocyclohexanone[24] (13.1 g., 0.1 mole) and 30% hydrogen peroxide (11.3 ml., 0.1 mole) was shaken for 0.5 hr. During this period the temperature rose to about 40°. The reaction mixture became homogeneous after standing for *ca.* 12 hr. The reaction mixture was concentrated by removal of water at 2-mm. Hg pressure and room temperature. The resulting slurry was mixed with a solution of benzene in petroleum ether, and the product was collected on a filter. The white product was washed several times with a benzene–petroleum ether mixture. The combined mother liquors were concentrated and worked up in a similar manner. The solid (13.5 g., 92%) melted at 76°.

Anal. Calcd. for $C_6H_{11}O_3Cl$: C, 43.20; H, 6.62; Cl, 21.3;

(16) G. J. Minkoff, *Proc. Roy. Soc. London*, **224**, 176 (1954).

(17) R. W. Foreman and H. P. Lankelma, *J. Am. Chem. Soc.*, **79**, 409 (1957).

(18) O. D. Shreve, H. B. Knight and co-workers, *Anal. Chem.*, **23**, 282 (1951).

(19) A. R. Philpotts and W. Thain, *Anal. Chem.*, **24**, 639 (1952).

(20) M. R. Leadbeter, *Compt. rend.*, **230**, 829 (1950).

(21) J. U. Nef, *Ann.*, **298**, 292 (1898).

(22) H. Wieland and A. Wingler, *Ann.*, **431**, 301 (1923).

(23) Melting and boiling points are uncorrected.

(24) M. S. Newman, M. D. Farbman, and H. Hipsher, *Org. Syntheses*, **25**, 22 (1945).

active oxygen, 9.65%. Found: C, 42.83, H, 6.82; Cl, 21.5; active oxygen, 8.90%.

This product is practically insoluble in petroleum ether, slightly soluble in benzene, and soluble in ether or acetone. When stored at room temperature, the compound decomposed, liberating hydrochloric acid. From the resultant liquid, adipic acid was isolated, m.p. 150°; the melting point of a mixture with an authentic sample showed no depression.

2-Bromocyclohexanone. To a stirred mixture of cyclohexanone (33 g., 0.34 mole) and water (100 ml.), bromine (54 g., 0.34 mole) was added over a period of 3 hr., during which the temperature was maintained between 25 and 30° by external cooling. Stirring was then discontinued, and the heavy organic layer was separated from the aqueous layer. The aqueous layer was extracted with ether, and the ethereal extracts combined with the organic layer. The solution was dried over calcium chloride; ether was removed at reduced pressure, and 2-bromocyclohexanone (40 g., 67%) was obtained by distillation, b.p. 96–99°/18 mm.; n_D^{20} 1.5120.

1-Hydroxy-2-bromocyclohexyl hydroperoxide (VII, X = Br). A mixture of 2-bromocyclohexanone (36 g., 0.2 mole) and 30% hydrogen peroxide (25 ml., 0.2 mole) was shaken for about 1 hr. During this period the reaction mixture became warm, and when allowed to stand overnight it became homogeneous. When the walls of the vessel were scratched, a solid separated. The crystalline mass was mixed with a solution of benzene in petroleum ether and collected on a filter. The mother liquor was concentrated at reduced pressure and more of the solid was recovered. The combined white solid (30 g., 70%) was recrystallized from benzene, m.p. 82–83° (dec.).

Anal. Calcd. for $C_6H_{11}O_3Br$: C, 34.16; H, 5.22; Br, 37.95; active oxygen, 7.5%. Found: C, 34.27; H, 5.26; Br, 37.80; active oxygen, 8.4%.

1,12-Dodecanedioic acid. (a) *Decomposition of 1-hydroxy-1'-hydroperoxydicyclohexyl peroxide by ferrous ion.* A solution of ferrous sulfate heptahydrate (14 g., 0.05 mole) and concentrated sulfuric acid (1 ml.) in water (25 ml.) was added rapidly to a stirred solution of the peroxide (6.2 g., 0.025 mole) in methanol (80 ml.) under an atmosphere of nitrogen gas. The exothermic reaction was moderated by external cooling with ice water. After 0.5 hr. the reaction mixture was diluted with water (200 ml.) and acidified with sulfuric acid to *p*H 1. The mixture was then extracted with 4*N* sodium hydroxide, washed with water, and dried over sodium sulfate. After removal of ether by distillation cyclohexanone (1.25 g., 26%) was recovered: 2,4-dinitrophenyl hydrazone, m.p. 155°. The alkaline extract was acidified with sulfuric acid, and the liberated acids were taken up in ether. After removal of the ether at reduced pressure, a white solid remained; this was washed thoroughly with petroleum ether to remove liquid impurities. After recrystallization from methanol-ether, the pure acid (2.2 g., 38% yield, based on starting material) melted at 127–128°.[7]

Anal. Calcd. for $C_{12}H_{22}O_4$: C, 62.58; H, 9.63. Found: C, 62.30; H, 9.30%.

(b) *Decomposition of 1,1'-dihydroxydicyclohexyl peroxide.* The procedure described in the preceding experiment was employed. The peroxide (5.9 g., 0.025 mole) gave cyclohexanone (2.8 g., 54%) and 1,12-dodecanedioic acid (1.2 g., 20%). From the liquid portion a substance was isolated by distillation, b.p. 98–100°/2 mm.; n_D^{20} 1.4510. This substance may be caprolactone.

Anal. Calcd. for $C_6H_{10}O_2$: C, 63.13; H, 8.83. Found: C, 63.00; H, 9.26.

Dichloro-1,12-dodecanedioic acid. An aqueous solution of ferrous sulfate heptahydrate (6 g. in 15 ml. water) was rapidly added to a stirred solution of 1-hydroxy-2-chlorocyclohexyl peroxide (3.3 g., 0.02 mole) in methanol (10 ml.). The exothermic reaction was moderated by external

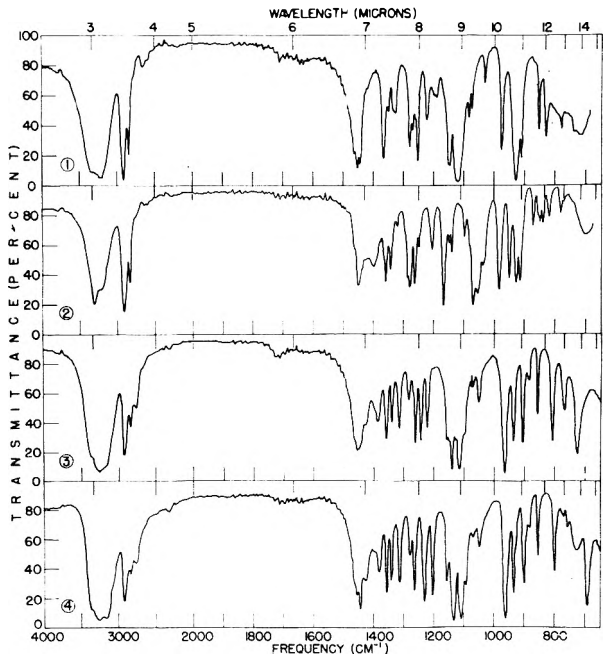


Fig. 1. Infrared absorption spectra of peroxides:
1. 1,1'-Dihydroxydicyclohexyl peroxide (KBr disk)
2. 1-Hydroxy-1'-hydroperoxy dicyclohexyl peroxide (Kbr disk)
3. 1-Hydroxy-2-chlorocyclohexyl hydroperoxide (KBr disk)
4. 1-Hydroxy-2-bromocyclohexyl hydroperoxide (KBr disk)

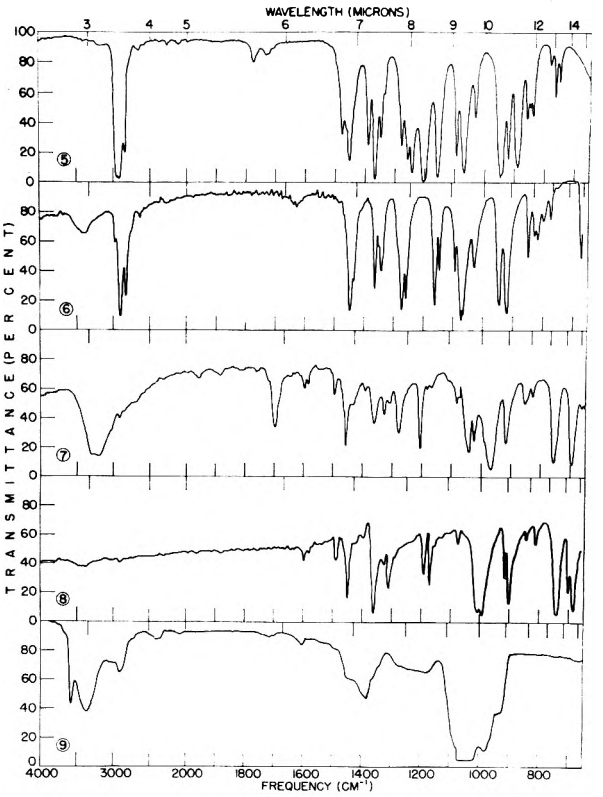


Fig. 2
5. 1,1-Di-*tert*-butylperoxy cyclohexane (pure liquid)
6. Dicyclohexylidene diperoxide (KBr disk)
7. Bis(1-hydroxybenzyl) peroxide (KBr disk)
8. Dibenzaldiperoxide (KBr disk)
9. Bis(hydroxymethyl)peroxide (1% $CHCl_3$ solution, 1-mm. cell)

cooling with ice water. A solid phase (ferric salt of the organic acid) separated from the reaction mixture. After decantation of the liquid, this solid mass was moistened with methanol, and sulfuric acid was added to liberate the organic acid. The acidic solution was extracted with ether and the ether layer, in turn, was extracted with 2*N* sodium hydroxide. The alkaline extract was acidified and the crude acid (1.9 g.) was collected on a filter, washed thoroughly with petroleum ether, and recrystallized from a mixture of methanol and ether, m.p. 117–118°.

Anal. Calcd. for $C_{12}H_{20}O_4Cl_2$: C, 48.20; H, 6.70; Cl, 23.42; molecular weight, 298. Found: C, 48.32; H, 6.78; Cl, 23.44; molecular weight, 295 (Rast).

Hydrolysis of compound V. Dilute sulfuric acid (20%, 60 ml.) was added to a stirred solution of V (10.2 g., 0.042 mole) in methanol (160 ml.) at room temperature. The reaction mixture was diluted with water, and saturated with sodium chloride. Cyclohexanone (6 g., 75%) was extracted with ether, b.p. 155°.

Dicyclohexylidene diperoxide (X). A 30% solution of hydrogen peroxide (28 ml., 0.25 mole) was added at room temperature to cyclohexanone (24.5 g., 0.25 mole). After 15 min., glacial acetic acid (50 ml.) was added; then a solution of perchloric acid (10%) in glacial acetic acid (3 ml.) was also added. When the reaction mixture was warmed on a steam bath, a precipitate was formed. The reaction mixture was then diluted with water, and the solid (3.9 g., 14%) was collected on a filter. The product, after recrystallization from methanol, melted at 127–128°.

Anal. calcd. for $C_{12}H_{20}O_4$: C, 63.13; H, 8.83%. Found: C, 63.4; H, 8.90%. Cyclohexanone (8.2 g.) was recovered from the aqueous reaction mixture.

Bis(1-hydroxybenzyl)peroxide (XI). Benzaldehyde (10.6 g., 0.1 mole) was mixed with hydrogen peroxide (30%, 5.7 ml., 0.05 mole). The temperature rose to about 30°, and, after a few hours, crystals separated from the reaction mixture. These crystals were collected and washed with petroleum ether. The mother liquor was treated with an additional portion of hydrogen peroxide (5.7 ml., 0.05 mole). When the mixture thus formed was allowed to stand overnight, more crystals separated. This crystalline product was collected on a filter, washed with petroleum ether, and combined with the first crop of crystals obtained (total 11 g., 90%). Since the combined product was found to decompose on standing, the sample was thoroughly washed with petroleum ether, immediately prior to analysis, m.p. 86.5° (melting point reported by Nef,[21] 60–62°).

Anal. Calcd. for $C_{14}H_{14}O_4$: C, 68.28; H, 5.73%. Found: C, 68.40; H, 5.97%.

1,1-Di-tert-butylperoxycyclohexane (IX). (a) A mixture of cyclohexanone (10 ml., *ca.* 0.1 mole) and *tert*-butyl hydroperoxide (9.1 g., 0.1 mole) was stored for about 3 months at room temperature. The reaction mixture was then distilled at reduced pressure. *In view of the highly explosive nature of this mixture every possible precaution should be taken during this entire operation. Despite precautionary measures, an attempt to analyze 7 mg. of this substance for carbon and hydrogen resulted in a violent explosion which shattered the combustion tube.* Molecular weight: Calcd. for $C_{14}H_{28}O_4$: 260. Found: 262 (cryoscopic in benzene). Infrared max.: 1390^{-1}, 1365^{-1} (*t*-butyl group); no carbonyl or hydroxy group absorption.

(*b*) *From 1,1'-dihydroxydicyclohexyl peroxide.* A mixture of 1,1'-dihydroxydicyclohexyl peroxide (5.8 g., 0.025 mole) and *tert*-butyl hydroperoxide (16 g., 0.18 mole) was stored for several months at room temperature. The reaction mixture was carefully distilled at reduced pressure. The product (5 g., b.p. 52–54°/0.15 mm., n_D^{25} 1.4395) appeared to be identical with that of the preceding experiment. This identity was confirmed by comparison of the infrared spectra.

Bis(hydroxymethyl)peroxide (XII). (*a*) *Preparation of ethereal formaldehyde solution.* A mixture of aqueous formaldehyde (38%, Merck, 100 ml.) and ether (200 ml.) was refluxed for a few minutes. The ether layer was separated and dried over sodium sulfate. For analysis the following procedure was employed: 0.1*N* sodium hydroxide solution (0.1*N*, 20 ml.) and 3% hydrogen peroxide (*ca.* 10 ml.) were added to the ethereal solution (0.5 ml.). The mixture was warmed on a steam bath until gas evolution ceased (*ca.* 30 min.). Excess sodium hydroxide was then titrated with 0.1*N* hydrochloric acid. The concentration of formaldehyde in the ethereal solution was found to be 4.3%.

(*b*) *Preparation of ethereal hydrogen peroxide solution.* 30% hydrogen peroxide (100 ml.), excess ether (200 ml.), and anhydrous sodium sulfate were mixed and thoroughly shaken in a separatory funnel. The ethereal solution was separated and its hydrogen peroxide content determined as follows: A small portion of the solution (2 ml.) was added to iodide reagent (potassium iodide, 1 g.; concentrated sulfuric acid, 30 ml.; and water, 200 ml.). The liberated iodine was titrated with a 0.1*N* sodium thiosulfate solution. The concentration of hydrogen peroxide in the ethereal solution was found to be 2%.

A mixture of the ethereal formaldehyde solution (140 ml., 0.2 mole) and the hydrogen peroxide solution (180 ml., 0.1 mole) was concentrated by removal of ether at reduced pressure. When the ether had been removed, the pressure was reduced to 0.1 mm. Hg and the mixture was maintained at room temperature for several hours to remove all traces of moisture. The resulting thick oil was chilled in Dry Ice, and the walls of the container were gently scratched. The peroxide crystallized slowly. Anhydrous ether was then added and the reaction mixture was allowed to stand at 0° for several hours. Then the crystalline product (2.5 g.) was collected by rapid filtration, washed with ice cold ether, pressed gently between filter papers, and dried for several hours at 0.1 mm. Hg, m.p. 62.5°.

Anal. Calcd. for $C_2H_6O_4$: C, 25.54; H, 6.43. Found: C, 25.69; H, 6.30%.

It should be noted that the product is sensitive to heat and friction.

Dibenzaldiperoxide (XIII). The procedure of Baeyer and Villiger[25] was followed. A sample of the product was purified for analysis by solution in chloroform, followed by precipitation with methanol, m.p. 202°.

Anal. Calcd. for $C_{14}H_{12}O_4$: C, 68.84; H, 4.95%. Found: C, 68.90; H, 5.2%.

Acknowledgment. Sincere thanks are due to Dr. T. P. Rudy and Dr. N. C. Yang for helpful discussions during the preparation of this manuscript, and to Mr. W. Saschek for microanalyses.

CHICAGO, ILL.

(25) A. Baeyer and V. Villiger, *Ber.*, **33**, 2479 (1900).

[CONTRIBUTION FROM AVERY LABORATORY, UNIVERSITY OF NEBRASKA]

Amine Adducts of β-Benzoylacrylic Acid and Its Methyl Ester. Hydrogenation Products

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Catalytic hydrogenation of the amine adducts of β-benzoylpropionic acid in glacial acetic acid employing palladium-on-charcoal produces the α-amino-γ-phenylbutyric acids while the sodium borohydride reaction of these materials in aqueous base gives either α-amino-γ-hydroxy-γ-phenylbutyric acid or the α-amino-γ-phenyl-γ-butyrolactones. Catalytic hydrogenation with palladium-on-charcoal in benzene or isopropyl ether solutions of methyl α-amino-β-benzoylpropionates led to methyl α-amino-γ-hydroxy-γ-phenylbutyrates, which react with amines to produce α-amino-γ-hydroxy-γ-phenylbutyramides.

In an earlier investigation[1] evidence was presented which supports the assignment of the α-amino-β-benzoylpropionic acid and methyl α-amino-β-benzoylpropionate structures to the amine adducts of β-benzoylacrylic acid and its methyl ester. Catalytic hydrogenation of methyl α-morpholino-β-benzoylpropionate in methanol apparently produced methyl α-morpholino-γ-hydroxy-γ-phenylbutyrate which on distillation or treatment with hydrogen chloride gave α-morpholino-γ-phenyl-γ-butyrolactone,[1] the first member of an interesting new series of lactones.[2]

Acid catalysis is often necessary to reduce a carbonyl group directly to a methylene group by catalytic hydrogenation.[3] Since it was found that the α-amino-β-benzoylpropionic acids were reasonably stable in acetic acid, several of these compounds were subjected to catalytic hydrogenation in this solvent employing palladium-on-charcoal (Pd/C) as a catalyst. In this way α-morpholinol, α-benzylamino, and α-methylamino γ-phenylbutyric acids were prepared from the corresponding α-amino-β-benzoylpropionic acids. These keto-amino acids, which were prepared by the previously reported technique,[1] were unstable in some solvents and thus were difficult to purify for analysis. On the other hand, the hydrochlorides of the α-amino-β-benzoylpropionic acids were readily obtained in analytical form. The α-morpholino-γ-phenybutyric acid, as prepared in this way, was identical with a sample obtained by treating α-bromo-γ-phenylbutyric acid with morpholine. These experiments definitely establish the structures of these amine adducts of β-benzoylacrylic acid and its methyl ester as the α-amino and not the β-amino[4] products.

α-Amino and α-morpholino-γ-phenylbutyric acids were obtained by the catalytic (Pd/C) hydrogenation of the corresponding β-benzoylpropionic acids in methanol containing dry hydrogen chloride.

The hydrogenation of methyl α-benzylamino β-benzoylpropionate in benzene containing a small amount of glacial acetic acid also produced the α-benzylamno-γ-phenylbutyric acid, while similar experiments in the absence of any acid produced the methyl α-morpholino and α-piperidino-γ-hydroxy-γ-phenylbutyrates from the corresponding α-amino-γ-ketoesters.

By analogy with the previously reported studies[1] α-dimethylamino-β-benzoylpropionate was reduced with lithium aluminum hydride to 3-dimethylamino-phenyl-1,4-butandiol which was found to be a solid with a surprisingly high melting point for an amino diol of this type.[1]

Reduction of the α-amino-β-benzoylpropionic acids with sodium borohydride in aqueous base produced either the α-amino-γ-hydroxy-γ-phenylbutyric acids or their dehydration products, the α-amino-γ-phenyl-γ-butyrolactones, which were usually isolated as the hydrochlorides. α-Piperidino-γ-hydroxy-γ-phenylbutyric acid was dehydrated to the lactone on heating under vacuum, but the corresponding α-cyclohexylamino hydroxy acid resisted all attempts to ring-close it to a lactone. Both the α-piperidino and α-cyclohexylamino-γ phenyl-γ-butyrolactones were isolated as their hydrochlorides after the hydrogenation (Pd/C) of the corresponding methyl α-amino-β-benzoylpropionates were carried out in methanol and isopropyl ether, respectively.

Methyl α-piperidino-γ-hydroxy-γ-phenylbutyrate reacted readily on heating with dimethylamine or piperidine to produce the corresponding

(1) N. H. Cromwell, P. L. Creger, and K. E. Cook, *J. Am. Chem. Soc.*, **78**, 4412 (1956).

(2) After our investigations (K. E. Cook, Ph.D. thesis, University of Nebraska, July 1957) had been completed, W. L. Meyer and W. R. Vaughan, *J. Org. Chem.*, **22**, 1560 (1957), reported that the aniline adduct of β-benzoylacrylic acid may be reduced with sodium borohydride to give α-anilino-γ-phenyl-γ-butyrolactone which was then hydrogenated to α-anilino-γ-phenylbutyric acid with palladium-on-charcoal in abs. ethanol. This latter amino acid was identical with the product from the reaction of aniline with α-bromo-γ-phenylbutyric acid.

(3) W. H. Hartung and R. Simonoff, *Org. Reactions*, **VII**, 268 (1953).

(4) The β-amino structure was tentatively proposed by P. Chabrier, *et al.*, *Compt. rend.*, **226**, 1378 (1948); **228**, 1952 (1949); **230**, 212 (1950); **232**, 2326 (1951); **233**, 1367 (1951); **234**, 2541 (1952); **237**, 66, 1420 (1953).

N,N-disubstituted α-piperidino-γ-hydroxy-γ-phenylbutyramides.

Infrared absorption spectra. The α-morpholino, α-benzylamino, and α-methylamino γ-phenylbutyric acids showed ionized COO^- bands at 1628, 1610, and 1587 cm.$^{-1}$, respectively, in their solid state infrared spectra. The latter two secondary amino acids also showed NH^+ bands between 3050 and 3100 cm.$^{-1}$ The methyl α-amino-γ-hydroxy-γ-phenylbutyrates had ester carbonyl bands between 1720 and 1730 cm.$^{-1}$ and associated OH bands from 3210 to 3462 cm.$^{-1}$. 3-Dimethylamino-1-phenyl-1,4-butandiol had a highly associated OH band at 3310 cm.$^{-1}$. The α-amino-γ-phenyl-γ-butyrolactone hydrochlorides all show lactone carbonyl bands between 1765 and 1800 cm.$^{-1}$. with the parent α-amino compound showing two such bands in this region. The *N,N*-disubstituted α-piperidino-γ-hydroxy-γ-phenylbutyramides showed amide carbonyl bands at 1610–1613 cm.$^{-1}$ and associated OH bands between 3390 and 3420 cm.$^{-1}$

EXPERIMENTAL

Methyl α-amino-β-benzoylpropionates. The procedure previously described[1] was used for the preparation of these compounds from the addition of the corresponding amines to methyl β-benzoylacrylate. The yields of the α-morpholino, α-piperidino, and α-benzylamino products ranged from 90–98%. The *methyl α-dimethylamino-β-benzoylpropionate* was obtained in 77% yield, m.p. 43–45°. This material was unstable and decomposed to dimethylamine and methyl-β-benzoylacrylate on standing in the solid form at room temperature.

α-Amino-β-benzoylpropionic acids and hydrochlorides. The previously described[1] procedures were used for the preparation of these acids. The yield of the crude parent α-amino acid[4] was 79% while those of the α-morpholino and α-piperidino acids[1] were nearly quantitative. The hydrochlorides of the various α-amino-β-benzoylpropionic acids were prepared by passing dry hydrogen chloride gas into methanol suspensions of the acid. After the solid material had dissolved the methanol was removed under reduced pressure and the residues recrystallized from methanol and ether mixtures. The yields were nearly quantitative.

α-Benzylamino-β-benzoylpropionic acid, yield 98%, m.p. 165° (dec.); *hydrochloride,* m.p. 144–146° (dec.).

Anal. Calcd. for $C_{17}H_{18}NO_3Cl$: N, 4.38. Found: N, 4.30.

α-Piperidino-β-benzoylpropionic acid hydrochloride, m.p. 202–204°.

Anal. Calcd. for $C_{15}H_{20}NO_3Cl$: N, 4.70. Found: N, 4.43.

α-Cyclohexylamino-β-benzoylpropionic acid, yield 87%, m.p. 167°; *hydrochloride,* m.p. 177–180°.

Anal. Calcd. for $C_{16}H_{22}NO_3Cl$: C, 61.63; H, 7.11; N, 4.49. Found: C, 61.79; H, 7.23; N, 4.60.

α-Methylamino-β-benzoylpropionic acid. A 10 g. sample of β-benzoylacrylic acid was dissolved in a mixture of 8 ml. of aqueous 40% methylamine and 200 ml. of water. The solution was evaporated to dryness and the residue digested with 25 ml. of cold 95% ethanol. Filtration left 7.75 g. (66% yield) of nearly colorless material, m.p. 181°; *hydrochloride,* m.p. 193–196°.

Anal. Calcd. for $C_{11}H_{14}NO_3Cl$: C, 54.21; H, 5.79; N, 5.75. Found: C, 54.29; H, 5.73; N, 5.76.

α-Dimethylamino-β-benzoylpropionic acid. Following the procedure used for the α-methylamino acid, this product was obtained in 76% yield, m.p. 140°; *hydrochloride,* m.p. 147–150°.

Anal. Calcd. for $C_{12}H_{16}NO_3Cl$: C, 55.92; H, 6.26; N, 5.44. Found: C, 55.71; H, 6.07; N, 5.43.

α-Amino-γ-phenylbutyric acids. Ten-gram samples of the various α-amino-β-benzoylpropionic acids were dissolved in 130 ml. of glacial acetic acid and shaken with 1 g. of 10% palladium-on-charcoal under 45 lbs./in.^{2} of hydrogen at room temperature for 4 to 7 hr.

α-Morpholino-γ-phenylbutyric acid, m.p. 185–187°, yield 42%, recrystallized from 95% ethanol. Infrared spectrum[5] (Nujol): ν(coo)′, 1628 cm.$^{-1}$; ν(C_6H_5), 1610 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{19}NO_3$: C, 67.44; H, 7.68; N, 5.62. Found: C, 67.53; H, 7.70; N, 5.84.

(*a*) This product was also prepared by refluxing 2.0 g. of α-bromo-γ-phenylbutyric acid[6] with 1.5 ml. of morpholine in 10 ml. of benzene for 2 hr. Morpholine hydrobromide was removed by filtration and the benzene solution concentrated to produce a 50% yield of the amino acid, m.p. 186–187°, identical with the material described above.

(*b*) Hydrogenation of α-morpholino-β-benzoylpropionic acid (5.0 g.) using 10% palladium-on-charcoal in a 100 ml. methanol solution containing excess dry hydrogen chloride produced the crude hydrochloride of α-morpholino-γ-phenylbutyric acid, m.p. 220–225°. This material was converted with aqueous sodium carbonate to the amino acid which was crystallized from aqueous ethanol; wt. 2.4 g. (51% yield); m.p. 185°.

α-Amino-γ-phenylbutyric acid. This known amino acid was obtained in a 63% yield as the hydrochloride, m.p. 152–155°, following procedure (*b*), used for α-morpholino-γ-phenylbutyric acid. This hydrochloride was converted to the amino acid, m.p. 291–293°,[7] with aqueous ammonia.

α-Benzylamino-γ-phenylbutyric acid. (*a*) Following the general procedure in glacial acetic acid this compound was obtained in 64% yield and recrystallized from glacial acetic acid, m.p. 222–224°. Infrared spectrum (hexachlorobutadiene, LiF optics): ν(N=H), 3050 cm.$^{-1}$, ν(coo-), 1610 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.20. Found: C, 75.60; H, 7.11; N, 5.72.

(*b*) A 5.0 g. sample of methyl α-benzylamino-β-benzoylpropionate[1] in 75 ml. of benzene and 1 ml. of glacial acetic acid was shaken under 40 lbs./in.^{2} of hydrogen in the presence of 1.0 g. of 10% palladium-on-charcoal for 3.5 hr. The product, which had precipitated from the solution during the hydrogenation, was recrystallized from glacial acetic acid, m.p. 223–224°; wt. 2.6 g. (57% yield). A mixed melting point determination with the product from procedure *a* showed no depression.

α-Methylamino-γ-phenylbutyric acid. Hydrogenation in glacial acetic acid produced a 56% yield of this acid, m.p. 239–241°, recrystallized from 50% ethanol. Infrared spectrum (Nujol): ν(N=H), 3100 cm.$^{-1}$; ν(CH-), 1587 cm.$^{-1}$

Anal. Calcd. for $C_{11}H_{15}NO_2$: C, 68.37; H, 7.82; N, 7.25. Found: C, 68.37; H, 8.03; N, 7.36.

Methyl α-morpholino and α-piperidino-γ-hydroxy-γ-phenylbutyrates. The methyl α-amino-β-benzoylpropionates (8 g.) were shaken under 40 lbs./in.^{2} of hydrogen in benzene (60 ml.) solution in the presence of 10% palladium-on-charcoal catalyst for 4.0 hr. The catalyst was removed by filtration and the solution concentrated under vacuum at room temperature and petroleum ether added to precipitate the products. Recrystallization from ether and petroleum ether mixtures produced analytical samples.

Methyl α-morpholino-γ-hydroxy-γ-phenylbutyrate, m.p. 64–67°, 83% yield. Infrared spectrum (Nujol): ν(OH), 3462 cm.$^{-1}$, ν(C=O), 1730 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{21}NO_4$: C, 64.49; H, 7.58; N, 5.01. Found: C, 64.68; H, 7.71; N, 5.03.

Warming this material with concd. hydrochloric acid gave

(5) All infrared spectra were determined over the range of 4000–400 cm.$^{-1}$ with a Perkin-Elmer double beam instrument, Model 21, employing NaCl optics unless otherwise indicated.

(6) C. L. Stevens and W. Holland, *J. Org. Chem.*, **18**, 1112 (1953).

(7) F. Knopp and H. Hoessli, *Ber.*, 39, 1479 (1906).

α-morpholino-γ-phenyl-γ-butyrolactone hydrochloride, m.p. 243°.

Methyl α-piperidino-γ-hydroxy-γ-phenylbutyrate, m.p. 72.5–74°, 87% yield. Infrared spectrum (Nujol): ν(OH), 3210 cm.$^{-1}$; ν(C=O), 1720 cm.$^{-1}$; ν(C_6H)$_5$, 1602 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.64; H, 8.43; N, 5.06.

This same product resulted in 85% yield when isopropyl ether was substituted for benzene as solvent in the catalytic hydrogenation.

3-Dimethylamino-1-phenyl-1,4-butanediol. A 5.0 g. sample of methyl α-dimethylamino-β-benzoylpropionate was reduced with lithium aluminum hydride by the procedure previously[1] described for analogous preparations. A 23% yield of a colorless product, slightly soluble in cold ether, but readily recrystallized from benzene was obtained, m.p. 137.5–139°. Infrared spectrum (Nujol): ν(OH), 3310 cm.$^{-1}$

Anal. Calcd. for $C_{12}H_{19}NO_2$: C, 68.86; H, 9.15; N, 6.69. Found: C, 69.32; H, 8.95; N, 6.21.

Reduction of α-amino-β-benzoylpropionic acids with sodium borohydride. A 0.019-mole amount of the α-amino-β-benzoylpropionic acid was dissolved in a solution of 0.85 g. of potassium hydroxide in 25 ml. of water. To this solution was added 0.36 g. (0.0095 mole) of sodium borohydride in one lot. After standing at room temperature for 48 hr., the solution was made acidic with concd. hydrochloric acid and evaporated to dryness on a steam bath under slight vacuum. The residue was extracted with hot 95% ethanol. Cooling of the ethanol solution produced the products described as follows.

α-Morpholino-γ-phenyl-γ-butyrolactone hydrochloride, m.p. 243°, yield 37%. Infrared spectrum (hexachlorobutadiene, LiF optics): ν(C=O), 1780 cm.$^{-1}$

Anal. Calcd. for $C_{14}H_{18}NO_3Cl$: C, 59.26; H, 6.39; N, 4.94. Found: C, 59.45; H, 6.63; N, 4.79.

α-Amino-γ-phenyl-γ-butyrolactone hydrochloride, m.p. 236°; yield, 70%; Infrared spectrum (Nujol): ν(C=O), 1800, 1786 cm.$^{-1}$

Anal. Calcd. for $C_{10}H_{12}NO_2Cl$: C, 56.21; H, 5.66; N, 6.56. Found: C, 56.17; H, 5.66; N, 6.83.

α-Benzylamino-γ-phenyl-γ-butyrolactone hydrochloride, yield 88%, m.p. 223–224° (dec.), after recrystallization from glacial acetic acid. Infrared spectrum (Nujol): ν(C=O), 1765 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{18}NO_2Cl$: C, 67.21; H, 5.97; N, 4.61. Found: C, 67.41; H, 6.08; N, 4.62.

α-Cyclohexylamino-γ-hydroxy-γ-phenylbutyric acid. A 10 g. (0.036 mole) sample of α-cyclohexylamino-β-benzoylpropionic acid and 3.2 g. of sodium bicarbonate were dissolved in 100 ml. of water and 0.7 g. (0.019 mole) of sodium borohydride added. This mixture was stirred for 3 hr. After standing for 48 hr. at room temperature the precipitated material was filtered, wt. 4.44 g., m.p. 180–210°. This crude product was recrystallized, first from glacial acetic acid and then from 95% ethanol to give colorless crystals, m.p. 236–236.5° (yield 45%). Infrared spectrum (Nujol): ν(OH/NH), 3350, 3160 cm.$^{-1}$; ν(COO^-), 1595 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{23}NO_3$: C, 69.28; H, 8.36; N, 5.05. Found: C, 69.43; H, 8.26; N, 5.38.

This γ-hydroxy-α-amino acid resisted all attempts to dehydrate it to the α-aminolactone. Heating with concd. hydrochloric acid gave no change. When a portion was heated in a solids distillation flask at 0.3-mm. pressure and 180°, material sublimed which when recrystallized from benzene had a m.p. 142–145° and showed no infrared spectrum (Nujol) bands between 1700 and 1850 cm.$^{-1}$, but a weak band at 1660 cm.$^{-1}$. This product was not investigated further.

α-Piperidino-γ-hydroxy-γ-phenylbutyric acid. A 1.0-g. (0.0038 mole) sample of α-piperidino-β-benzoylpropionic acid and 0.5 g. of sodium bicarbonate were dissolved in 20 ml. of water and 0.1 g. of sodium borohydride added. After standing at room temperature for 20 hr. the mixture was made acidic with concd. hydrochloric acid and evaporated to dryness on a steam bath under slight vacuum. The residue was extracted with hot 95% ethanol. The ethanol solution on cooling produced a 43% yield of the product, m.p. 244° (dec.). Infrared spectrum (Nujol): ν(OH), 3225 cm.$^{-1}$; ν(COO^-), 1618 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{21}NO_3$: C, 68.41; H, 8.04; N, 5.32. Found: C, 68.86; H, 8.55; N, 5.35.

α-Piperidino-γ-phenyl-γ-butyrolactone. A 1.0-g. sample of α-piperidino-γ-hydroxy-γ-phenylbutyric acid was heated to 230° at a pressure of 0.2 mm. with a flow of nitrogen gas. A small amount of material distilled over and was recrystallized from a mixture of benzene and petroleum ether, m.p. 68–69°; infrared spectrum (CCl_4): ν(C=O), 1752 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{19}NO_2$: N, 5.71. Found: N, 5.50.

α-Piperidino-γ-phenyl-γ-butyrolactone hydrochloride. A 5.0-g. (0.018 mole) sample of methyl α-piperidino-β-benzoylpropionate was dissolved in 50 ml. of methanol and shaken with 0.5 g. of 10% palladium-on-charcoal under 15 lbs./in.^{2} of hydrogen for 3 hr. The catalyst was removed by filtration and the methanol by distillation. The residue was dissolved in ether and treated with dry hydrogen chloride gas to precipitate a gummy material which was crystallized from methanol and ether mixtures; m.p. 211–215°, yield 66%. Infrared spectrum (Nujol) ν(C=O,) 1765 cm.$^{-1}$

Anal. Calcd. for $C_{15}H_{20}NO_2Cl$: C, 63.93; H, 7.15; N, 4.97. Found: C, 63.65; H, 7.21; N, 5.16.

α-Cyclohexylamino-γ-phenyl-γ-butyrolactone hydrochloride. A 9.85-g. (0.034 mole) sample of methyl α-cyclohexylamino-β-benzoylpropionate was dissolved in 75 ml. of isopropyl ether and shaken with 1.5 g. of 10% palladium-on-charcoal under 45 lbs./in.^{2} of hydrogen for 3 hr. The catalyst was removed by filtration and the solvent evaporated under reduced pressure The residue was dissolved in concd. hydrochloric acid and the solution evaporated to dryness. The residue was recrystallized from methanol to give 5.0 g. of colorless crystals, m.p. 270°. Infrared spectrum (Nujol): ν(C=O), 1774 cm.$^{-1}$

Anal. Calcd. for $C_{16}H_{22}NO_2Cl$: C, 64.96; H, 7.50; N, 4.74. Found: C, 65.03; H, 7.45; N, 4.92.

Reaction of methyl α-piperidino-γ-hydroxy-γ-phenylbutyrate with amines. A 1.0-g. sample of the hydroxyaminoester was mixed with an excess of the amine and heated (with piperidine for 4 hr. under reflux; with dimethylamine for 12 hr. at 70° in a sealed tube).

α-Piperidino-γ-hydroxy-γ-phenylbutyropiperidide, 41% yield, m.p. 106–108°, recrystallized from benzene and petroleum ether. Infrared spectrum (Nujol): ν(OH), 3420 cm.$^{-1}$; ν(C=O), 1610 cm.$^{-1}$

Anal. Calcd. for $C_{20}H_{30}N_2O_2$: C, 72.69; H, 9.15; N, 8.48. Found: C, 72.64; H, 9.10; N, 8.18.

N,N-Dimethyl-α-piperidino-γ-hydroxy-γ-phenylbutyramide, 76% yield, m.p. 105.5–106.5°, recrystallized from ether. Infrared spectrum (Nujol): ν(OH), 3390 cm.$^{-1}$; ν(C=O), 1613 cm.$^{-1}$

Anal. Calcd. for $C_{17}H_{26}N_2O_2$: C, 70.31; H, 9.02; N, 9.65. Found: C, 70.35; H, 8.93; N, 9.36.

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Schmidt Reactions in Polyphosphoric Acid. I. Rearrangement of Ketones

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A method for effecting the Schmidt transformation of ketones employing polyphosphoric acid as both the solvent and catalyst is described. Rearrangement products have been obtained in a relatively pure state and in high yield from diaryl, aryl-alkyl, and symmetrical and unsymmetrical alicyclic ketones, indicating that polyphosphoric acid may be superior to other reagents as a catalyst in the Schmidt reaction.

Since the original observation by Schmidt[1] that certain ketones were converted to the corresponding amides on treatment with hydrazoic acid in the presence of acidic dehydrating agents, extensive studies of the scope, limitations, and mechanism of this transformation have appeared. Applications of the Schmidt reaction have been important in both preparative and theoretical chemistry and many different conditions have been developed for effecting the reaction between ketones and hydrazoic acid. These matters have been adequately discussed in an excellent review by Wolfe[2] and more recently by Smith[3] in a rather detailed series of papers.

In the course of an investigation of the abnormal Beckmann rearrangement of certain disubstituted ketoximes in polyphosphoric acid,[4,5] it became of interest, as a correlative study, to investigate the similarity between the Beckmann and Schmidt reactions in this medium. As a portion of this study, it was found necessary to investigate the polyphosphoric acid catalysis on the reaction. Only two examples of Schmidt reactions of ketones in this medium have been reported. Elston[6] rearranged benzophenone to benzanilide in 80% yield at 50° in polyphosphoric acid. Recently, Arcus, Marks, and Coombs[7] reported an unsuccessful attempt to rearrange fluorenone by a method similar to the procedure reported here. The latter report, has prompted the author to report the initial results of this investigation.

It has now been found that a variety of ketones on treatment with hydrazoic acid using polyphosphoric acid as the solvent and catalyst results in the isolation of the normal amide or lactam rearrangement products in high yield. It is felt that this method has certain advantages over previously reported methods.[2] Since polyphosphoric acid is a reasonably good solvent for organic materials, the use of an organic solvent was eliminated. The amide or lactam products of the rearrangement are not subject to further reactions due to the medium[5] or the catalyst, therefore many of the tarry by-products which are often obtained using other methods are reduced.

The method employs a 15 to 20 fold excess of polyphosphoric acid to ketone. To this mixture, while agitated, small portions of sodium azide are added. The mixture is then maintained at a temperature between 25 and 75° until the evolution of nitrogen ceases. Generally, the products are isolated by standard methods. However, when the reaction products are soluble in the hydrolysis mixture, extraction methods had to be employed and the yields were slightly reduced. The ketones rearranged in this study are summarized in Table I. The yields and the experimental conditions for the rearrangements are those which were found to be the optimum in this study. Examples of typical rearrangement procedures are given in the experimental section. The rearrangement products were identified in all cases with authentic samples prepared by reported procedures. The criteria of identity were two; no depression in mixed melting point and identical infrared spectra.

The unsymmetrical alkyl substituted cyclopentanones and cyclohexanones all yielded a single rearrangement product. It was observed that the yields obtained from the rearrangement of the substituted cyclohexanones were higher than those obtained from the rearrangement of the corresponding cyclopentanones. These results agree favorably with the studies made by Shechter and Kirk[8] on these compounds using other methods and also the analogous increase in yield observed in the Beckmann rearrangement of the oximes of these ketones.[9] 2-Cyanocyclohexanone (I) on rearrangement yielded two products, 7-Cyano-2-keto-hexamethyl-

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TABLE I
SUMMARY OF SCHMIDT REACTIONS IN POLYPHOSPHORIC ACID

Ketone	Product	Yield, %	M.P., °C.	Time, Hr.	Temp., °C.
Cyclopentanone	Piperidone	83	38.5–39.5[a]	9.5	55
2-Methylcyclopentanone	6-Methylpiperidone	87	87–88[b]	12.5	50
2-Propylcyclopentanone	6-Propylpiperidone	82	91–93[c]	14.0	50
Cyclohexanone	2-Keto-hexamethylenimine	89	64–67[d]	8.5	50
2-Methylcyclohexanone	2-Keto-7-methyl-hexamethylenimine	96	90–91[e]	9.0	50
2-Propylcyclohexanone	2-Keto-7-propyl-hexamethylenimine	95	97–98[f]	8.5	50
2-Cyanocyclohexanone	7-Cyano-2-keto-hexamethylenimine	76	126–127[g]	10.0	25
	7-Carboxamido-2-keto-hexamethylenimine	8	239–241[h]		
2-Carbethoxycyclohexanone	7-Carbethoxy-2-keto-hexamethylenimine	75	96.5–98[i]	12.0	25
Cycloheptanone	2-Keto-heptamethylenimine	83	96.5–97[j]	9.0	50
1-Hydrindone	Dihydrocarbostyril	90	162–163[k]	10.0	50
1-Tetralone	Homodihydrocarbostyril	95	141–142[l]	10.0	50
Acetophenone	Acetanilide	98	113–114[m]	7.0	50
p-Methoxyacetophenone	*p*-Methoxyacetanilide	98	125–126[n]	7.5	50
Benzophenone	Benzanilide	99	160–162[o]	8.5	50
p,p'-Dimethoxybenzophenone	Anisoylanisidine	91	200–203[p]	8.5	50
Fluorenone	Phenanthridone	92	286–288[q]	22.0	70
1-Acetonaphthone	1-Acetanaphthalide	72	158–159[r]	12.0	55
2-Acetonaphthone	2-Acetanaphthalide	81	132–134[s]	12.0	55
1-Benzoylnaphthalene	1-Naphthanilide	72	161–163[t]	10.0	50
o-Benzoylbenzoic acid	*N*-Benzoylanthranilic acid	87	178–179[u]	10.0	50
Benzalacetone	*N*-Methylcinnamamide	58	110–111[v]	8.0	25
Benzylacetone	*N*-(2-phenylethyl)-acetamide	95	114–115[w]	7.5	25
Phenylacetone	*N*-Benzylacetamide	50	53–54[x]	7.5	25

[a] Ref. 12, m.p. 39–40°. [b] Ref. 8, m.p. 87.5–88.0°, Ref. 3a, m.p. 87.2–88.0°. [c] Ref. 8, m.p. 91.4–92.6°, Ref. 3a, m.p. 91.5–92.5°. [d] Ref. 12, m.p. 65–68°, Ref. 23, m.p. 68–70°. [e] Ref. 8, m.p. 90.5–91.5°, O. Wallach, *Ann.*, **346**, 252 (1906) reports m.p. 90.5–91.5°. [f] Ref. 8, m.p. 98.6–99.2°, Ref. 9c, m.p. 100.5–101.5°. [g] Ref. 8, m.p. 126.6–127.4°. [h] New compound. [i] Ref. 8, m.p. 97.2–98.0°. [j] O. Wallach, *Ann.*, **312**, 205 (1900) reports m.p. 95–96.5°. [k] Friedlander and Weinberg, *Ber.*, **15**, 1423 (1882) report m.p. 163°. [l] L. H. Briggs and G. E. De Ath, *J. Chem. Soc.*, 456 (1937) report m.p. 141°. [m] Ref. 12, m.p. 114°. [n] Ref. 12, m.p. 127°. [o] Ref. 12, m.p. 162–163°. [p] Ref. 12, m.p. 202°. [q] Ref. 25, m.p. 293°. [r] Ref. 3a, m.p. 160°. [s] C. Libermann and F. Scheiding, *Ann.*, **183**, 267 (1876) report m.p. 132°. [t] Ref. 3a, m.p. 162–163°. [u] Ref. 3a, m.p. 179°. [v] L. H. Briggs, G. C. Ath, and G. E. De Ath, *J. Chem. Soc.*, 61 (1942) report m.p. 111°. [w] Ref. 3a, m.p. 114–115°. [x] Ref. 11, m.p. 51–55°.

enimine (II) and 7-Carboxamido-2-keto-hexamethylenimine (III). These products were separated by elution chromatography over alumina. The amido-lactam III product was found to be formed by the hydration of the cyano group by the polyphosphoric acid.[10] The variation of the products of the rearrangement of 2-cyanocyclohexanone with temperature is tabulated in Table II. It was found

TABLE II
THE VARIATION OF THE PRODUCTS OF THE REARRANGEMENT OF 2-CYANOCYCLOHEXANONE WITH TEMPERATURE

Temp., °C.	Yield, %	Product (-hexamethylenimine)
25	76	7-Cyano-2-keto-
	8	7-Carboxamido-2-keto-
35	54	7-Cyano-2-keto-
	30	7-Carboxamido-2-keto-
45	37	7-Cyano-2-keto-
	45	7-Carboxamido-2-keto-
65	0	7-Cyano-2-keto-
	83	7-Carboxamido-2-keto-

that the cyano-lactam II could be quantitatively converted to the amido-lactam III by treatment

(10) See H. R. Snyder and C. T. Elston, *J. Am. Chem. Soc.*, **76**, 3039 (1954) for discussion of nitrile hydration in polyphosphoric acid.

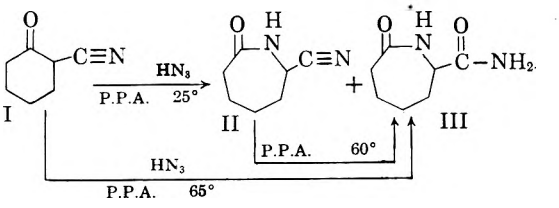

Figure 1.

with polyphosphoric acid at 60°. These transformations are shown in Figure 1. The structure of the amido-lactam was established by combustion analysis, Rast determination of the molecular weight, and by hydrolysis with 30% sulfuric acid to 2-amino-1,7-heptandioic acid.

Fluorenone, which has been observed to give no rearranged product under conditions similar to those used in this study,[7] has been found to rearrange in good yield using more strenuous conditions. A qualitative study of the temperature dependence of this reaction has indicated that the rearrangement proceeds extremely slowly below 50°. These results can be correlated to those obtained in the Beckmann rearrangement of fluorenone oxime in polyphosphoric acid,[11] in which it was observed

(11) E. C. Horning, V. L. Stromberg, and H. A. Lloyd, *J. Am. Chem. Soc.*, **74**, 5153 (1952).

that the oxime could be recovered unchanged at 120°; however at 180° an almost quantitative yield of phenanthridone was obtained. The rearrangement of benzalacetone and phenylacetone proceeded smoothly, however, in low yield. In both cases, an appreciable quantity of an intractable black tar was formed. Further work was not attempted in an effort to obtain an increased yield.

The general reaction conditions employed in this study were found to differ from those previously reported.[2] In this medium, in all the rearrangements studied, the reaction proceeds at a very slow rate. This appears to indicate that the polyphosphoric acid does not have as vigorous a catalytic effect on the reaction as the other reagents usually employed. This observation is in general agreement with the role of polyphosphoric acid in the Beckmann rearrangement.[12] While no detailed description of the mechanism can be advanced as yet, since it is possible that the catalytic role of the reagent may be through the formation of a phosphate ester type intermediate, similar to the intermediate proposed for the Beckmann rearrangement,[12] the general mechanism appears to follow the mechanism proposed for the general acid catalysis of the Schmidt reaction, involving the formation of a hydroxycarbonium ion[13] (in this case, a phosphate ester carbonium ion), followed by the addition of hydrogen azide and subsequent elimination of water (phosphate elimination), followed by electrophilic attack on the nitrogen through a Beckmann type intermediate,[3] which is the major factor governing the course of the rearrangement. This mechanism has been supported in this study as in those previously carried out by the rearrangement of diaryl, alkyl-aryl, and unsymmetrical cycloalkanones.[8] It has been shown that the amide and lactam products are stable in polyphosphoric acid;[14] therefore, the absence of hydrolysis and dehydrated species in the reaction products was not unexpected. While exceptions may possibly be found to the generality of the method reported here, our results indicate that polyphosphoric acid may be the reagent of choice for effecting this transformation.

Other special cases of the Schmidt reaction of ketones are currently under investigation and while these studies are not complete, it has been observed that certain 2,2 disubstituted ketones undergo abnormal rearrangements similar to those observed in the Beckmann rearrangements of their respective oximes in this medium. It is hoped to report the results of these and the Schmidt reactions of acids in this medium in the near future.

(12) E. C. Horning and V. L. Stromberg, *J. Am. Chem. Soc.*, **74**, 2680 (1952).

(13) M. S. Newman and H. Gildenhorn, *J. Am. Chem. Soc.*, **70**, 317 (1948).

(14) See R. K. Hill, *J. Org. Chem.*, **22**, 830 (1957) for possible exceptions to this observation.

EXPERIMENTAL

All melting points are corrected. The infrared spectra used for comparison were determined using a Baird, model 2-B, double beam, recording spectrophotometer. *Reactants:* 2-Methylcyclopentanone,[15] 2-propylcyclopentanone,[16] 2-methylcyclohexanone,[17] 2-propylcyclohexanone,[8,18] 2-cyanocyclohexanone,[19] 2-carbethoxycyclohexanone,[20] 1-hydrindone,[21] and 1-tetralone[21] were prepared by reported procedures. Benzylacetone was prepared from benzalacetone by reduction with Raney nickel according to the procedure outlined by Cornubert.[22] All other reactants were obtained from commercial sources and purified by distillation or recrystallization where necessary.

2-Keto-hexamethylenimine from cyclohexanone. To a mixture of 9.81 g. (0.1 mole) of cyclohexanone in 190 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The temperature was slowly increased to 50° on a water bath. The reaction temperature was maintained at the specified temperature for 8.5 hr. and then poured into 1000 g. of crushed ice and water. The solution was alkalized with cold 50% sodium hydroxide and the resulting solution extracted 5 times with 200-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous magnesium sulfate, filtered, and evaporated to yield a mass of crystals, 2-keto-hexamethylenimine; wt. 10.1 g. (89%). Recrystallization from benzene–petroleum ether produced a colorless product, m.p. 64–67° (lit., 65–68°,[12] 68–70°[23]).

7-Cyano-2-keto-hexamethylenimine from 2-cyanocyclohexanone. To a mixture of 12.30 g. (0.1 mole) of 2-cyanocyclohexanone in 196 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. After stirring for 10 hr. at room temperature, the mixture was hydrolyzed in 1000 g. of crushed ice and water. The aqueous solution was neutralized in the cold with dilute sodium hydroxide and extracted 3 times with 300-ml. portions of chloroform. The chloroform extracts were combined, dried over anhydrous sodium sulfate, filtered, and evaporated. The light yellow residue was dissolved in a minimum amount of chloroform and chromatographed over an ether packed alumina column. The first cut, 7-cyano-2-keto-hexamethylenimine was obtained by elution with ether; wt. 10.4 g. (76%) m.p. 126–127° (lit., 126.6–127.4°[8]). A second product was obtained from the elution of the column with a 1:1 mixture of chloroform and ether and identified as 7-carboxamido-2-keto-hexamethylenimine; wt. 1.24 g. (8%) m.p. 239–241°.

Anal. Calcd. for $C_7H_{11}N_2O_2$: C, 54.18; H, 7.15; N, 18.06; mol. wt., 155. Found: C, 54.10; H, 7.14; N, 18.11; mol. wt. (Rast), 151.

2-Amino-1,7-heptanedioic acid from 7-carboxamido-2-keto-hexamethylenimine. The structure of 7-carboxamido-2-keto-hexamethylenimine was established by hydrolysis to 2-amino-1,7-heptanedioic acid. 7-Carboxamido-2-keto-hexamethylenimine (1.5 g.) was refluxed with 30% sulfuric acid

(15) F. H. Case and E. E. Reid, *J. Am. Chem. Soc.*, **50**, 3064 (1928); Van Rysselberge, *Bull. sci. acad. roy. Belg.* (5), **11**, 171 (1921) (*Chem. Abstr.*, **21**, 375 (1927)).

(16) G. Chuirdoglu, *Bull. soc. chim. Belg.*, **43**, 35 (1934).

(17) M. S. Newman and H. M. Walborsky, *J. Am. Chem. Soc.*, **72**, 4296 (1950).

(18) R. Cornubert and A. Maurel, *Bull. soc. chim.*, (4), **49**, 1498, 1506 (1931).

(19) M. S. Newman, M. D. Farbmann, and H. Hypsher, *Org. Synthesis*, **25**, 22 (1945); R. E. Meyer, *Helv. Chim. Acta.*, **16**, 1291 (1933).

(20) H. R. Snyder, L. A. Brooks, and S. H. Shapiro, *Org. Synthesis*, **Coll. Vol. II**, 531 (1943).

(21) H. R. Snyder and F. X. Weber, *J. Am. Chem. Soc.*, **72**, 2965 (1950).

(22) R. Cornubert, *Bull. chim. soc. France*, 522 (1954).

(23) O. Wallach, *Ann.*, **312**, 187 (1900).

(25 ml.) for 8 hr. The solution was diluted with water and almost neutralized with hot, saturated barium hydroxide solution. The mixture was centrifuged and the decantate evaporated to dryness under vacuum to yield white crystals of 2-amino-1,7-heptanedioic acid; wt. 0.72 g., (41%) m.p. 221–223° (lit., 225°[24]).

7-Carboxamido-2-ketohexamethylenimine from 7-cyano-2-ketohexamethylenimine. Two grams of 7-cyano-2-ketohexamethylenimine was added to 25 g. of polyphosphoric acid at 65°. After 8 hr., the mixture was hydrolyzed and extracted as described above to yield 7-carboxamido-2-ketohexamethylenimine; wt. 2.05 g. (91%) m.p. 239–241°. On mixing with the product obtained from the Schmidt reaction, no depression of the melting point was observed; m.p. 239–241°.

7-Carboxamido-2-ketohexamethylenimine from 2-cyanocyclohexanone. To a mixture of 12.30 g. (0.1 mole) of 2-cyanocyclohexanone in 192 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The mixture was slowly heated at 65° and the temperature maintained at the specified temperature for 8 hr. The reaction mixture was hydrolyzed and the products isolated in the usual manner to yield 12.87 g. (83%) of 7-carboxamido-2-keto-hexamethylenimine; m.p. 238–241°. No trace of the nitrile was detected in the infrared spectrum of the crude product.

Acetanilide from acetophenone. To a mixture of 12.10 g. (0.1 mole) of acetophenone in 225 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. After stirring at 50° for 7 hr. the mixture was poured over 500 ml. of crushed ice and water. The product was filtered from the solution to yield 13.35 g. (98%) of acetanilide after air drying. The acetanilide was once recrystallized from water; m.p. 113–114° (lit., m.p. 114°[12]).

Phenanthridone from fluorenone. To a mixture of 18.10 g. (0.1 mole) of fluorenone in 350 g. of polyphosphoric acid, 6.80 g. (0.105 mole) of sodium azide was added in small portions over 1 hr. with slow agitation. The temperature was cautiously raised to 70° and maintained at that temperature for 22 hr. with constant stirring. The product was collected on hydrolysis by filtration to yield 17.94 g. (92%) of phenanthridone; m.p. 286–288° (lit., m.p. 293°[25]).

Acknowledgments. The author wishes to express his gratitude to the Research Corp. for a Frederick Gardner Cottrell grant in support of this study and to Dr. Richard K. Hill of Princeton University for his suggestions during the course of this investigation.

BUFFALO 8, N. Y.

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(25) O. Dimroth and W. Wislicenus, *Ber.*, **38**, 1573 (1905).

[CONTRIBUTION FROM THE ORGANIC DIVISION OF THE DEPARTMENT OF CHEMISTRY, UNIVERSITY OF FLORIDA]

Derivatives of Piperazine. XXX. Reactions of 1-Arylpiperazines with Epoxides

C. B. POLLARD AND JOAN B. CHRISTIE

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The search for new pharmaceuticals led to the synthesis of 25 new compounds resulting from the reactions of various 1-arylpiperazines with substituted 1,2-epoxides.

Seven of the 1-arylpiperazines used in these syntheses were prepared by the method of Pollard, *et al.*[1,2] The method of Prelog, *et al.*[3–5] proved more satisfactory for the preparation of the alkoxypiperazines. The hydrobromide of 1-(2-methoxyphenyl)-piperazine was reported by Prelog, Driza, and Hanousek.[3] The free amines, 1-(2-methoxyphenyl)-piperazine and 1-(2-ethoxyphenyl)piperazine were prepared in this laboratory by the Prelog method. The acetic acid salts of these amines were prepared for analyses and subsequent identification.

The reactions of ammonia and amines with 1,2-epoxides to form amino alcohols have been thoroughly investigated by Goldfarb,[6] Horne and Shriner,[7] and Wurtz.[8] Krassousky[9] investigated these reactions with unsymmetrical epoxides and obtained secondary amino alcohols. Castro and Noller[10] established that arylamines reacted with epoxides to produce secondary amino alcohols. The experimental work of Boyd and Knowlton,[11] Boyd,[12] and Stephens[13] also confirmed the secondary alcohol formation from these reactions. Kitchen and Pollard[14] showed that piperazine reacts with epoxides to produce mono as well as disubstituted piperazines, both being secondary amino alcohols. In view of the previous work establishing the for-

(1) C. B. Pollard and L. G. MacDowell, *J. Am. Chem. Soc.*, **56**, 2199 (1934).

(2) C. B. Pollard and T. H. Wicker, Jr., *J. Am. Chem. Soc.*, **76**, 1853 (1954).

(3) V. Prelog, G. J. Driza, and V. Hanousek, *Collection Czechoslov. Chem. Communs.*, **3**, 578 (1931).

(4) V. Prelog and G. J. Driza, *Collection Czechoslov. Chem. Communs.*, **5**, 497 (1933).

(5) V. Prelog and Z. Blazek, *Collection Czechoslov. Chem. Communs.*, **6**, 211 (1934).

(6) A. R. Goldfarb, *J. Am. Chem. Soc.*, **63**, 2280 (1941).

(7) W. R. Horne and R. L. Shriner, *J. Am. Chem. Soc.*, **54**, 2925 (1932).

(8) A. Wurtz, *Ann.*, **114**, 51 (1860).

(9) K. Krassousky, *Compt. rend.*, **146**, 236 (1908).

(10) A. J. Castro and C. R. Noller, *J. Am. Chem. Soc.*, **68**, 203 (1946).

(11) D. R. Boyd and H. S. Knowlton, *J. Chem. Soc.*, 1803 (1909).

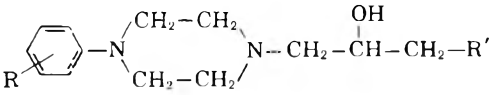
(12) D. R. Boyd, *J. Chem. Soc.*, 1791 (1910).

(13) D. W. Stephens, *Chem. & Ind. (London)*, **51**, 375 (1932).

(14) L. J. Kitchen and C. B. Pollard, *J. Org. Chem.*, **8**, 338 (1943).

TABLE I

DATA CONCERNING COMPOUNDS HAVING THE GENERAL FORMULA



Empirical Formula	R	Yield, %	M.P., °C. (Corr.)	Analyses, % Calcd. C	Calcd. H	Calcd. N	Found C	Found H	Found N
			R′ = –S–						
$C_{19}H_{24}N_2OS$	H	28.9	95–96	69.47	7.36		69.10	7.52	
$C_{19}H_{24}Cl_2N_2OS$	*o*-Cl·HCl	18.0	158–161	57.14	6.06		56.85	6.03	
$C_{19}H_{23}ClN_2OS$	*m*-Cl	28.0	121.5–122.5	62.87	6.39		62.84	6.25	
$C_{19}H_{23}ClN_2OS$	*p*-Cl	20.5	119–120	62.87	6.39		62.56	6.62	
$C_{20}H_{27}ClN_2OS$	*o*-CH_3·HCl	13.4	174–176	63.39	7.18		63.04	7.19	
$C_{20}H_{26}N_2OS$	*m*-CH_3	24.8	109.1–109.6	70.15	7.65		69.80	7.68	
$C_{20}H_{26}N_2OS$	*p*-CH_3	18.1	99–101	70.15	7.65		70.11	7.47	
$C_{20}H_{26}N_2O_2S$	*o*-OCH_3	27.8	92–93	67.01	7.31		67.14	7.34	
$C_{21}H_{28}N_2O_2S$	*o*-OC_2H_5	32.0	100–101	67.71	7.58	7.52	67.86	7.61	7.55
			R′ = –$(CH_2)_8CH_3$						
$C_{22}H_{38}N_2O$	H	31.4	78.3–79.3	76.25	11.06	8.09	76.03	11.32	8.00
$C_{22}H_{37}ClN_2O$	*m*-Cl	15.7	65.7–66.7	69.37	9.79	7.36	69.16	9.43	7.20
$C_{22}H_{37}ClN_2O$	*p*-Cl	23.6	84.5–85.5	69.37	9.79	7.36	69.60	9.83	7.65
$C_{23}H_{40}N_2O$	*m*-CH_3	13.9	63.7–64.7	76.61	11.18	7.77	76.71	11.20	7.75
$C_{23}H_{40}N_2O$	*p*-CH_3	24.4	74.8–75.8	76.61	11.18	7.77	76.40	11.19	7.80
			R′ = –O– (OCH₃)						
$C_{20}H_{25}ClN_2O_3$	*o*-Cl	31.9	60.6–61.6	63.74	6.69	7.44	63.76	6.62	7.05
$C_{20}H_{25}ClN_2O_3$	*m*-Cl	53.0	67.7–68.7	63.74	6.69	7.44	64.00	7.03	7.45
$C_{20}H_{25}ClN_2O_3$	*p*-Cl	29.2	75.8–76.8	63.74	6.69	7.44	64.07	6.99	7.45
$C_{21}H_{28}N_2O_3$	*p*-CH_3	53.0	93–94	70.76	7.92	7.86	70.90	8.10	7.95
			R′ = –O– (OCH₃)						
$C_{20}H_{26}N_2O_3$	H	40.3	99–101	70.17	7.66	8.18	70.11	7.59	7.75
$C_{20}H_{26}Cl_2N_2O_3$	*o*-Cl·HCl	8.7	179–180	58.11	6.34	6.78	58.60	6.65	6.70
$C_{20}H_{25}ClN_2O_3$	*m*-Cl	57.8	74.8–75.8	63.74	6.69	7.44	63.30	6.59	7.75
$C_{20}H_{25}ClN_2O_3$	*p*-Cl	42.7	85.9–87.9	63.74	6.69	7.44	63.60	6.69	7.29
$C_{21}H_{29}ClN_2O_3$	*o*-CH_3·HCl	36.4	168.2–170.2	64.17	7.44		64.06	7.51	
$C_{21}H_{28}N_2O_3$	*m*-CH_3	50.8	71.2–72.2	70.75	7.92	7.86	70.40	7.45	7.94
$C_{21}H_{28}N_2O_3$	*p*-CH_3	37.9	69.7–71.7	70.75	7.92	7.86	70.30	7.70	8.06

mation of secondary amino alcohols, structure studies were considered unnecessary in this project.

EXPERIMENTAL

1-(2-Ethoxyphenyl)piperazine monohydrobromide. Two moles (624 g.) of bis(β,β′-bromoethyl)amine hydrobromide and 1500 ml. of methanol were placed in a 3-l. flask. Two moles (274.18 g.) of freshly distilled *o*-phenetidine were added slowly. The mixture was refluxed for 10 hr. using an efficient, water-cooled condenser. One mole (106 g.) of sodium carbonate was added and refluxing was continued for 10 hr. The original volume was reduced by one half by distillation of methanol. Cooling the solution produced crystals of 1-(2-ethoxyphenyl)piperazine monohydrobromide. Neut. equivalent: calcd., 287.15; found, 285.00.

1-(2-Ethoxyphenyl)piperazine. One mole (287.15 g.) of 1-(2-ethoxyphenyl)piperazine monohydrobromide was slurried in 200 ml. of water and then neutralized with 40% sodium hydroxide. The oil which formed was removed and distilled under water-pump vacuum to remove water. Distillation at 0.08 mm., 112–114° (uncorr.) gave a 26% yield of the free amine.

1-(2-Ethoxyphenyl)piperazinium acetate. Three and one-tenth grams (0.05 mole) of glacial acetic acid was added dropwise with stirring to 10.32 g. (0.05 mole) of 1-(2-ethoxyphenyl)piperazine dissolved in acetone. The precipitated salt was recrystallized four times from acetone and ethanol. M.p. 113.1–114.1° (corr.); yield, 28%.

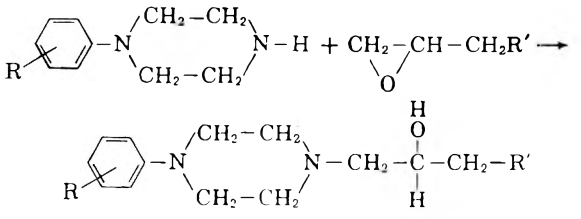
Anal. Calcd. for $C_{14}H_{22}N_2O_3$: C, 63.14; H, 8.35; N, 10.52. Found: C, 63.35; H, 8.56; N, 10.32.

1-(2-Methoxyphenyl)piperazine was prepared in the same manner as 1-(2-ethoxyphenyl)piperazine. B.p., 130–133° at 0.1 mm. (uncorr.).

1-(2-Methoxyphenyl)piperazinium acetate was prepared in the same manner as the 1-(2-ethoxyphenyl)piperazinium acetate. M.p., 128.3–129.3° (corr.).

Anal. Calcd. for $C_{13}H_{20}N_2O_3$: C, 61.88; H, 7.99; N, 11.10. Found: C, 61.90; H, 8.01; N, 10.90.

Reactions of 1-arylpiperazines with 1,2-epoxides. The various 1-arylpiperazines were treated with various 1,2-epoxides, illustrated by the general equation:



The 1-arylpiperazine (0.10 mole) was thoroughly mixed with the 1,2-epoxide in an Erlenmeyer flask, and allowed to stand for from one to two days. Either a crystalline solid or a viscous liquid, which showed no tendency to flow, was formed. In some cases crystallization was induced by scratching the flask or by seeding. Purification of these products was extremely difficult. Ethanol proved to be the best crystallizing solvent for all the reported products except 1-(2-chlorophenyl)-4-[2-hydroxy-3-(2-methoxyphenoxy)propyl] piperazine. It was crystallized from freshly distilled ethyl ether. The omissions of certain members of series result from the fact that analytical samples of these members could not be obtained. Data concerning the new compounds prepared are given in Table I.

The 1,2-epoxydodecane was obtained from the Becco Chemical Division of Food Machinery Chemical Corp. The 1,2-epoxy-3-aryloxypropanes were prepared by Dr. Jaime B. Fernandez using the method of the Shell Development Co.[15]

Acknowledgment. During the period in which this research was conducted, Joan B. Christie held a Parke, Davis & Co. Research Fellowship. The authors express their appreciation for this research grant.

GAINESVILLE, FLA.

(15) Shell Development Co., Emeryville, Calif. Technical Booklet SC: 49-35, p. 18 (1949).

[CONTRIBUTION FROM JOHN HARRISON LABORATORY OF CHEMISTRY, UNIVERSITY OF PENNSYLVANIA]

A Procedure for Phthaloylation under Mild Conditions

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By allowing phthalic anhydride to react with a number of amino acids and related primary amines in refluxing nonpolar solvents in the presence of triethylamine and separating the water formed, the phthalimide derivative may be prepared in good yield and without racemization. Phthaloylation without racemization may also be carried out in *N*,*N*-dimethylformamide medium.

Sheehan, Chapman, and Roth[3] have shown that phthaloylation by the fusion of an amino acid with phthalic anhydride can lead to racemization if the reaction temperature is higher than 150°. More recently it has been reported[4] that some substituted amino acids like *N*-benzylcysteine undergo racemization if the fusion temperature exceeds 110°. Baker and co-workers[5] have reported a mild two-step process for phthaloylation which involves the preparation of a phthalamic acid in the first step and its cyclization *via* a mixed anhydride in the second step. Evidently this process is suitable only for those amino compounds which do not also possess a free carboxyl group. Balenović and Gašpert[4] have developed a two-step procedure applicable to amino acids which involves the cyclization of a phthalamic ester obtained by the reaction of an amino acid with *o*-carbethoxythiobenzoic acid.

We wish to report here a one-step process for phthaloylation that avoids high temperature.

This phthaloylation procedure consists in treating one equivalent of phthalic anhydride with an amino compound in a refluxing solvent (*e.g.*, toluene or benzene) in the presence of triethylamine, a water separator being used to remove the water formed in the reaction. In the phthaloylation of an amino acid the best yield is obtained when the quantity of triethylamine used is about one-tenth of an equivalent.

Using this method ethyl phthalimidoacetate was obtained from glycine ethyl ester hydrochloride in 96% yield when toluene was the reaction medium. When, however, a water separator was not used the yield was reduced to 50%; the rest of the glycine ester was presumably in the form of the corresponding phthalamic acid because on standing in a dilute hydrochloric acid solution, this material was slowly converted to ethyl phthalimidoacetate. Drefahl and Fischer[6] have recently reported that mineral acids catalyze the dehydration of some phthalamic acids to phthalimide derivatives in the presence of an excess of water.

Due to the instability of aminoacetonitrile to heat, the fusion method is unsuitable for the phthaloylation of this compound. However, by treating aminoacetonitrile bisulfate with phthalic anhydride and triethylamine in benzene medium, phthal-

(1) Supported in part by U. S. Public Health Service Grant CY-2189.

(2) Supported in part by U. S. Public Health Service Grant CY-2790.

(3) J. C. Sheehan, D. W. Chapman, and R. W. Roth, *J. Am. Chem. Soc.*, **74**, 3822 (1952).

(4) K. Balenović and Gašpert, *Chem. & Ind. (London)*, 115 (1957).

(5) B. R. Baker, J. P. Joseph, R. E. Schaub, and J. H. Williams, *J. Org. Chem.*, **19**, 1786 (1954).

(6) G. Drefahl and F. Fischer, *Ann.*, **610**, 166 (1957).

imidoacetonitrile was prepared in 81% yield. The yield dropped when a higher reaction temperature was provided by substituting toluene for benzene. Reaction of phthalic anhydride and aminoacetonitrile bisulfate in pyridine at 85–90° gave phthalimidoacetonitrile in 85.5% yield.

It has been reported[7] that by treating phthalic anhydride with glycine in refluxing *p*-cymene (b.p. 177°) and separating the water formed, *N*-phthaloylglycine is obtained in 90% yield. We found that when refluxing toluene (b.p. 110°) was substituted for *p*-cymene, the water separated was 30% but the yield of phthaloylglycine was 70%. Addition of 3% of one equivalent of triethylamine led to 52% water separation and the formation of *N*-phthaloylglycine in 80% yield. The yield of the phthaloylated product rose to 90% when 10% of one equivalent of triethylamine was used. Excess triethylamine afforded the calculated amount of water but an 80% yield of phthaloylglycine. When toluene was replaced by benzene as the reaction medium, the yield of phthaloylglycine was lowered to 55%.

Fischer[8] had prepared *N*-phthaloyl-L-alanine, $[\alpha]_D^{20}$ −17.8°, in 68% yield by fusing together phthalic anhydride and L-alanine for seven hours. Using our method *N*-phthaloyl-L-alanine was obtained in 91.3% yield in less than three hours and its rotation was found to be higher ($[\alpha]_D^{24}$ −24.2°) than that reported by Fischer.

Phthaloylation of D-phenylalanine by this method was found to proceed without racemization.

Reaction of an amino compound (without a free carboxyl group) with phthalic anhydride in chloroform medium has been used for obtaining the corresponding phthalamic acid in good yield.[5] When, however, glycine and phthalic anhydride were heated in refluxing chloroform (b.p. 61°) for five hours, no water separated and phthalic anhydride was recovered in 89% yield. In the presence of triethylamine some water separated and *N*-phthaloylglycine was obtained in a fair yield (see Table 1). When triethylamine was used but the flask was not fitted with a water separator, very little phthaloylglycine was produced. Even with such a low boiling solvent as dichloromethane (b.p. 40°) as the reaction medium, phthaloylation proceeded to the extent of 44%. Thus, by a proper choice of solvent, phthaloylation can be carried out at any temperature and in one step. Furthermore, phthaloylamino acids obtained in this way are essentially pure as indicated by their melting points and need no recrystallization.

It is interesting to note that when triethylamine is present in the reaction mixture, the unreacted phthalic anhydride remains in aqueous solution during the working up. Even when two equivalents of phthalic anhydride were used for one equivalent of an amino acid in the presence of an excess of triethylamine in chloroform, the water-insoluble product was an oil which partially crystallized on standing. The crystalline material was found to be quite pure phthaloylaminoacid.

Wanag and Veinbergs[9] found that phthaloylation of α-aminoacids proceeds normally in acetic acid medium but the rate of reaction is slow—in some cases ten hours were required for completion of reaction.

The use of pyridine as the medium for the reaction of phthalic anhydride with α-aminoacids gives poor yield; *N*-phthaloyl-L-leucine prepared in this way showed no racemization.

Baker and co-workers[10] have used boiling *N*,*N*-dimethylformamide (b.p. 153°) as the reaction medium for phthaloylating certain amino compounds.

We have found that phenylalanine or glycine and an equivalent of phthalic anhydride will react in dimethylformamide (at above 100°) to yield the phthaloyl derivative in more than 80% yield. If, however, the reaction temperature is below 100°, the yield is almost nil. Phthaloylation of D-phenylalanine by this method was found to take place without racemization.

Dioxane has been found to be a suitable medium for the phthaloylation of certain aminoacids.[11]

Phthalimido-L-glutamic acid and phthalimido-L-aspartic acid have been prepared by the acid hydrolysis of the corresponding ethyl esters[4,12–16] since direct phthaloylation of these free amino acids leads to racemization and side products.[13] Two-[4,16] or three-[12,15] step methods have been used for converting diethyl L-glutamate hydrochloride and diethyl L-aspartate hydrochloride into the corresponding phthalimidoesters. Using the procedure described above, we have converted diethyl L-glutamate hydrochloride to *N*-phthalyl L-glutamic acid ethyl ester in one step in very good yield and without racemization.

EXPERIMENTAL[17]

Ethyl phthalimidoacetate. (*a*) A suspension of phthalic anhydride (1.5 g.) and glycine ethyl hydrochloride (1.4 g.) in 20 ml. of triethylamine was heated under reflux for 30 min.,

(7) J. J. O'Neill, F. P. Veitch, and T. Wagner-Jauregg, *J. Org. Chem.*, **21**, 363 (1956).

(8) E. Fischer, *Ber.*, **40**, 498 (1907).

(9) G. Wanag and A. Veinbergs, *Ber.*, **75**, 1558 (1942).

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(17) All melting points are uncorrected.

when a clear liquid and a gum were obtained. The liquid was poured into dilute hydrochloric acid, but no solid separated. On triturating with water, the gum gave 0.25 g. (11%) of colorless ethyl phthalimidoacetate, m.p. 111° (lit.,[18] m.p. 112–113°). In another experiment, heating under reflux was continued for 6 hr., and then triethylamine was removed from the reaction mixture under reduced pressure. When the residue was extracted with ether and the ether solution was evaporated, 1.2 g. (51.5%) of colorless, crystalline material, m.p. 110°, was obtained.

(*b*) A suspension of phthalic anhydride (1.5 g.) and glycine ethyl ester hydrochloride (1.4 g.) in 10 ml. of triethylamine and 40 ml. of benzene was heated under reflux for 1 hr. On filtering the hot reaction mixture, the calculated amount of triethylammonium hydrochloride was obtained. When the filtrate was evaporated under reduced pressure, a pasty mass was obtained. On triturating this mass with 5 ml. of water, 1 g. (50% yield) of crystalline material, m.p. 107–109°, separated. The filtrate on standing for a few days afforded another 0.45 g. of the product.

(c) A mixture of phthalic anhydride (6.0 g.), glycine ethyl ester hydrochloride (5.6 g.), triethylamine (10 ml.), and toluene (200 ml.) was heated under reflux in a flask fitted with a Dean-Stark tube. The calculated amount of water separated in 2 hr. The hot reaction mixture was filtered and the filtrate further heated for 30 min. Evaporation gave an almost quantitative yield of colorless, crystalline material, m.p. 112–113°. In a second experiment, crystalline material, m.p. 108°, was obtained in 96% yield. Use of xylene in place of toluene gave an equally high yield, but the product was somewhat colored. When benzene was used as the solvent, the yield of material, m.p. 108–110°, was 62%.

Phthalimidoacetonitrile. (*a*) A mixture of 10 g. of aminoacetonitrile bisulfate, 10 g. of phthalic anhydride, 22 ml. of triethylamine, and 100 ml. of benzene was heated under reflux in a flask fitted with a water separator. All volatile material was removed from the reaction mixture in a steam bath under reduced pressure. The residue was treated with 200 g. of cracked ice. The slightly colored, crystalline solid that separated was collected by filtration, washed with cold water, and dried. The yield of phthalimidoacetonitrile so obtained, m.p. 124–126°, was 9.7 g. (81%).

When toluene was substituted for benzene the higher reaction temperature led to a low yield of highly colored material.

(*b*) Aminoacetonitrile bisulfate (30 g.) and phthalic anhydride (30 g.) were added to 60 ml. of dry pyridine with shaking. Some heat was evolved and most of the solid went into solution. The reaction mixture was then heated in an oil bath maintained at 90°, giving a clear solution which became dark. Heating was stopped after 1.5 hr. and the reaction mixture was poured over 200 g. of ice. Hydrochloric acid was added until the reaction mixture was acidic. The crystalline solid was collected, washed with 50 ml. of ice cold water, and dried. The yield of phthalimidoacetonitrile so obtained, m.p. 124–125° (after one recrystallization from ethanol, m.p. 127–128°), was 31 g. (85.5%).

Anal. Calcd. for $C_{10}H_6N_2O_2$: C, 64.51; H, 3.25; N, 15.05. Found: C, 64.73; H, 3.21; N, 14.87.

N-Phthaloylglycine. A mixture of glycine, an equivalent of phthalic anhydride, triethylamine, and a solvent was heated under reflux in a flask fitted with a water separator. At the end of the reaction all volatile matter was removed on a steam bath under reduced pressure and the residual sirup was triturated with dilute acid. The colorless crystalline material that separated was filtered, washed with cold water, and dried. The yields obtained under different reaction conditions are given in Table 1. The melting point of the product in each case was very close to that reported,[19] 191–192°.

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(19) E. Drechsel, *J. pract. Chem.*, (2) **27**, 418 (1883).

TABLE 1

REACTION BETWEEN GLYCINE AND AN EQUIVALENT OF PHTHALIC ANHYDRIDE

Reaction Medium	Triethylamine, Eq.	Reaction Time, Hr.	Water Separated, %	Yield of Phthaloylglycine, %
Toluene	...	2.5	30	70
Toluene	0.03	2.5	52	80
Toluene	0.10	2	97	90
Benzene	0.10	2.5	56	55
Toluene	Excess	2.5	100	80
Chloroform	...	5	...	...[a]
Chloroform	Excess	2	...	2.5[b]
Chloroform	Excess	5	*ca.* 25	57.5
Methylene dichloride	Excess	4.5	*ca.* 30	44
N,N'-Dimethylformamide	...	2 (at 110°)	...	83

[a] Phthalic anhydride was recovered in 89% yield. [b] No water separator was used.

N-Phthaloyl-L-alanine. (*a*) A mixture of 1.78 g. of L-alanine (chromatographically pure, $[\alpha]_D^{25}$ 14.5° (c = 2 in 2*N* HCl); supplied by Mann Research Laboratories, New York, N. Y.), 3.05 g. of phthalic anhydride, 0.1 ml. of triethylamine, and 50 ml. of toluene was heated under reflux for 2.5 hr. The water separated amounted to 83%. On working up in the general manner indicated for phthaloylglycine, the yield of phthaloyl-L-alanine, m.p. 145–147° (lit.,[6] m.p. 150–151° with softening starting at 139°) was 4 g. (91.3%). On recrystallization from acetone–petroleum ether mixture, the material was obtained as colorless crystals, m.p. 144–146°, $[\alpha]_D^{24}$ −24.2° (c = 2.6 ethanol) (lit.,[3] $[\alpha]_D^{20}$ −17.8°).

(*b*) A suspension of 1 g. of L-alanine and 1.66 g. of phthalic anhydride in 10 ml. of *N,N*-dimethylformamide was heated on a water bath. In 45 min. a clear solution was obtained which was poured into water. There was no separation of any solid product. When 0.9 g. of L-alanine, 1.5 g. of phthalic anhydride and 10 ml. of dimethylformamide was heated at 110–115° for 13 hr. and the clear solution so obtained was poured into 90 ml. of water, an emulsion was obtained. On seeding with *N*-phthalyl-L-alanine, 0.7 g. (32% yield) of a crystalline solid, m.p. 144–145° was obtained. (The use of such a large volume of water may have reduced the yield.)

(c) A mixture of 1.8 g. (0.02 mole) of DL-alanine, 6 g. (0.04 mole) of phthalic anhydride, 10 ml. of triethylamine, and 150 ml. of chloroform was heated under reflux for 2.5 hr. Only a small amount of water separated. When all volatile matter was removed from the reaction mixture and dilute acid added, a yellow oil separated which partially crystallized on standing for several hours. The crystals were separated by filtration and washed several times with cold water and on drying 1 g. (23% yield) of phthaloyl-DL-alanine, m.p. 161.5–162.5° (lit.,[9] m.p., 164°) was obtained.

On substituting 1.5 g. of glycine for alanine in the above experiment, the water-insoluble product again was an oil which partially crystallized to afford 1.32 g. (32% yield) of phthaloylglycine, m.p. 191.5–192.5°.

N-Phthaloylphenylalanine. (*a*) D-phenylalanine (0.459 g.), phthalic anhydride (0.412 g.), triethylamine (2 ml.), and benzene (30 ml.) were heated together under reflux for 2 or 3 hr. On removing the solvent and adding dilute hydrochloric acid, an oil separated that crystallized on standing overnight. The yield was 0.75 g. (58%), m.p. 182–183°, $[\alpha]_D^{21}$ +213° (0.0491 g. in 4 ml. of ethanol) showing 100% optical purity (lit.,[3] $[\alpha]_D^{26.5}$ −212° for phthaloyl-L-phenylalanine).

(b) A mixture of 3.02 g. of DL-phenylalanine, 3.00 g. of phthalic anhydride, 2.5 ml. of triethylamine, and 100 ml. of toluene was heated under reflux for 2.5 hr. in a flask fitted

with a water separator. On working up in the manner indicated for glycine, the yield of phthaloyl-DL-phenylalanine, m.p. 176.5–177.5° (lit.,[20] m.p. 174–175°), was 5.05 g. (90% yield).

(c) D-Phenylalanine (0.300 g.) and phthalic anhydride (0.254 g.) were heated in 10 ml. of refluxing dimethylformamide for 45 min. The product, isolated by pouring the reaction mixture into 30 ml. of ice and water, weighed 0.43 g. (83.5%) and melted at 175–177°. For a sample recrystallized from aqueous methanol, m.p. 182–183.5°, $\alpha[^{20}_{D}]$ was +211° (0.0566 g. in 3.5 ml. of ethanol), showing 100% optical purity.

N-Phthaloyl-L-leucine. L-Leucine and phthalic anhydride heated in pyridine at 100–105° for 1 hr. afforded *N*-phthaloyl-L-leucine in poor yield. A sample recrystallized from aqueous methanol, m.p. 121–122°, showed $[\alpha]^{20}_{D}$ −25.5° (0.0915 g. in 3.5 ml. ethanol); (lit.,[3] m.p. 118.5–119.5°, $[\alpha]^{26.5}_{D}$ −24°).

Diethyl N-phthaloyl-L-glutamate. A suspension of 12 g. of diethyl L-glutamate hydrochloride and 7.4 g. of phthalic anhydride in 10 ml. of triethylamine and 150 ml. of toluene was heated under reflux for 2.5 hr. in a flask fitted with a Dean-Stark tube. Nearly the calculated amount of water was collected. The reaction mixture was filtered and the filtrate was washed with dilute hydrochloric acid and then with water and dried over sodium sulfate. On removing the solvent from the dried solution, a light yellow colored, viscous oil was obtained (14.6 g., 88%). A sample was purified by distillation, giving close to quantitative recovery of nearly colorless distillate: n^{25}_{D} 1.5234; $[\alpha]^{25}_{D}$ −35.2° (ethanol) [lit.,[12] n^{22}_{D} 1.5220; $[\alpha]^{19}_{D}$ −33.5° (ethanol)].

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[CONTRIBUTION FROM E. I. DU PONT DE NEMOURS & CO., INC., EASTERN LABORATORY]

Reaction of Cyclohexane with Nitrosyl Chloride

L. G. DONARUMA

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The preparation of nitrosocyclohexane dimer from cyclohexane and nitrosyl chloride is described. Data are presented which may explain the fact that, under the reaction conditions employed, the major reaction product is nitrosocyclohexane dimer and not cyclohexanone oxime hydrochloride.

The reaction of nitrosyl chloride with cyclohexane (I) in the presence of light to yield cyclohexanone oxime hydrochloride (III) has been known for many years.[1] More recently, Mueller and Metzger[2] found that they could prepare nitrosocyclohexane dimer (II) by the reaction of cyclohexane (I) with a mixture of nitric oxide and chlorine in the presence of light: Cyclohexyl nitrate and 1-chloro-1-nitrosocyclohexane were formed as by-products of the reaction. They used a nitric oxide–chlorine volume ratio of 8:1. It seemed logical that the flow of gas through the system resulted in the removal, by entrainment, of the hydrogen chloride formed before it could isomerize the nitroso compound (II) to cyclohexanone oxime (IV). To test this assumption, cyclohexane (I) was reacted with nitrosyl chloride in the presence of excess nitrogen. The reaction was carried out by entraining nitrosyl chloride, with a stream of dry nitrogen, into an irradiated solution of cyclohexane (I) in benzene. In this manner good yields (30–50%) of nitrosocyclohexane dimer (II) and small amounts of cyclohexanone oxime hydrochloride (III) were obtained. If the flow of the gas stream was slow, or if the gas stream was passed into the bottom of a container holding a benzene-cyclohexane solution of considerable depth, the major product was the oxime salt (III). These observations prompted us to measure the rate of isomerization of the nitroso dimer (II) to cyclohexanone oxime (IV) in various media. Table I shows the results obtained from the measurement of the rate of isomerization of nitrosocyclohexane dimer to cyclohexanone oxime in cyclohexane and in the presence of several different catalysts.

Surprisingly, the data in Table I show that the nitroso dimer (II) did not isomerize to cyclohex-

(1) German Appln. **W5051** (1952), (to Matheson Chemical Corp.); *French Patent* **992,772** (1951) (to Svit, Narodni Podnik). W. Zerneck and H. Ritter, (to Cassella Farbewerke Mainkur), Ger. Appln., C, **2,405** (1952); B. B. Brown (to Olin Matheson), U. S. Patent **2,719,116** (1955); M. A. Naylor and A. W. Anderson, *J. Org. Chem.*, **18**, 115 (1953).

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TABLE I

DATA OBTAINED BY MEASUREMENT OF THE RATE OF ISOMERIZATION OF NITROSOCYCLOHEXANE DIMER TO CYCLOHEXANONE OXIME IN VARIOUS MEDIA

Temperature, °C.	Reaction Medium	10^3k · (Min.$^{-1}$)
50.2	Cyclohexane	Very small
69.7	Cyclohexane	Very small
80.0	Cyclohexane	Very small
89.8	Cyclohexane-CH_3CO_2H[a]	4.80
23.5	Cyclohexane-HCl[b]	.640
23.0	Cyclohexane-Cyclohexylamine[a]	1.24
38.8	Cyclohexane-Cyclohexylamine[a]	10.5
24.6	Cyclohexane-Pyridine[a]	.232
59.5	Cyclohexane-Pyridine[a]	9.25

[a] Catalyst concentration = 28.6% by volume. [b] Catalyst concentration = 0.2 g./100 ml.

anone oxime (IV) in cyclohexane solution over the concentration range of 0.1–0.2 g./100 ml. even at 80°. After heating the solution at 50° for twenty-seven hours and at 70° and 80° for several hours, no detectable drop in the concentration of II was observed. The data also show that by the addition of suitable acids or bases the isomerization will proceed in cyclohexane solution. Hydrogen chloride is not a good isomerization catalyst at or near room temperature. This latter observation explains why under the conditions employed for the reaction of nitrosyl chloride with cyclohexane (I) the major product was II and not III. Below 70°, glacial acetic acid was not a good isomerization catalyst. After heating at 69–70° for two hours in an acetic acid–cyclohexane mixture, no change in the concentration of II in cyclohexane occurred. Under similar conditions at 89.8°, the nitroso compound (II) was isomerized to the oxime (IV). The best catalyst found to effect the isomerization in cyclohexane was cyclohexylamine. Pyridine was slightly less effective.

Studies of the rate of isomerization of nitrosocyclohexane dimer to cyclohexanone oxime also were carried out in methanol. The results of these investigations are shown in Table II.

TABLE II

RATE OF ISOMERIZATION OF NITROSOCYCLOHEXANE DIMER TO CYCLOHEXANONE OXIME IN METHANOL

Temperature, °C.	10^3k(Min.$^{-1}$)
50.3	0.702
65.0 (Refluxing methanol)	5.48

The data in Table II indicate that methanol is a much better solvent for the isomerization than cyclohexane and that perhaps methanol is a catalyst for the isomerization.

EXPERIMENTAL

Materials. Nitrosocyclohexane dimer (II) was prepared by the oxidation of *N*-cyclohexylhydroxylamine[2] or by the action of nitrosyl chloride on cyclohexane. It was purified by recrystallization from cyclohexane. The pure dimer melted at 116–118°.

The cyclohexane used as a solvent in the rate studies was distilled through a 12-inch Vigreux column. Undistilled cyclohexane was unsatisfactory for the infrared analyses.

The methanol used in the isomerization studies was Baker Analyzed Reagent Grade (99.5% methanol).

The cyclohexylamine, pyridine, and acetic acid used as catalysts were purified by repeated distillation. The gaseous hydrogen chloride employed as a catalyst was generated from concentrated aqueous hydrochloric acid.

Apparatus. The constant temperature bath was capable of holding the temperature within one-tenth degree of the desired temperature. A stainless steel basket divided into twelve compartments held the samples. The basket was agitated by a shaft which was attached in an offset manner to a flywheel powered by a motor. The sample containers were 10-ml. flat-bottomed cylindrical flasks fitted with individual reflux condensers.

Analyses. The samples employed in the isomerization studies in methanol and pure cyclohexane were analyzed by methods based on the absorption maximum of nitrosocyclohexane dimer (II) at a wave length of 290 millimicrons (mμ) in the ultraviolet region of the spectrum. Working curves were set up for the analysis of II by the measurement of its absorbance at 290 mμ for both methanol and cyclohexane solutions. Both curves obeyed Beer's Law. The working curves were checked with solutions of known concentration, and the results were within the experimental error.

The samples from the acid and base catalyzed isomerizations were analyzed for nitrosocyclohexane dimer (II) by the infrared method described in a previous publication.[3]

Procedures. The experiments in pure cyclohexane and methanol were carried out by dissolving 0.05–0.2 g. of the nitroso-dimer (II) in the appropriate solvent and diluting the solution to 100 ml. Two to five milliliters of the stock solution was placed in each of the twelve containers and, if desired, the requisite amount of catalyst was added. The basket was then lowered into the bath at the proper temperature. The samples were allowed 5 min. to reach the reaction temperature. The zero time sample was removed and timing of the other samples started. When the reaction mixtures involving pure methanol or cyclohexane were removed, the reaction was stopped by the addition of cold methanol (−10°) or cold cyclohexane (10°) to the samples. The sample was then diluted to 100 ml. and analyzed by the ultraviolet methods. The acid or base catalyzed isomerizations were stopped by removing the catalyst. Pyridine and cyclohexylamine were removed by washing the sample with 4 20-ml. portions of distilled water. The acid catalysts were removed by washing the samples successively with 10 ml. of water, 10 ml. of saturated aqueous sodium bicarbonate solution, and 10 ml. of water. The washed samples were passed through filter paper to remove traces of water and analyzed by the infrared method.[3] The washing technique had no appreciable effect on the concentration of nitrosocyclohexane dimer.

Catalyst Removed	Nitrosocyclohexane Dimer (G./100 Ml.) Before wash	After wash
Acetic acid	0.0520	0.0512
Hydrogen chloride	0.0690	0.0690
Cyclohexylamine	0.0478	0.0465
Pyridine	0.0490	0.0478

All reactions ran were at least 65% complete. The yield of cyclohexanone oxime in these reactions ranged from

(3) L. G. Donaruma and D. J. Carmody, *J. Org. Chem.*, 22, 1024 (1957).

90–95% by instrumental analysis and from 60–80% by actual isolation techniques.

Handling of data. Substitution of ultraviolet absorbances or concentrations (II g./100 ml. of solvent) into the first order rate equation at appropriate time intervals gave values of the first order rate constant (k) which did not drift appreciably. When the logarithm of the absorbance or concentration was plotted versus time, unambiguous straight lines were obtained in all the experiments. The least number of points on any curve was eight.

The rate constants were calculated by integration of the first order rate equation over two widely separated time units[4] and by the determination of the slope of the curve obtained by plotting the log of the absorbance or concentration versus time. The slope was determined statistically by the method of least mean squares.[5] Agreement between the two methods was excellent.

Error. The maximum error in concentration in the ultraviolet analyses was 0.008 absorbance unit. The maximum concentration error for the infrared analyses was 3% relative. The maximum time error was about one minute.

Preparation of nitrosyocclohexane dimer (II) *by nitrosation of cyclohexane.* A 4-liter beaker having a glass cooling coil fitted inside was charged with 1 liter of cyclohexane and 500 ml. of benzene. Ice water was pumped through the cooling coil until the temperature of the mildly agitated mixture was below 10°. Irradiation by a 150-watt spotlight placed against the bottom of the beaker or 2–4 inches above the solution surface was started. Dry nitrogen gas (at 4 l./hr.) was passed into a cold trap containing 7.9 grams (0.12 mole) of nitrosyl chloride at a temperature between −50° and −20°. The entrained nitrosyl chloride was conducted into the reaction mixture (temperature = 20–25°) by means of a tube which was just slightly (about 1 inch) below the surface of the solution. The addition of nitrosyl chloride was complete in 6 hr. Irradiation of the reaction mixture was continued for an additional 15 min. The reaction mixture was left standing in an evaporating dish in the hood until the solvent evaporated. The crude product was scraped out of the evaporating dish. The yield was 6.5 grams (47%). After recrystallization from cyclohexane the yield of pure nitrosocyclohexane dimer (m.p. 116°–118°) was 5.5 grams (40%).

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(5) W. E. Roseveare, *J. Am. Chem. Soc.*, **53**, 1651 (1931). L. J. Reed and E. J. Theriault, *J. Phys. Chem.*, **35**, 673 (1931).

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

gem-Dinitro Esters. II. Preparation and Properties of α,α-Dinitro Esters[1]

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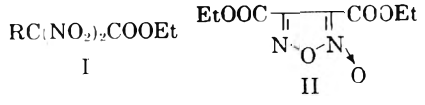
α,α-Dinitro esters can be prepared, although in poor yield, by nitration of half esters of malonic acid and alkyl malonic acids with 70% nitric acid. The dinitro esters are stable colorless oils. With hydrazine hydrate, ethyl dinitroacetate yields a hydrazine salt which can be converted to the hydrazine salt of dinitroacethydrazide. Ethyl dinitropropionate and higher homologs are cleaved by hydrazine hydrate to give 1,1-dinitroparaffins.

Ethyl dinitroacetate (I, R = H) has been prepared by nitration of the half ester of malonic acid with fuming nitric acid at 25–30°.[2] It is accompanied by dicarbethoxyfuroxan (II) from which it



can be separated by extraction with alkali. Although this reaction has been known for over 50 years, it apparently has not been applied to higher homologs of monoethyl malonate. Some of these half esters have now been prepared by a modification of the method of Marguery[3] and nitrated under various conditions. Nitration with concentrated nitric and sulfuric acids leads to destruction of the half esters, even at low temperatures. Fuming or 100% nitric acid produces esters with nitro and nitrato groups, but 70% nitric acid at 60° furnishes low yields of α,α-dinitro esters reasonably free from contaminants. The α,α-dinitro esters are colorless oils with faint odor. The yields and properties of these compounds are given in Table I.

Ethyl dinitroacetate has been converted stepwise to the hydrazine salt and to dinitroacethydrazide hydrazine salt.

The homologous α,α-dinitro esters, $RC(NO_2)_2COOEt$, undergo cleavage with alcoholic hydrazine hydrate at room temperature. With ethyl α,α-dinitropropionate this reaction takes place rapidly, giving a 50% yield of 1,1-dinitroethane hydrazine salt in 30 min. The analogous reaction with ethyl α,α-dinitrobutyrate yields 1,1-dinitropropane hydrazine salt so that the reaction may be formulated as follows:

(1) This work was performed under the auspices of the Atomic Energy Commission. Paper I: L. W. Kissinger, W. E. McQuistion, M. Schwartz and L. Goodman, *J. Org. Chem.*, **22**, 1658 (1957).

(2) L. Bouveault and A. Wahl, *Compt. rend.*, **136**, 159 (1903).

(3) F. Marguery, *Bull. soc. chim.*, [3], **33**, 552 (1905).

$$RC(NO_2)_2COOEt + 2H_2NNH_2 \xrightarrow{EtOH} RC(NO_2)_2\overset{-}{}\overset{+}{H_3}NNH_2 + H_2NNHCOOEt$$

The authentic salts of the two 1,1-dinitroparaffins have been prepared by action of hydrazine hydrate on the dinitroparaffins in ethanol.

TABLE I

α,α-Dinitro Esters, $RC(NO_2)_2COOEt$

R	B.P., °C. (0.1 Mm.)	n_D^{25}	Yield, %	$\lambda(C{=}O)^a$ μ	$\lambda(NO_2)^a$ μ	$\lambda(NO_2)^a$ μ
H	--	1.4321	11	5.65	6.31	7.51
Me	45	1.4327	17	5.66	6.31	7.52
Et	50	1.4340	17	5.66	6.31	7.54
Bu	60	1.4393	8	5.67	6.32	7.58

	Analyses					
	Calcd.			Found		
R	C	H	N	C	H	N
H	—	—	—	—	—	—
Me	31.26	4.19	14.58	31.24	3.83	14.60
Et	34.95	4.89	13.59	35.11	4.62	13.20
Bu	41.03	6.02	11.96	41.58	5.93	11.93

[a] Determined in capillary cells as liquid films.

EXPERIMENTAL[4]

Preparation of monoethyl alkylmalonates. Monoethyl malonate was obtained according to Freund,[5] whereas the homologs were prepared by a modified procedure[3] which is given in detail for monoethyl *n*-butylmalonate. Ethyl *n*-butylmalonate (100 g., 0.462 mole), dissolved in 250 ml. of absolute ethanol, was added to a cold solution of potassium hydroxide (26.0 g., 0.462 mole) in 250 ml. of absolute ethanol. The mixture was stirred and allowed to stand at room temperature for 16 hr. It was refluxed for 0.5 hr., filtered, and evaporated under reduced pressure. The semisolid opaque residue was dissolved in 100 ml. of water and extracted twice with 50 ml. of petroleum ether. The extract was dried and evaporated giving 10 g. (10%) of starting ester, n_D^{25} 1.4213. The aqueous layer was acidified with concentrated hydrochloric acid (with cooling) and extracted with benzene. The extracts were washed with water, dried by distilling the benzene-water azeotrope, and evaporated from a steam bath at 50 mm. The colorless oil was used without further purification. The yields and properties of the half esters are listed in Table II.

TABLE II

Preparation of Monoethyl Alkylmalonates, $RCH(COOH)COOEt$

R	Recovered Diester, %	n_D^{25}	Half Ester Yield, %	n_D^{25}	$\lambda_{C=O}$,	μ^a
H	0	1.4121	51	1.4233	5.75	5.80
Me	7–11	1.4126	51–63	1.4253	5.75	5.80
Et	16	1.4153	72	1.4281	5.74	5.80
n-Bu	10	1.4213	82	1.4352	5.75	5.80

[a] Determined as liquid films.

(4) All temperatures are uncorrected. Analyses by M. Naranjo.

(5) M. Freund, *Ber.*, **17**, 780 (1884)

The nitration of monoethyl methylmalonate with 100% nitric acid.

Monoethyl methylmalonate (7.3 g., 0.05 mole) was added dropwise with stirring and cooling to 30 ml. of 100% nitric acid. The exothermic reaction was controlled by ice cooling. The reaction mixture was allowed to stand at room temperature for 22 hr. Then it was poured on ice and extracted with chloroform. The extract was washed with water, dried over sodium sulfate, and distilled to remove the solvent. The residue (4.0 g.) was distilled from a Hickman still, giving 3 g. of a colorless oil, b.p. 80° (0.1 mm.), n_D^{25} 1.4432. Besides carbonyl absorption at 5.67μ and the nitro band at 6.29μ, this oil had bands at 6.07 and 7.88μ and increased absorption at 11–12μ.

Anal. Calcd. for $C_5H_8N_2O_7$ (nitronitrato ester): C, 28.86; H, 3.87; N, 13.46. Found: C, 29.96; H, 3.98; N, 12.92.

Ethyl α-nitratopropionate,[6] b.p. 64° (7 mm.), n_D^{25} 1.4129, had the following absorption bands: $\lambda(C{=}O)$ 5.70μ, $\lambda(NO_3)$ 6.06, 7.84, 11.74μ.

The nitration of monoethyl alkylmalonates with 70% nitric acid. The monoethyl alkylmalonate (10 g.) was added in small portions with stirring to 70 ml. of 70% nitric acid maintained at 45–50°. The reaction had an induction period of 15–20 min. and was exothermic. The mixture turned green and evolved carbon dioxide and nitrogen dioxide which were removed by suction. After the addition had been completed, the mixture was stirred for 1 hr. at 45–50° and poured on ice. The aqueous solution was extracted with chloroform and the extract was washed with water and dried over sodium sulfate. The dry chloroform solution was evaporated at 50 mm. and below 25°. The residual pale yellow oil was distilled from a Hickman still under reduced pressure. The yields and properties of the dinitro esters appear in Table I.

Ethyl dinitroacetate hydrazine salt. A yellow solution was formed when ethyl dinitroacetate (3.56 g., 0.02 mole) was dissolved in 10 ml. of 95% ethanol. The solution became orange and warmed exothermically on addition of hydrazine hydrate (1.0 g., 0.02 mole). On cooling, yellow plates separated which were filtered with suction, washed with ice-cold methanol, and dried at 60°; yield 3.17 g. (75%), m.p. 119–121°. A small second crop was combined with this material and the mixture was recrystallized from hot 95% ethanol. The salt separated in pale yellow needles weighing 2.44 g. It was not sensitive to heat or impact, melted at 119.5–120°, and had strong absorption bands at 6.69, 7.88, and 8.83μ.[7]

Anal. Calcd. for $C_4H_{10}N_4O_6$: C, 22.86; H, 4.79; N, 26.67. Found: C, 23.14, 23.16; H, 4.62, 5.31; N, 26.48.

Dinitroacethydrazide hydrazine salt. The hydrazine salt of ethyl dinitroacetate (1.05 g., 0.005 mole) was dissolved in 10 ml. of water. To this solution was added hydrazine hydrate (0.25 g., 0.005 mole) and the mixture was allowed to stand at room temperature for 18 hr. The yellow aqueous solution was evaporated under reduced pressure (1 mm.). The residue was a yellow sirup which solidified on standing, yield 1.01 g. (theory 0.98 g.). It was crystallized twice from 95% ethanol and dried at 60° to yield 0.15 g. of yellow plates, m.p. 106° (dec.), $\lambda(NH)$ 3.14μ, $\lambda(C{=}O)$ 5.94μ, $\lambda(NH$ def.) 6.22μ. $\lambda[{-}C(NO_2)_2]$ 6.75, 7.94. 8.90μ.[7]

Anal. Calcd. for $C_2H_8N_6O_5$: C, 12.24; H, 4.11; N, 42.88. Found: C, 12.29; H, 3.94; N, 42.76.

1,1-Dinitroethane hydrazine salt. Pure ethyl dinitropropionate (0.84 g., 0.0043 mole) was dissolved in 10 ml. of 95% ethanol and treated with 0.225 g. (0.0045 mole) of hydrazine hydrate. The solution was allowed to stand. A yellow product crystallized in plates after 0.5 hr. at room temperature,

(6) A. F. Ferris, K. W. McLean, I. G. Marks, and W. D. Emmons, *J. Am. Chem. Soc.*, **75**, 4078 (1953).

(7) According to J. F. Brown [*J. Am. Chem. Soc.*, **77**, 6346 (1955)], potassium salts of 1,1-dinitroparaffins absorb at 8.05 and 8.69 μ. The salts investigated in this laboratory always showed a third strong band at 6.72 ± 0.03μ (in KBr disks).

was filtered with suction, and dried at 60°; yield 0.33 g. (50%), m.p. 137–138° (dec.). Its infrared spectrum, characterized by strong bands at 6.70, 8.10, and 8.70μ,[7] was identical with that of an authentic specimen, prepared as follows:

1,1-Dinitroethane (12.0 g., 0.1 mole) was dissolved in 50 ml. of 95% ethanol. To this solution was added with shaking hydrazine hydrate (5.0 g., 0.1 mole). The mixture was cooled to 5° and filtered with suction. The yellow plates were washed with ethanol and dried at 60°; yield 14.0 g. (92%), m.p. 135.8° (dec.).

Anal. Calcd. for $C_2H_8N_4O_4$: C, 15.79; H, 5.26; N, 36.85. Found: C, 15.94; H, 5.22; N, 36.77.

1,1-Dinitropropane hydrazine salt. Ethyl α,α-dinitrobutyrate (1.2 g., 0.0058 mole), dissolved in 10 ml. of 95% ethanol, was refluxed with hydrazine hydrate (0.291 g., 0.00582 mole) for 2 hr. The oily product (0.97 g.) remaining after removing the solvent was crystallized from little 95% ethanol and furnished yellow needles; yield 0.29 g. (30%), m.p. 102° (dec.), which had the same infrared spectrum as the authentic salt described below.

Equimolar portions of 1,1-dinitropropane and hydrazine hydrate in ethanol gave an 81% yield of yellow hydrazine salt, m.p. 102–103° (dec.), with strong absorption bands at 6.76, 8.20 and 8.88μ.[7]

Anal. Calcd. for $C_3H_{10}N_4O_4$: C, 21.69; H, 6.06; N, 33.73. Found: C, 21.95; H, 6.18; N, 33.68.

Infrared absorption spectra were determined with a Perkin Elmer Model 21 spectrophotometer.

Los Alamos, N. M.

[Contribution from the Los Alamos Scientific Laboratory, University of California]

Some Michael-Like Additions of Primary Nitramines*

L. W. KISSINGER and M. SCHWARTZ

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Several primary nitramines react with acrylonitrile, methyl acrylate, methyl vinyl ketone, acrylamide, and diethyl maleate under basic conditions to give secondary nitramines. Some chemical and physical properties of the adducts are given.

In the course of studies of the chemistry of nitramines we have observed Michael-like additions of several primary aliphatic nitramines to certain activated unsaturated systems giving secondary nitramines in good yields. The reaction offers an alternate route for the preparation of such substituted secondary nitramines which were reported previously by Frankel and Klager.[1] Primary aliphatic nitramines react with the unsaturated systems indicated below:

$$RNHNO_2 + XCH{=}CHY \xrightarrow{\text{Base}} RN(NO_2)CHX{-}CH_2Y$$

Y = acetyl, carbethoxy, amido, or cyano;
X = hydrogen except where X and Y are carbethoxy

The adducts are best obtained by warming the primary nitramine with an excess of the unsaturated compound in the presence of catalytic amounts of Triton B without solvent. The same compounds also arise when aqueous methanol solutions of the alkali metal salts of primary nitramines are treated with the unsaturated compounds. However, as is anticipated from the known retrogression of the Michael reaction,[2] the yields are much lower under these conditions. The simultaneous addition of methanol to the unsaturated systems to give the β-methoxy compounds also contributes to the low yields when the latter method is used. Thus, with acrylonitrile the secondary nitramines are accompanied by β-methoxypropionitrile.[3]

Reaction conditions, yields, physical properties, and analytical data for the individual adducts are given in Table I. 4-Nitro-4-aza-pentanenitrile (I) and methyl 4-nitro-4-azapentanoate (II) are reported by Frankel and Klager;[1] 4,7 dinitro-4,7-diazadecanedinitrile (X) was previously prepared by the nitration of the adduct obtained from ethylenediamine and acrylonitrile.[4]

The methyl vinyl ketone–methylnitramine adduct appears to form in a normal way and crude 5-nitro-5-aza-2-hexanone (III) can be washed free of methylnitramine with water to give a crude product which, however, is high in carbon. Attempts at purification by distillation give instead a mixture in which methylnitramine is a major constituent. The ketone III also resists purification by chromatographic treatment on an acid washed alumina packed column.

These compounds show ultraviolet[5] and infrared[6] absorption spectra typical of secondary nitramines, the most important features of which are also given in Table I.

The adducts are assigned the secondary nitramine structure primarily on the basis of their infrared and ultraviolet absorption spectra. Samples of

* This work was performed under the auspices of the U. S. Atomic Energy Commission.

(1) M. B. Frankel and K. Klager, *J. Am. Chem. Soc.*, **78**, 5428 (1956).

(2) C. K. Ingold, *Structure and Mechanism in Organic Chemistry*, Cornell Univ. Press, Ithaca, N. Y., 1953, p. 691.

(3) H. A. Bruson, U. S. Patent **2,280,791** [*Chem. Abstr.*, **36**, 5589 (1942)].

(4) M. H. Gold, Aerojet-General Corp., Azusa, Calif., personal communication.

(5) R. N. Jones and G. D. Thorn, *Can. J. Research*, **27B**, 828 (1949).

(6) L. J. Bellamy, *The Infrared Spectra of Complex Molecules*, Wiley and Sons, New York, 1954, p. 252.

TABLE I

METHOD OF PREPARATION AND PROPERTIES OF SECONDARY NITRAMINES PREPARED

Reactants		Method and Conditions[a]			Product	Yield, %	B.P.		$n_D^{25°}$
Nitramine	Conjugated compound		°C.	Hr.			°C.[b]	mm.	
Methyl-	Acrylonitrile	A[a]	55	3	4-Nitro-4-azapentanenitrile (I)[1]	78	84–86	0.06	1.4858
	Methyl acrylate	A	55	6	Methyl 4-nitro-4-azapentanoate (II)	62	64	0.03	1.4694
	Methyl acrylate	B	40	36	Methyl 4-nitro-4-azapentanoate (II)	30	70–74	0.1	
	Methyl vinyl ketone	A	60	6	2-Nitro-2-aza-5-hexanone (III)	38	[Crude oil]		1.4795
Ethyl-	Acrylonitrile	A	75	5	4-Nitro-4-azahexanenitrile (IV)	72	110	0.1	1.4792
	Methyl acrylate	A	75	5	Methyl 4-nitro-4-azahexanoate (V)	51	62–65	0.1	1.4651
	Methyl acrylate	B	60	2	Methyl 4-nitro-4-azahexanoate (V)	15	62–65	0.1	
	Methyl vinyl ketone	A	60	6	3-Nitro-3-aza-6-heptanone (VI)	68	114	2	1.4715
	Acrylamide	A	60	24	4-Nitro-4-azahexanamide (VII)	75	[M.p. 95–96]		
	Diethyl maleate	A	80	96	Ethyl 3-carbethoxy-4-nitro-4-azahexanoate (VIII)	15	112–115	0.1	1.4544
n-Butyl-	Methyl acrylate	A	75	20	Methyl 4-nitro-4-azaoctanoate (IX)	45	110–113	0.1	1.4622
	Methyl acrylate	B	55	6	Methyl 4-nitro-4-azaoctanoate (IX)	22	110–113	0.1	1.4622
Ethylenedi-	Acrylonitrile	A	75	6	4,7-Dinitro-4,7-diazadecanedinitrile (X)	70	[M.p. 128–129]		
	Methyl acrylate	A	70	24	Dimethyl 4,7-dinitro-4,7-diazadecane dioate (XI)	72	[M.p. 122–124]		
	Methyl acrylate	B	50	2	Dimethyl 4,7-dinitro-4,7-diazadecanedioate (XI)	20	[M.p. 122–124]		
N-Methylethylenedi-	Acrylonitrile	A[c]	60	8	4,7-Dinitro-4,7-diazaoctanenitrile (XII)	70	[M.p. 91–92]		
	Ethyl acrylate	A[c]	55	8	Ethyl 4,7-dinitro-4,7-diazaoctanoate (XIII)	48	[M.p. 38–39]		
	Methyl acrylate	A[c]	60	8	Methyl 4,7-dinitro-4,7-diazaoctanoate (XIV)	74	[M.p. 61–62]		

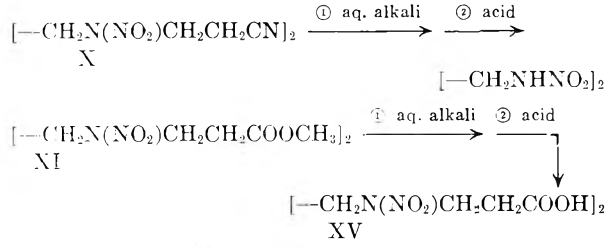
Compound	Analyses[d] Calcd. Formula	C	H	N	Found C	H	N	Infrared Absorption[e] λC = 0, μ	λ NO_2, μ	Ultraviolet Absorption[h] λ_{max}, mμ	Log ε
I	$C_4H_7N_3O_2$	37.21	5.46	32.54				[4.50][f]	6.53, 7.76	239	3.84
II	$C_5H_{10}N_2O_4$	37.03	6.22	17.28	37.29	6.49	16.82	5.72	6.63, 7.78		
II	$C_5H_{10}N_2O_4$	37.03	6.22	17.28	37.08	6.43	17.21				
III	$C_5H_{10}N_2O_3$	41.09	6.90	19.17	45.94	7.43		5.80	6.55, 7.75		
IV	$C_5H_9N_3O_2$	41.95	6.34	29.36	42.51	6.41	29.26	[4.49][f]	6.50, 7.82	240	3.84
V	$C_6H_{12}N_2O_4$	40.90	6.87	15.90	41.01	7.14	15.46	5.66	6.50, 7.77	241	3.86
V	$C_6H_{12}N_2O_4$	40.90	6.87	15.90	40.72	6.83	15.89				
VI	$C_6H_{12}N_2O_3$	44.99	7.55	17.49	45.01	7.50	17.52	5.80	6.60, 7.85		
VII	$C_5H_{11}N_3O_3$	37.26	6.88	26.08	37.49	6.92	26.16	5.92	6.61, 7.79	241	3.83
VIII	$C_{10}H_{18}N_2O_6$	45.79	6.92	10.68	45.95	7.19	10.19	5.78	6.57, 7.70		
IX	$C_8H_{16}N_2O_4$	47.05	7.90	13.72	47.09	7.40	14.24	5.74	6.61, 7.78	242[i]	3.89[i]
IX	$C_8H_{16}N_2O_4$	47.05	7.90	13.72			13.24				
X	$C_8H_{12}N_6O_4$	37.50	4.72	32.80	37.07	4.77	31.63		6.55,[g] 7.86[g]	239[i]	4.04[i]
XI	$C_{10}H_{18}N_4O_8$	37.27	5.63	17.39	36.79	5.02	16.95	5.77	6.57, 7.88		
XII	$C_6H_{11}N_5O_4$	33.18	5.11	32.25	32.91	5.22	31.90	[4.51][f]	6.55, 7.88		
XIII	$C_8H_{16}N_4O_6$	36.36	6.10	21.20	36.69	6.36	20.78	5.77	6.55, 7.87		
XIV	$C_7H_{14}N_4O_6$	33.60	5.64	22.39	33.75	6.09	22.12	5.75	6.55, 7.88		

[a] Refer to Experimental Section for details of methods A and B. [b] All temperatures are uncorrected. [c] At the end of the reaction period these products were isolated by stripping off the volatiles under reduced pressure and crystallizing the residues from methanol. [d] Microanalyses by M. J. Naranjo and C. A. Esquibel. [e] Infrared absorption spectra were determined with a Model 21 Perkin-Elmer recording instrument in matched 0.1-mm. sodium chloride cells in chloroform solution unless otherwise specified. [f] C≡N stretching absorption. [g] In acetonitrile solution. [h] Ultraviolet absorption spectra were determined by H. E. Ungnade with a Model DR Beckman instrument in 1-cm. fused silica cells in 95% ethanol unless otherwise specified. [i] In 92 parts of 95% ethanol and 8 parts acetonitrile.

compounds I and X kindly furnished by Gold[4] were indistinguishable from ours in other physical properties as well. Thus, we feel that the alternate structure, $R—N{=}N(\uparrow O)—O—CH(|)—CH_2Y$, arising by addition of the *aci*-form of the primary nitramine, is eliminated.

The secondary nitramines, with the exception of the ketones already noted, are chemically stable compounds undergoing reactions typical of the functional groups which they contain. Apparently only where there is sufficient activation on the carbon atom *beta* to the nitramine does strong alkali reverse the original condensation. Thus, 4,7-dinitro-4,7-diazadecanedinitrile (X) reacts rapidly with excess aqueous alkali to give ethylenedinitra-

mine and decomposition products of acrylonitrile while dimethyl 4,7-dinitro-4,7-diazadecanedioate (XI) under the same conditions is converted to the anion of 4,7-dinitro-4,7-diazadecanedioic acid (XV) which is stable in excess alkali.



EXPERIMENTAL

Methyl- and ethylnitramine, ethylenedinitramine, and *N*-methylethylenedinitramine were prepared as described by Franchimont and Klobbie;[7] *n*-butylnitramine was obtained by the method of van Erp.[8]

Michael additions: Method A. A mixture of the nitramine, 1.3–2.0 equivalents of the conjugated unsaturated compound, and a few drops of Triton B (commercial trimethylbenzyl ammonium hydroxide solution) was heated with stirring as specified in Table I. The progress of the reaction was followed by observing the relative intensities of the primary and secondary nitramine bands in the infrared. At the end of the reaction period the mixtures, except where noted, were poured into water and ether extracted. After decolorizing with charcoal and drying, solvent was removed from the ether extracts and liquid mixtures were separated by distillation through a small Vigreaux column; solid residues were purified by recrystallization from aqueous ethanol or methanol.

Method B. A solution of the sodium or potassium salt of the nitramine in 50% aqueous methanol was stirred while an equivalent weight of the conjugated unsaturated compound was added. After treating the mixture as specified in Table I, the product was isolated by diluting with an equal volume of cold water and extracting with ether. The dried ether extracts were then treated as described under Method A.

Action of alkali on 4,7-dinitro-4,7-diazadecanedinitrile (X). A suspension of 1 g. of 4,7-dinitro-4,7-diazadecanedinitrile (0.004 mole) in 6 ml. of water containing 1.3 g. (0.02 mole) of 85% potassium hydroxide was warmed on a steam bath for 1 hr. during which the suspension slowly cleared and ammonia was evolved. After chilling and acidification with 25% sulfuric acid, 0.49 g. (82%) of ethylenedinitramine, m.p. 174–178°, was obtained. The infrared spectrum of this sample in acetonitrile was indistinguishable from that of authentic ethylenedinitramine.

Action of alkali on dimethyl 4,7-dinitro-4,7-diazadecanedioate (XI); *preparation of 4,7-dinitro-4,7-diazadecanedioic acid* (XV). A suspension of 1 g. of dimethyl 4,7-dinitro-4,7-diazadecanedioate (0.003 mole) in 10 ml. of water containing 1.0 g. (0.018 mole) of 85% potassium hydroxide was warmed on a steam bath for 1 hr., cooled to room temperature, and acidified with concentrated hydrochloric acid. After chilling the mixture, 0.67 g. (76%) of 4,7-dinitro-4,7-diazadecanedioic acid (XV), m.p. 134.5–136.5°, was collected by filtration. Recrystallization from water gave plates melting at 142–143°, (Gold[4] gave the melting point of this compound as 141.5–142.5°.)

Anal. Calcd. for $C_8H_{14}N_4O_8$: C, 32.66; H, 4.80; N, 19.04; *neut. equiv.* 147. Found: C, 32.24; H, 4.58; N, 18.68; *neut. equiv.* 147.

Los Alamos, N. M.

(7) A. P. N. Franchimont and E. A. Klobbie, *Rec. trav. chim.*, **7**, 343, 347, 354, and 356 (1888).

(8) M. H. van Erp, *Rec. trav. chim.*, **14**, 26 (1895).

[Contribution No. 830 from the Chemistry Laboratories of Indiana University]

Reaction of Diethyl Oxalate with Some *ortho*-Substituted Anilines[1]

E. CAMPAIGNE and J. E. VAN VERTH[2]

Received January 30, 1958

Ethyl 2-benzothiazolecarboxylate (I) may be obtained in excellent yield by refluxing *o*-aminobenzenethiol with excess diethyl oxalate. However, *o*-aminophenol condenses with diethyl oxalate to yield a different type of product, the oxanilide III, while *o*-phenylenediamine formed still a third type of condensation product, the quinoxaline IV. The nature of the condensation products in these reactions was not altered by varying the conditions.

In connection with another problem, it was desirable to obtain large samples of esters of heterocyclic carboxylic acids, such as 2-benzothiazolecarboxylic acid. Ethyl 2-benzothiazolecarboxylate (I) has been previously prepared from the acid,[3] which, in turn, was prepared in several steps from other 2-substituted benzothiazoles.[4] A direct and more convenient method for preparing this ester from commercially available materials has now been found, which involves the condensation of 2-aminobenzenethiol with diethyl oxalate.

Hofmann,[5] in 1880, isolated 2,2′-bibenzothiazolyl (II) when these reactants were heated for "a long time and at a high temperature." It seemed reasonable that the reaction proceeded through the

(1) This work was supported by a contract between the Office of Naval Research, Department of the Navy, and Indiana University.

(2) Taken in part from the thesis of J. E. Van Verth, presented in partial fulfillment of the requirements for the degree of Doctor of Philosophy at Indiana University, 1957.

(3) (a) S. G. Fridman, *Zhur. Obshcheĭ Khim.*, **20**, 1191 (1950); *Chem. Abstr.*, **45**, 1579 (1951); (b) A. Reissert, *Ber.*, **37**, 3708 (1904).

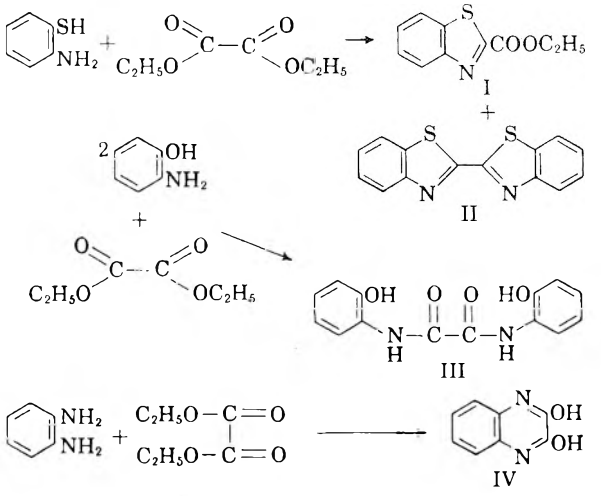
(4) (a) H. Gilman and J. A. Beel, *J. Am. Chem. Soc.*, **71**, 2328 (1949); (b) Y. Mizuno, *J. Pharm. Soc. Japan*, **72**, 1263 (1952); (c) H. Salkowski and W. Kunze, German Patent 613,067, May 11, 1935; *Chem. Abstr.*, **29**, 5461 (1935).

(5) A. W. Hofmann, *Ber.*, **13**, 1223 (1880).

intermediate I, which presumably would react slowly enough to be isolated. It was found that I could be obtained by refluxing the reactants in a molar excess of diethyl oxalate for four hours. The ester was isolated by pouring the resulting solution into a mixture of dilute hydrochloric acid and ethanol which dissolved the excess ethyl oxalate and unreacted aminothiol, so that I could solidify and be removed by filtration. The crude ester, obtained in 80% yield, was contaminated with about 6% by weight of crude II, which was removed by virtue of the latter's insolubility in hot petroleum ether, from which I readily crystallized. Although quite insoluble in most solvents, II was easily crystallized from dioxane.

This synthesis of ethyl 2-benzothiazolecarboxylate achieves in one step what previously required four to six steps, by way of the acid. Indeed, the hydrolysis of the ester prepared in this way may provide the most convenient route to the acid itself, and no doubt *benz*-substituted analogs could be prepared similarly, contingent on the availability of the necessary *o*-aminothiols.

In view of this result, we decided to reinvestigate the reactions of diethyl oxalate with *o*-phenylenediamine and *o*-aminophenol, in the hope of obtaining esters of 2-benzimidazolecarboxylic acid and 2-benzoxazolecarboxylic acid. A one- or two-molar excess of oxalate ester was used as solvent; in each case only the product which had been previously reported[6] was obtained. It is remarkable that each of the three *o*-substituted amines gave a different type of product.



Although Reissert and Goll[7] had reported that the reaction of 4-nitro-2-aminodiphenylamine with diethyl oxalate produced some benzimidazole ester in addition to the quinoxaline, all efforts to isolate ethyl 2-benzimidazolecarboxylate from the reaction mixture of *o*-phenylenediamine with diethyl oxalate were unavailing; only 2,3-quinoxalinediol (IV) was obtained. Since acid catalysts might promote the ring closure, these were examined briefly. Zinc chloride increased the rate but did not change the course of the reactions of diethyl oxalate with *o*-phenylenediamine and *o*-aminophenol. Essentially the same yield (87–89%) of IV was obtained when the reactants were heated without catalyst for one hour as when they were heated at approximately the same temperature with a small amount of zinc chloride for only twenty minutes. With *o*-aminophenol, at least, the rate of reaction was apparently affected more by the temperature than by the addition of catalyst, 69% of *o,o'*-dihydroxyoxanilide (III) being obtained after one hour on the steam bath and 89% after fifteen minutes at reflux. The addition of a small amount of a solution of zinc chloride in absolute ethanol lowered the reflux temperature of the mixture to about that of a steam bath and under these conditions 86% of III was obtained after one hour. Meyer and Seeliger[6] had found that III was formed even when diethyl oxalate was present in large excess. In an attempt to promote the reaction of ethyl oxalate with *o*-aminophenol in a 1:1 molar ratio, one-tenth mole of the latter in pyridine was added over a period of three hours to a boiling pyridine solution of two-tenths mole of the ester, using pyridine hydrochloride as catalyst. Only III was isolated.

In the case of 2-aminobenzenethiol, the results were somewhat different. When zinc chloride in absolute ethanol was added as catalyst, the yield of I was lowered. This was undoubtedly due to the effect of the added ethanol in lowering the initial reflux temperature, which in the absence of catalyst, approached the boiling point of diethyl oxalate. In either case the temperature dropped as the reaction proceeded, because of the formation of ethanol. The catalyst apparently promoted further reaction of I with 2-aminobenzenethiol, for the amount of by-products (presumably chiefly II) formed in the presence of the catalyst was two to three times as much as without catalyst.

EXPERIMENTAL[8]

Ethyl 2-benzothiazolecarboxylate (I) *from 2-aminobenzenethiol.* A. *Without catalyst.* A mixture of 12.5 g. (0.1 mole) of 2-aminobenzenethiol and 29.2 g. (0.2 mole) of diethyl oxalate was heated at mild reflux for 4 hr., during which time the temperature decreased from 147 to 93°. After cooling, the mixture was poured into a solution consisting of 50 ml. of concentrated hydrochloric acid, 150 ml. of water, and 70 ml. of 95% ethanol. With stirring, the oil dissolved and a solid formed The mixture was cooled in an ice bath (to 9°), the product was removed by filtration, and washed with 75 ml. of chilled aqueous ethanol (*ca.* 25%) in two portions, then dried overnight in a vacuum desiccator. The 16.5 g. (80%) of crude ester melted at 69–69.5° (cloudy melt). When this was recrystallized from 53 ml. of 63–99° petroleum ether, 12.5 g. of needles melting at 69.8–70.5° were obtained in two crops. The ester is reported[3a,b] to melt at 70–71°.

(6) R. Meyer and A. Seeliger, *Ber.*, **29**, 2640 (1896).
(7) A. Reissert and G. Goll, *Ber.*, **38**, 90 (1905).

(8) Melting points are uncorrected. The authors are indebted to Miss Joanna Dickey for microanalyses.

Anal. Calcd. for $C_{10}H_8O_2NS$: N, 6.76. Found: N, 6.77.

A small amount (1.0 g.) of solid melting about 175–250° was insoluble in the hot petroleum ether. This was boiled with about 100 ml. of toluene; the hot mixture was filtered, and the filtrate was cooled in the refrigerator to produce 0.09 g. of crystals of 2,2′-bibenzothiazolyl (II), which were removed and washed with toluene and benzene. The tan platelets melted at about 310°. A melting point of "about 300°" was reported by Hofmann.[5] The analytical sample, white platelets, was obtained by recrystallizing from dioxane and washing with ether.

Anal. Calcd. for $C_{14}H_8N_2S_2$: N, 10.44. Found: N, 10.37.

B. With zinc chloride catalyst. A mixture of 12.5 g. (0.1 mole) of 2-aminobenzenethiol, 29.8 g. (0.2 mole) of diethyl oxalate, and 5 ml. of a 2*M* solution of fused zinc chloride in absolute ethanol was boiled under reflux for 4 hr., during which time the temperature decreased from 108 to 92°. After cooling, the solution was filtered to remove a small amount of inorganic solid, then worked up as in part A. The 14.4 g. (70%) of crude product, m.p. 69–69.5° (very cloudy melt), on recrystallization from 47 ml. of 63–99° petroleum ether, produced 7.1 g. of crystals melting at 69.8–70.5°. An additional crop of 0.5 g. was obtained from the mother liquor. The material insoluble in the hot petroleum ether weighed 2.7 g., and melted at *ca.* 150–210°. Even after extraction with hot petroleum ether (63–99°), 2.0 g., melting about 160–215°, remained.

2-Benzothiazolecarboxyhydrazide. A mixture of 20.7 g. of I and 6.0 g. of hydrazine hydrate (pract.) in 30 ml. of ethanol was refluxed for 15 min., and then cooled. The light yellow crystals were collected and washed with cold ethanol. They weighed 18.5 g. (95%) and melted without further purification at 175.0–175.6°. Y. Mizuno[4b] reported 2-benzothiazolecarboxyhydrazide to melt at 171°.

Anal. Calcd. for $C_8H_7ON_3S$: C, 49.69; H, 3.65; N, 21.73. Found: C, 49.62; H, 3.55; N, 21.83.

o,o′-Dihydroxyoxanilide (III) *from o-aminophenol. A. On the steam bath.* A mixture of 10.9 g. (0.1 mole) of *o*-aminophenol and 29.2 g. (0.2 mole) of diethyl oxalate was heated for 1 hr. on the steam bath. After cooling, the solid was removed and washed well with 95% ethanol. The yield was 9.4 g. (69%) of *o,o′*-dihydroxyoxanilide, melting at about 279–280° (dec.). Meyer and Seeliger[6] reported that this compound melted at 280–282°.

B. At reflux. The reaction was carried out as in part A, except that the mixture was heated at reflux (*ca.* 185°) for about 15 min., instead of on the steam bath. A 12.1 g. (89%) yield, m.p. 281–282° (dec.) was obtained.

C. With zinc chloride catalyst. The reaction was carried out as in part A, except that 5 ml. of a 2*M* solution of fused zinc chloride in absolute ethanol was added and the mixture heated under reflux for 1 hr. (The temperature fell from 109 to 91°), and worked up as before. The granular solid weighed 11.7 g. (86%) and melted at 283.5–284° (dec.).

When the reactants were heated under reflux in 55 ml. of 95% ethanol containing 0.5 g. of fused zinc chloride, only 3.9 g. (29%) of product was obtained on cooling.

D. With pyridine hydrochloride catalyst in pyridine. A stream of dry hydrogen chloride was passed into 500 ml. of dry pyridine to produce a weight increase of about 6 g. (0.16 mole). After the addition of 30.3 g. (0.207 mole) of diethyl oxalate, the solution was boiled under reflux while a solution of 10.9 g. (0.1 mole) of o-aminophenol in 200 ml. of pyridine was added dropwise, with stirring, over a period of 3 hr. After being heated for an additional 15 min., the solution was allowed to cool and divided into 2 equal parts. One part was poured slowly, with stirring, into 2 l. of water. The pink precipitate was removed and washed with water. A 4.4 g. (65%) yield of III was obtained. About 300 ml. of pyridine was distilled from the second half of the solution, which was then treated with 200 ml. of water, to yield 6.6 g. (97%) of III.

2,3-Quinoxalinediol (IV) *from o-phenylenediamine. A. Without catalyst.* A mixture of 10.8 g. (0.1 mole) of *o*-phenylenediamine (Eastman Kodak) and 43.9 g. (0.3 mole) of diethyl oxalate was heated for 1 hr. on the steam bath. After cooling, the solid was removed and washed with 95% ethanol. The yield was 14.4 g. (89%) of a gray-green solid, not melting below 300°, as reported by Meyer and Seeliger.[6] After recrystallization from methanol by Soxhlet extraction, the pure material decomposed at 372–373° (Fieser block).

Anal. Calcd. for $C_8H_6O_2N_2$: C, 59.25; H, 3.73. Found: C, 59.41; H, 3.67.

B. With zinc chloride catalyst. A mixture of 10.8 g. (0.1 mole) of *o*-phenylenediamine and 29.2 g. (0.2 mole) of diethyl oxalate was treated with 5 ml. of 2*M* solution of fused zinc chloride in absolute ethanol, and heated to boiling. Solid formed in the mixture very rapidly. After the mixture had refluxed for about 20 min., the temperature decreasing from about 100° to 83°, it was allowed to cool, filtered, and the solid washed with 95% ethanol. After combining with a small amount that separated from the filtrate, a yield of 14.1 g. (87%) of IV was obtained.

BLOOMINGTON, IND.

[CONTRIBUTION FROM KEDZIE CHEMICAL LABORATORY, MICHIGAN STATE UNIVERSITY]

A Study of the Alkylation of 2-Phenylbutanenitrile with Butyl Chlorides[1]

GORDON L. GOERNER AND ANDREW A. HOLZSCHUH

Received December 18, 1957

2-Phenylbutanenitrile has been alkylated with the butyl chlorides, using both sodamide and sodium hydride as condensing agents. With sodium hydride, the yields of products were found to be from 3 to 15% less than with sodamide. As predicted on the basis of Newman's *six-member* concept the highly hindered nitriles thus produced failed to hydrolyze. The "arylation" and alkylation of propionitrile has also been investigated briefly.

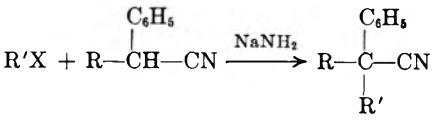
Previous papers from this laboratory have reported the alkylation of hydratroponitrile Ia with butyl[2] and amyl halides[3] (see equation page 1347).

In a continuation of these studies 2-phenylbu-

(1) Based in part on the M.S. thesis of Andrew A. Holzschuh, Michigan State University, June 1955. Presented at the 130th meeting of the American Chemical Society, Atlantic City, N. J., September 16–21, 1956.

(2) G. L. Goerner and W. R. Workman, *J. Org. Chem.*, 19, 37 (1954).

(3) R. L. Jacobs and G. L. Goerner, *J. Org. Chem.*, 21, 837 (1956).



I a, R = CH_3 II a, R = CH_3
b, R = C_2H_5 b, R = C_2H_5

tanenitrile Ib has been alkylated with the butyl chlorides. Although sodamide is the usual condensing agent for the alkylation of nitriles, sodium hydride has been used occasionally in this laboratory for the alkylation of certain substituted phenylacetonitriles with various benyzl chlorides. Since sodium hydride is readily available and easily handled, it appeared desirable to investigate its use as the condensing agent for the work at hand and to compare it with sodamide for this purpose.

Investigation showed that sodium hydride could be used in a manner similar to sodamide. The procedure adopted was essentially the high temperature sodamide method of Ziegler and Ohlinger,[4] with toluene serving as a suitable solvent. Since sodium hydride does not react directly with alkyl halides,[5] the mixture of butyl chloride, nitrile, and solvent could be charged directly into the reaction vessel and the sodium hydride could be added practically all at once at any temperature below the initial reflux temperature. The temperature of the reaction mixture gradually climbed as the reaction progressed and became constant as the reaction reached completion.

With sodamide as the condensing agent, the yields of alkylated nitrile with *n*-butyl, *sec*-butyl, and isobutyl chlorides varied from 87 to 93% and were in the order secondary>iso>normal. This order is essentially that observed when hydratroponitrile was alkylated with the butyl and amyl chlorides.[2,3] However with sodium hydride as the condensing agent, the yields were less, ranging from 78% with sec-butyl chloride to 85% with *n*-butyl chloride. In general the alkylations with sodium hydride proceeded more slowly than those with sodamide. With the *sec*-butyl and isobutyl chlorides, the alkylation took place at a more rapid rate than with *n*-butyl chloride. When the former were used, the reaction proceeded with a vigorous, rolling boil under our experimental conditions, the color of the solution soon became rust colored or red, and the sodium hydride was consumed at a reasonable rate. The reaction appeared to be complete in approximately two to three hours and a longer period of heating did not increase the yield appreciably. With *n*-butyl chloride on the other hand, the reaction appeared sluggish, the dark gray or black color of the sodium hydride persisted longer and at no time did the reaction proceed at the full rolling boil characteristic of the reactions involving the sec-butyl and isobutyl chlorides.

The physical properties of the 2-butyl-2-phenylbutanenitriles are shown in Table I and the derivatives prepared from them in Table II. The only reaction which these nitriles were found to undergo was reduction to the amine with lithium aluminium hydride. No derivative of nitrile IV was made since it was obtained in such small quantities. The amines were converted into either phenylthioureas or α-naphthylureas. Numerous unsuccessful attempts were made to hydrolyze the nitriles to either amides or acids employing strenuous acidic and basic conditions.

The behavior of these nitriles (I, II, and III) toward hydrolysis is identical with that observed previously with similar highly hindered nitriles prepared in our laboratory. Nitriles with an α-phenyl substituent and with a minimum *effective six-number* of 8 did not hydrolyze under conditions such as those employed in the present work.[2,3] Consequently it was anticipated that the four nitriles prepared here would not undergo hydrolysis since they all have an *effective six-number* of 8 or more. Recently Tsai, Miwa, and Newman[6] have reported that using vigorous acidic conditions, they were able to hydrolyze aliphatic nitriles with a *six number* of 12 fairly readily and a nitrile with a *six-number* of 15 to a limited extent. They also found that amides such as mesitamide were dehydrated by ethylene glycol–alkali to the corresponding nitriles at high temperatures. The discrepancy between our inability to hydrolyze nitriles with an *effective six-number* of 8 and the ability of Newman and co-workers[6] to hydrolyze nitriles with a *six-number* of 12 and 15 arises largely in the use of terms since the effect of a ring is not known precisely. The term *effective six-number*[7] has been used by us[2,3] to denote the number of atoms which are the sixth atom removed from the multiple bonded atom (nitrogen in this case) not counting those carbon atoms which are included in an aromatic ring. On the other hand the term *six-number*[7] customarily refers to those atoms which occupy the six position when no rings are involved From Stuart models it appears that the cyano group in a nitrile such as II above is hindered to approximately the same extent as the cyano group in ethyldiisopropylacetonitrile (*six-number* 15) which was hydrolyzed to a small extent by Newman and co-workers.[3] Indeed it appears that the phenyl group has a shielding effect and hindrance approximately equal to an isopropyl group in the nitriles under consideration.

In 1945 Bergstrom and Agostinho[8] reported the preparation of hydratroponitrile (α-phenylpropionitrile) by the "catalytic phenylation" of propionitrile with chlorobenzene in the presence of

(4) K. Ziegler and H. Ohlinger, *Ann.*, **495**, 84 (1932).

(5) S. J. Cristol, J. W. Ragsdale, and J. S. Meek, *J. Am. Chem. Soc.*, **71**, 1863 (1949).

(6) L. Tsai, T. Miwa, and M. S. Newman, *J. Am. Chem.* **79**, 2530 (1957).

(7) M. S. Newman, *J. Am. Chem. Soc.*, **72**, 4783 (1950).

(8) F. W. Bergstrom and R. Agostinho, *J. Am. Chem. Soc.*, **67**, 2152 (1945).

TABLE I

PHYSICAL PROPERTIES OF 2-BUTYL-2-PHENYLBUTANENITRILES[a]

No.	Compound	B.P., °C. (5 Mm.)	n_D^{25}	d^{25}	N, %[b]	Effective Six-Number
I	2-Phenyl-2-ethylhexanenitrile	127–128	1.4970	0.9320	6.90	8
II	2-Phenyl-2-ethyl-3-methylpentanenitrile	127–128	1.5037	.9466	6.91	11
III	2-Phenyl-2-ethyl-4-methylpentanenitrile	120–121	1.4969	.9326	7.02	8
IV	2-Phenyl-2-ethyl-3,3-dimethylbutanenitrile	123–126[c]	1.5107	.9571	6.86	14

[a] Determined on redistilled samples. [b] Calculated for $C_{14}H_{19}N$: N, 6.96. [c] Oil crystallized spontaneously after standing overnight. Recrystallized from ligroin, then methanol, m.p. 57.2–58° (corr.).

TABLE II

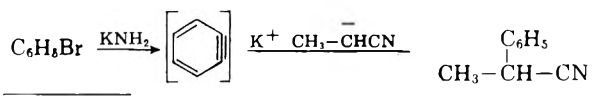
PROPERTIES OF THE 1-AMINO-2-BUTYL-2-PHENYLBUTANES

$$CH_3-CH_2-\underset{\displaystyle C_6H_5}{\overset{|}{C}}R-CH_2-NH_2$$

R	B.P., °C. (5 Mm.)	D^{25}	n_D^{25}	N,[a] %	Phenylthioureas M.P., °C.	N,[b] %	S,[b] %
n-Butyl	134.0	0.9283	1.5125	6.51	118.5–119	8.04	9.53
s-Butyl	129.5	0.9471	1.5116	6.62	176–177[c]	7.57[c]	
i-Butyl	120.5	0.9279	1.5130	7.06	140.5–141	8.06	9.30

[a] Calculated for $C_{14}H_{23}N$: N, 6.82. [b] Calculated for $C_{21}H_{28}N_2S$: N, 8.23; S, 9.42. [c] α-Naphthylurea. Calculated for $C_{26}H_{30}N_2O$: N, 7.48.

excessive amounts of potassium amide. It was hoped that a similar phenylation could be achieved with sodium hydride instead of potassium amide. However, when such a reaction was carried out using the alkylation procedure already described, only gums and extremely high boiling materials resulted. These materials were largely acid soluble and were presumed to be dimers or trimers of propionitrile. Dimers and trimers, both acid soluble, are known to form when aliphatic nitriles are treated with alkali metals.[9] The special arylation procedure of Bergstrom and Agostinho was next repeated. With potassium amide in liquid ammonia, the results were approximately the same as those reported. Sodamide gave a much smaller yield of hydratroponitrile under these same special conditions. Information coming to our attention since this work was completed makes it appear probable that the arylations described by Bergstrom and Agostinho proceed *via* the "benzyne" intermediate postulated by Roberts *et al.*[10] and others.[11] Consequently one would not anticipate that the reaction would proceed in the presence of sodium hydride since it is not a strong enough base to attack the aryl halide.[5] The arylation may be represented by the following equation



In the experimental procedure used by Bergstrom and Agostinho, the nitrile was first converted into is potassio derivate by potassium amide, to this was added an equivalent of chlorobenzene followed by a second equivalent of potassium amide. It is during the latter addition that the vigorous arylation occurs.

Since it was found impossible to arylate propionitrile in the presence of sodium hydride and since dimers and trimers were apparently formed from the propionitrile, it appeared desirable to try to alkylate an aliphatic nitrile in the presence of sodium hydride. From the reaction between propionitrile and *n*-butyl bromide there was recovered about a 23% yield of 2-methylhexanenitrile. This reaction also produced an acid soluble oil, presumed to be either a dimer or trimer, or a mixture of both, which could account for about half the starting nitrile. This reaction was not further investigated.

On the basis of this work, sodium hydride appears to be a satisfactory condensing agent for the alkylation of unsubstituted or substituted phenylacetonitriles. Although the yields from sodium hydride condensations are from 3 to 15% less than those from sodamide condensations (see Table I), the ease of handling and storage and the ready availability of sodium hydride may outweigh the greater yields obtainable with sodamide. Its use, of course, will make unnecessary the preparation of sodamide from liquid ammonia if commercial sodamide is not available. On the other hand, the desirability of using sodium hydride in the alkylation of aliphatic nitriles appears questionable since the latter undergo extensive polymization in its presence.

(9) V. Migrdichian, *The Chemistry of Organic Cyanogen Compounds*, Reinhold Publishing Corp., New York, 1947, p. 349.

(10) J. D. Roberts, D. A. Semenow, H. E. Simmons, Jr., and L. A. Carlsmith, *J. Am. Chem. Soc.*, **78**, 601 (1956).

(11) G. Wittig and R. Ludwig, *Angew. chem.*, **68**, 40 (1956); W. W. Leake and R. Levine, *Chem. and Ind. (London)*, **37**, 1160 (1955).

EXPERIMENTAL[12]

2-Phenylbutanenitrile. The nitrile, prepared by the phosphorus oxychloride dehydration of Eastman practical grade α-phenylbutyramide,[13] distilled at 110–111.5° (9 mm.), n_D^{25} 1.5060; reported[13] b.p. 122–124° (16 mm.), n_D^{25} 1.5070.

The *butyl chlorides* were of Eastman White Label grade and were redistilled before use.

Sodamide. Powdered material, purchased from Farchan Research Laboratories, was placed in small bottles under a nitrogen atmosphere and stored in a desiccator.

Sodium hydride and *lithium aluminum hydride,* obtained from Metallic Hydrides, Inc., were likewise rebottled and stored in a desiccator.

Alkylation of 2-phenylbutanenitrile. (*a*) *Sodamide method.* All alkylations were carried out using the high temperature procedure of Ziegler and Ohlinger[4] *exactly* as described previously.[2,3] The same molar ratios of reactants were used as before and the reaction mixtures were worked up similarly and distilled through nearly identical equipment. The aqueous layers were saved and titrated for chloride ion. In a typical run using 48.1 g. (0.332 mole) 2-phenylbutanenitrile, 35.6 g. (0.386 mole) *sec*-butyl chloride, and 15.9 g. (0.408 mole) sodamide, the following fractions were collected at 5-mm. pressure: *Fraction 1,* 0.8 g., b.p. 82–105°, n_D^{25} 1.5005; *Fraction 2,* 1.6 g., b.p. 105–127°, rising almost instantly to 127°, n_D^{25} 1.5039; *Fractions 3–7,* 55.2 g., b.p. 127–128°, n_D^{25} 1.5037 to 1.5039; *Fraction 8,* 5.4 g., b.p. 128–131°, n_D^{25} 1.5040; *residue* and column holdup, about 1 g. Fractions 2 through 8 weighed a total of 62.2 g., yield 93.3%. The chloride ion titrated as 0.332 mole, or 100% based on starting nitrile.

Alkylations carried out with the other butyl chlorides gave the following yields of alkylated product: *n*-butyl 87%; isobutyl, 90%; *tert*-butyl, 7.7%.

(*b*) *Sodium hydride method.* Alkylations using sodium hydride were carried out in the same general manner as those using sodamide. A typical reaction is as follows. Into a 500-ml. three-necked flask equipped with a stirrer, thermometer, reflux condenser, and wide-bore dropping funnel protected by a drying tube was placed a mixture of 48.1 g. (0.332 mole) 2-phenylbutanenitrile, 35.6 g. (0.386 mole) *n*-butyl chloride, and 50 ml. of dry toluene. The sodium hydride (approximately 10.0 g., 0.416 mole) was weighed by difference from a closed bottle by shaking directly into the dropping funnel where it was immediately covered with 50 ml. of dry toluene. The stirred mixture in the reaction flask was heated to 90° by means of a mantle and the suspension of sodium hydride in toluene was carefully added portionwise during approximately 10 min. (the solid was pushed through the bore of the stopcock with a glass rod or a wire when necessary). During 15 min. the temperature was raised to 104°. Some gas evolution or boiling now occurred. Over the next 6 hr., the temperature of the reaction mixture rose to 116° and became constant. The total time of heating was 9 hr. The color of the mixture progressed through yellow to a dirty mustard color.

Any excess sodium hydride was destroyed by the *cautious addition* (dropwise) of 15 ml. of ethyl alcohol to the cold, stirred reaction mixture, followed by 50 to 75 ml. of water. After the addition of a small amount of Celite, the mixture was filtered and the filter cake washed. The oil layer was separated and the water layer extracted with toluene and ether and saved for chloride analysis. The combined organic layers were dried over anhydrous calcium chloride, the solvent was stripped at the water aspirator, and the residue fractionated through a 2 × 20 cm. column packed with $^3/_{16}$ in. glass helices. The following fractions were collected at 5-mm. pressure: *Fraction 1,* 2.0 g., b.p. 92–123°, n_D^{25} 1.5005; *Fraction 2,* 2.0 g., b.p. rising instantly to 126°, n_D^{25} 1.4970; *Fractions 3–8,* 53.2 g., b.p. 126–128.5°, n_D^{25} 1.4969 to 1.4973; *Fraction 9,* 1.9 g., b.p. 126.5° dropping to 119°, n_D^{25} *residue* and column holdup, about 4 g. Fractions 2 through 9 weighed a total of 57.1 g., yield 85.6%. The chloride ion titrated as 0.297 mole, or 89.6% based on starting nitrile.

When alkylations were carried out with other butyl chlorides for the time specified, the following yields were obtained: *n*-butyl, 2 hr., 73%; *sec*-butyl, from 3 to 7.5 hr., 77 to 80%; isobutyl, from 2.5 to 7 hr., 80%.

Phenylation of propionitrile. The procedure of Bergstrom and Agostinho was followed in detail, using potassium amide, to give (*a*) 7.3 g. liquid, b.p. 116–140° (20 mm.), n_D^{25} 1.5124, or 27.7% if calculated as hydratroponitrile and (*b*) 13.9 g., b.p. from 140° (20 mm.) to 162° (3 mm.), n_D^{25} 1.5700, or 33.6% if calculated as diphenylpropionitrile. Bergstrom and Agostinho reported 43% of presumed hydratroponitrile, b.p. 105–112° (8 mm.). Hydratroponitrile has a b.p. 114–116° (19 mm.), 107–110° (11 mm.); n_D^{20} 1.5120, n_D^{25} 1.5090.[3] When sodamide was substituted for potassium amide a smaller yield of material boiling up to 117° (9 mm.) was obtained.

2-Methylhexanenitrile. To a mixture of 36.6 g. (0.67 mole) redistilled propionitrile and 100 g. (0.73 mole) *n*-butyl bromide in the apparatus described above there was added portionwise 16.0 g. (0.67 mole) sodium hydride in 100 ml. toluene. No noticeable reaction occurred until the mixture was heated to 112°. After heating for 2 to 3 hr., the gray color changed to white. Unreacted sodium hydride was destroyed by the dropwise addition of alcohol, followed by water (care!). The mixture was filtered (Celite) and the oil layer separated, acid washed, water washed and distilled. There was obtained 17.5 g. of 2-methylhexanenitrile (23.6%), b.p. 70–93° (mostly 78–80°) at 30 mm., n_D^{25} 1.4070, d^{25} 0.7985. A second fraction distilled at 100–126°, n_D^{25} 1.4255. (+)-2-Methylhexanenitrile has a reported b.p. 43–50° (9 mm.), d^{25} 0.797.[14]

A sample of the nitrile (1 g.) was hydrolyzed by heating with 5 ml. of 75% sulfuric acid on the steam bath for 20 min. The crystalline amide, m.p. 64–67°, was isolated after pouring the sulfuric acid into ice water. Recrystallization from benzene raised the m.p. to 68.5–69°. 2-Methylhexanamide is reported to melt at 70–72.5°[15] and (+)-2-methylhexanamide at 66°.[14]

Amines. The nitriles were reduced to the corresponding amines with lithium aluminum hydride by the procedure of Amundsen and Nelson[16] as described previously.[3] The amines were recovered in about 65% yield.

Attempted hydrolyses of the hindered nitriles were carried out as follows: (*1*) heating the nitriles with potassium hydroxide and a high boiling alcohol such as benzyl alcohol or a glycol at temperatures of 190° to 240° for as long as 16 hr.; (*2*) fusion with 60% potassium hydroxide; (*3*) heating with sulfuric acid (75 to 95%) or concentrated hydrochloric acid (aqueous under pressure or with dioxane solvent) up to 2 hr. at temperatures as high as 190°. Although a trace of ammonia was observed in some alkaline hydrolyses, only insoluble oily nitrile could be recovered. A water soluble product resulted from some hydrolyses with 90 to 95% sulfuric acid; this was presumed to be a ring-sulfonated product and was not further investigated.

EAST LANSING, MICH.

(12) Melting points and boiling points are uncorrected. All analyses were by Micro-Tech Laboratories, Skokie, Ill.

(13) D. J. Cram and J. Allinger, *J. Am. Chem. Soc.,* **76,** 4516 (1954).

(14) P. A. Levene and L. A. Mikeska, *J. Biol. Chem.,* **84,** 571 (1929).

(15) P. Rasetti, *Bull. soc. chim. France,* [3] **33,** 687 (1905).

(16) L. H. Amundsen and L. S. Nelson, *J. Am. Chem. Soc.,* **73,** 242 (1951).

[CONTRIBUTION FROM CALIFORNIA RESEARCH CORP.]

Exchange of Nitrile and Carboxyl Groups in Aromatic Compounds

W. G. TOLAND AND L. L. FERSTANDIG

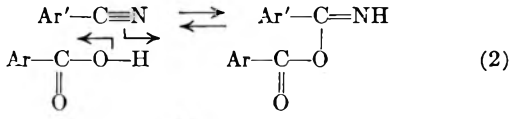
Received February 27, 1958

A method has been found to exchange quantitatively carboxylic acid and nitrile functions in aromatic compounds. The method involves heating a higher boiling nitrile with a lower boiling acid to form an equilibrium mixture containing the lower boiling nitrile and higher boiling acid. The equilibrium is displaced by distilling out the lower boiling nitrile. A mechanism of the exchange involving the isoimide intermediate is proposed. The general preparative value of the reaction and its application to the synthesis of iso- and terephthalic acids from the corresponding tolunitriles and xylenes are discussed.

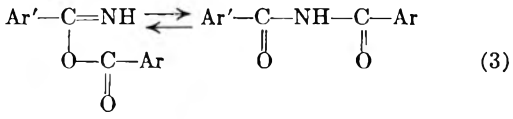
The reactions between nitriles and carboxylic acids have been known for some time.[1-6] Our work has shown that the reaction between aromatic nitriles and aromatic acids can be carried out to give nearly quantitative yields of the exchange products (Equation 1).

$$ArCO_2H + Ar'CN \longrightarrow ArCN + Ar'CO_2H \qquad (1)$$

We believe that the reaction of carboxyl and nitrile groups proceeds *via* Equations 2 and 3. In Equation 2



(2)



(3)

the acidic proton becomes attached to the cyanide nitrogen and, more or less simultaneously, the carboxylate oxygen forms a bond with the cyanide carbon. The isoimide intermediate then rearranges *via* Equation 3 to the dicarboximide. The mechanism proposed here is similar to that proposed by Davidson and Skovronek[7] for the reaction between anhydrides and amides. Their work indicates that the isoimide is, indeed, in equilibrium with dicarboximide, nitrile, carboxylic acid, *and amide and anhydride.* We did not examine our reaction mixtures for amide and anhydride, but we have no reason to doubt their presence. Other workers have also demonstrated that dicarboximide is in equilibrium with nitrile and carboxylic acid.[5] However, these authors do not mention the isoimide as an intermediate.

The work described in References 5 and 7 and our own work appear to be explained best by the mechanism above including the isoimide intermediate. The fact that electron-withdrawing groups accelerate the forward reaction[5] can be explained by this mechanism since withdrawing electrons increases the acidity of the acid, which, in turn, would facilitate protonation of the cyanide nitrogen. A striking example of the effect of a strong electron-withdrawing group is that trichloroacetic acid and its nitrile form the dicarboxamide quantitatively; *i.e.*, the equilibrium is shifted in favor of the dicarboxamide to a much greater extent in this case.

The reverse of Equations 2 and 3 does not show the exchange of nitrile and acid functions. However, when the original aromatic groups are different, the equilibrium mixture will, of course, contain both types of nitriles and acids, three types of dicarboxamides, and four types of isoimides, as well as amides and anhydrides. The actual distribution of components in equilibrium will depend upon the substituents on the aromatic groups. In our experiments, we used a simple device to avoid the tedious separation of such a mixture. The method depends upon the fact that nitriles invariably have lower boiling points than the corresponding acids. Thus, by starting with a high boiling nitrile and an acid, we can separate by distilling directly from the reaction vessel the lowest boiling component of the mixture; *i.e.*, the lower boiling nitrile. This route does more than simplify the preparation. The selective removal of the lowest boiling component shifts the equilibria in its favor and results in a nearly quantitative conversion to the new nitrile and new acid in a very short time. This has been done for various pairs of aromatic acids and nitriles in which the aromatic group was phenyl, tolyl, methoxyphenyl, chlorophenyl, cyanophenyl, and carboxyphenyl (Table I).

The reaction works well with equivalent quantities of acid and nitrile. However, when the lower boiling nitrile is the desired product, it is convenient to use an excess of higher boiling nitrile. A variation involves the use of a dinitrile as the source of nitrogen. This often results in an easy separation by virtue of large boiling point differences. A simple distillation column suffices for this purpose.

The rates and energies of activation for these

(1) A. Gautier, *Compt. rend.*, **67**, 1255 (1868); *Ann.*, **150**, 187 (1869).

(2) C. E. Colby and F. O. Dodge, *Am. Chem. J.*, **13**, 1 (1891).

(3) E. H. Miller, *J. Am. Chem. Soc.*, **16**, 433 (1894).

(4) J. A. Mathews, *J. Am. Chem. Soc.*, **20**, 648 (1898).

(5) R. H. Wiley and W. B. Guerrant, *J. Am. Chem. Soc.*, **71**, 981 (1949).

(6) The Distillers Co. Ltd., British Patent **722,843**, February 2, 1955.

(7) D. Davidson and H. Skovronek, *J. Am. Chem. Soc.*, **80**, 376 (1958).

TABLE I

EXAMPLES OF NITRILE FORMATION BY EXCHANGE

Reactants		Reaction Temp., °C.	Time, Hr.	Overhead Distillation Temp., °C.	Yield of[a] New Nitrile, % of Theory	Physical Constants of Crude Product
Acid, moles	Nitrile, moles					
Benzoic, 0.1	Isophthalo-, 0.2	237–287	3	190–194[b]	100	...
p-Toluic, 0.74	*p*-Carboxybenzo-, 0.68	230–242	3	210–216[c]	93	Neutral
Benzoic, 1.0	*p*-Chlorobenzo-, 0.4	240	1.5	191–195[b]	89	n_D^{20} = 1.5298[f]
p-Chlorobenzoic, 0.5	Isophthalo-, 1.0	259–294	0.7	220–223[d]	93	m.p. 88–91°[g]
Anisic, 0.5	Isophthalo-, 1.0	283–297	1.0	261–264[e]	95	Neutral. m.p. 53–60°[h]

[a] These yields do not include product which remained in the reaction vessel, column, and head. [b–h] Literature values for constants: [b] 190.7°, [c] 217°, [d] 223°, [e] 257°, [f] 1.5289, [g] 92°, [h] 62°.

equilibria have not been measured. We do know, however, from the literature and our own work that the reaction proceeds slowly at 150–175°, but rapidly at 200° and above. Under the latter conditions, the rate of formation of new products is usually limited by the rate of removal of the product, rather than by the rate of reaching equilibrium.

This interchange has been employed in a novel route to phthalic acids from xylenes.[8] In the oxidation of the xylenes to the phthalic acids, the toluic acids are intermediates. However, the toluic acids are oxidized more slowly to the phthalic acids than are toluic acid derivatives such as esters, anhydrides,[9,10] and nitriles. With the aid of the nitrile exchange reaction, tolunitrile is an excellent substitute for toluic acid. The tolunitrile is obtained in a cyclic process by nitrile-carboxyl exchange between the toluic acid and the tolunitrile oxidation product, cyanobenzoic acid. In this manner, xylene is oxidized to phthalic acid *via* tolunitrile with essentially complete conservation of nitrile groups. Equations 4–6 show the reactions involved:

$$CH_3C_6H_4CH_3 + {}^3/_2O_2 \longrightarrow CH_3C_6H_4CO_2H + H_2O \quad (4)$$

$$CH_3C_6H_4CO_2H + NCC_6H_4CO_2H \longrightarrow CH_3C_6H_4CN + HO_2CC_6H_4CO_2H \quad (5)$$

$$CH_3C_6H_4CN + {}^3/_2O_2 \longrightarrow HO_2CC_6H_4CN + H_2O \quad (6)$$

(8) W. G. Toland, California Research Corp., U. S. Patent 2,795,599, June 11, 1957.

(9) I. E. Levine, California Research Corp., U. S. Patent 2,653,165, September 22, 1953.

(10) Imhausen and Co., British Patent 727,989, April 13, 1955.

EXPERIMENTAL

A typical example of the nitrile exchange reaction is described below. The equipment and procedures are identical for all the examples listed in Table I. The reaction vessel is a 500-ml. round bottomed flask equipped with a thermowell for temperature readings and a standard taper joint for a column connection. The flask is heated with a Glas-Col mantle. The column is a 20-cm. length of 12-mm. glass tubing heated externally with Nichrome wire and packed with one-fourth inch glass helices. Above the column is a simple distillation head provided with a water condenser and a stopcock for control of reflux ratio.

p-Chlorobenzonitrile. A mixture of 128 g. (1 mole) of isophthalonitrile and 78.2 g. (0.5 mole) of *p*-chlorobenzoic acid was heated in the flask. As the flask temperature reached 259°, distillation began at 220° overhead. The pot temperature rose from 259° to 294° over a period of 40 min., while 64 g. of distillate was collected from 220° to 223°. The melting point of the crude product is 88° to 91°. Literature values for *p*-chlorobenzonitrile are: m.p. 92°, b.p. 223°. The yield of *p*-chlorobenzonitrile is 93%, but it should be noted that additional nitrile was present in the flask, column, and head.

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[CONTRIBUTION FROM THE U. S. NAVAL RESEARCH LABORATORY]

Alkylation of Amines with Alcohols Catalyzed by Raney Nickel. II. Aliphatic Amines

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Received March 17, 1958

Heating Raney nickel in ethanol with butylamine and dibutylamine gave 54 and 42% yields, respectively, of *N*-ethyldibutylamine. Butylamine, 1-propanol and Raney nickel gave a 57% yield of *N*-propylbutylamine. The reaction of 1,6-diaminohexane with 1,4-butanediol in the presence of Raney nickel afforded a 15% yield of *N*-(4-hydroxybutyl)hexahydroazepine (I) plus an unidentified viscous oil. The structure of I was established by an independent synthesis.

In a previous publication[2] we have reported the *N*-alkylation of aniline and benzidine with various aliphatic alcohols catalyzed by Raney nickel. Subsequently other investigators[3-5] described similar alkylations. The present communication is concerned with some reactions of butylamine with ethanol and 1-propanol, and a novel reaction of 1,6-diaminohexane with 1,4-butanediol, all in the presence of Raney nickel.

Alkylation products from butylamine. When a mixture of butylamine and Raney nickel in a large excess of ethanol was heated under reflux for 16 hr., a 54% yield of *N*-ethyldibutylamine was obtained. Substitution of dibutylamine for butylamine gave a 42% yield of *N*-ethyldibutylamine. A similar reaction mixture of butylamine, Raney nickel, and 1-propanol afforded a 57% yield of *N*-propylbutylamine.

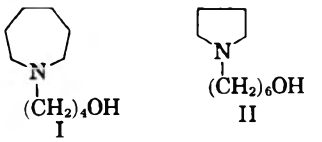
The *N*-ethyldibutylamine was identified by an independent synthesis from dibutylamine and ethyl bromide. Picrates prepared from this tertiary amine obtained by the three different reaction paths were found to melt identically, both alone and in admixture.

The above results contrast somewhat with those of Kao, Tilak, and Venkataraman,[3] who obtained unspecified yields of both *N*-ethylbutylamine and dibutylamine, along with a trace of *N*,*N*-diethylbutylamine, by heating under reflux for 3.5 hr. a mixture of butylamine, Raney nickel and excess ethanol. When the reaction was carried out at 30° for 20 hr., only *N*-ethylbutylamine and dibutylamine (unspecified yields) were obtained. *N*-Ethyldibutylamine was not reported as a product of either reaction mixture.

It appears, therefore, that the *N*-alkylation reaction, which apparently is specific when carried out with primary arylamines to yield only *N*-alkylarylamines, is not selective when applied to aliphatic amines.

Reaction of 1,6-diaminohexane with 1,4-butanediol. When an equimolar mixture of 1,6-diaminohexane with 1,4-butanediol in toluene was heated under reflux in the presence of Raney nickel, a considerable amount of ammonia was evolved. Although two liquid products were isolated from the reaction mixture, only the lower boiling product was identified. Attempts to distil the residual viscous oil resulted in decomposition. These properties suggest that the oil may be the expected polyamine.

The volatile component was indicated to be either *N*-(4-hydroxybutyl)hexahydroazepine (I) or the isomeric *N*-(6-hydroxyhexyl)pyrrolidine (II) on



the basis of results of elemental analyses, molecular weight determination, and standard qualitative tests. The formation of II is considered to be improbable since its mode of formation necessitates the replacement of an amine by an hydroxyl group. This replacement is not required in the formation of I.

The final decision in favor of the more logical structure I was made on the basis of an independent synthesis. The procedure of Moffett,[6] by which had been prepared *N*-(1,1-dimethyl-2-hydroxyethyl)pyrrolidine from the condensation of 1,4-dibromobutane with 2-amino-2-methylpropanol-1, was followed resulting in a 3% yield of I by the reaction of 1,6-dibromohexane with 4-aminobutanol-1. The two products (I) were shown to be the same by the identities of their infrared spectra and the melting points of their methiodide derivatives. Compound II was eliminated from consideration when it was synthesized by the reaction of 1,4-dibromobutane with 6-aminohexanol-1 and shown to have properties different from those of I obtained by the diamine-diol reaction.

(1) To whom correspondence should be addressed: Process Control Department, Convair, Fort Worth, Tex.

(2) R. G. Rice and E. J. Kohn, *J. Am. Chem. Soc.*, **77**, 4052 (1955).

(3) G. N. Kao, B. D. Tilak, and K. Venkataraman, *J. Sci. Ind. Research (India)*, **14B**, 624 (1955).

(4) C. Ainsworth, *J. Am. Chem. Soc.*, **78**, 1635 (1956).

(5) J. Horyna and O. Černý, *Chem. Listy*, **50**, 381 (1956); *Collection Czech. Chem. Communs.*, **21**, 906 (1956).

(6) R. B. Moffett, *J. Org. Chem.*, **14**, 866 (1949).

A somewhat similar condensation was carried out by Kao, Tilak, and Venkataraman[3] by heating *o*-phenylenediamine and ethylene glycol in the presence of Raney nickel. They obtained 1,2,3,4-tetrahydroquinoxaline in 20% yield together with an unidentified liquid. The yield of I obtained in the present investigation from the reaction of 1,6-diaminohexane and 1,4-butanediol was 15%.

Mechanisms of the reactions. Several logical reaction paths can be devised to explain the formation of the various products obtained. These involve dehydrogenation, addition-elimination, dehydration and hydrogenation reactions of types described elsewhere.[3–5,7,8] The limited experimental evidence obtained, however, does not permit a choice between these several possible reaction routes.

The formation of *N*-ethyldibutylamine from both butyl- and dibutylamines would seem to suggest that perhaps dibutylamine is an intermediate in condensations involving butylamine. At the same time, however, this view is negated by the fact that the reaction of butylamine with 1-propanol produced *N*-propylbutylamine and not *N*-propyldibutylamine.

Discussion of infrared spectra. The infrared spectra of the compound I prepared by the two methods described earlier, are identical in the 2–15 μ region, and are different from the spectrum of II. These spectra are presented in Figure 1. It is of interest that the infrared spectrum of 1-pentanol[9] is closely similar to, but not identical with, that of I. Apparently the seven membered heterocyclic ring adds no intense group absorption bands to the spectrum of the straight chain alcohol portion of I.

The spectrum of I indicates the presence of tertiary amine and hydroxyl groups which are hydrogen bonded. In solutions of carbon tetrachloride the position of the hydroxyl band in I is shifted to lower frequencies (3450 cm.$^{-1}$ in the liquid state, 3150 cm.$^{-1}$ in CCl_4 solution), which is in a direction opposite to that usually observed with hydrogen bonded hydroxyl groups. The explanation for this shift has not yet been determined. The results of dilution studies on this band, however, appear to be normal. An eight-fold dilution of the carbon tetrachloride solution is exactly compensated by an eight fold increase in cell thickness. Thus it may be concluded that the hydrogen bonding in I is intramolecular.

The spectrum of II is similar to that of the straight chain alcohol 1-heptanol, although the similarity is not so striking as in the previous case. Hydrogen bonding again is evident. The free hydroxyl group frequency at 3620 cm.$^{-1}$ appears in carbon tetrachloride solutions of II, so that the hydrogen bonding in this case must be intermolecular. It is possible that the differences in modes of hydrogen bonding in the two compounds can be explained on the basis of ring size. The intramolecularly bonded I embraces a seven-membered ring, whereas nine members are required for II. The nine-membered intramolecularly bonded ring is expected to be less stable than the intermolecularly bonded form.

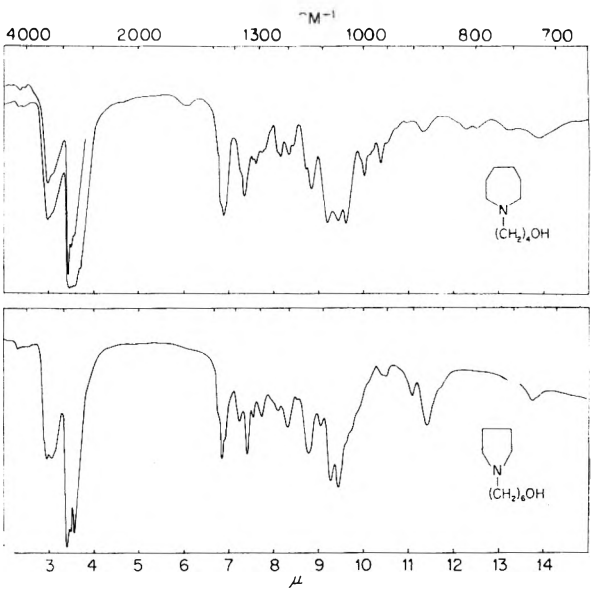


Fig. 1. Infrared spectra of I and II

EXPERIMENTAL[10]

Reagents. All chemicals used were of reagent grade. Raney nickel was prepared by the method of Mozingo,[11] stored under 95% ethanol, then washed with the appropriate alcohol immediately prior to use. 4-Aminobutanol-1 was obtained from Sapon Laboratories, Valley Stream, N. Y., and 1,6-dibromohexane and 1,4-dibromobutane were obtained from Columbia Organic Chemicals Co., Inc., Columbia, S. C.

Infrared measurements. The spectra in the range 2–15μ were obtained with a Perkin-Elmer Model 21 Infrared Spectrophotometer equipped with sodium chloride optics.

Alkylation products involving butylamines. The following standard procedure was employed: A mixture of 25 ml. of redistilled amine, 75 ml. of anhydrous alcohol, and 15 g. of Raney nickel was stirred and heated at reflux for 15 hrs. The nickel was filtered off and washed with 95% ethanol. After the filtrate and washings were combined, the solvents were removed by distillation at atmospheric pressure, then the residue was distilled *in vacuo*. In this manner butylamine and ethanol gave 10.80 g. (54% yield based upon butylamine) of *N*-ethyldibutylamine, b.p. 75–79° (30 mm.), n_D^{25} 1.4199; dibutylamine and ethanol gave 9.55 g. (42% yield based upon dibutylamine) of *N*-ethyldibutylamine, b.p. 169–170°. The picrate, recrystallized from 95% ethanol, in each case melted at 83.0–84.0°, both alone and in admixture. The methiodide, recrystallized from ethyl acetate, melted at 156.5–158.5° (uncorr.). Butylamine and 1-propanol gave 16.55 g. (57% yield) of *N*-propylbutylamine, b.p. 78–79° (30 mm.), n_D^{23} 1.4278. The hydrochloride

(7) E. J. Schwoegler and H. Adkins, *J. Am. Chem. Soc.*, 61, 3499 (1939).

(8) W. S. Emerson in *Org. Reactions*, IV, 174 (1948).

(9) American Petroleum Institute Collection of Infrared Spectra, No. 751.

(10) Analyses by Prof. M. Kathryn Gerdeman of the University of Maryland, College Park, Md. Melting points are corrected, except where otherwise noted; boiling points are uncorrected.

(11) R. Mozingo, *Org. Syntheses*, 21, 15 (1941).

melted at 266–267° (dec.) [lit.[12] 267–268° (dec.)]; however, the melting point of the α-naphthylthiourea (128.5–129.0°) failed to agree with the previously reported value[12] (136–137°) even after repeated recrystallization from 95% ethanol.

The molecular weight of *N*-ethyldibutylamine was 156 as determined by titration with standard hydrochloric acid using phenolphthalein indicator. The theoretical molecular weight is 157.3.

The absence of both primary and secondary amines was shown by the Hinsberg test.[13]

Independent synthesis of N-ethyldibutylamine. To 55 ml. (0.77 mole) of refluxing ethyl bromide was added with stirring 83 ml. (0.49 mole) of redistilled dibutylamine over a period of 2 hr. The mixture was refluxed an additional hr., cooled to room temperature and poured into 200 ml. of water. After extraction with ether the aqueous solution was made alkaline with 20% sodium hydroxide and the liberated oil extracted into ether. These extracts were dried over anhydrous magnesium sulfate, the ether removed under reduced pressure and the residue distilled. There was obtained 32.7 g. (42% yield based on dibutylamine) of crude *N*-ethyldibutylamine, b.p. 69–71° (32 mm.), n_D^{24} 1.4162. Residual secondary amine was removed by treating a portion of the crude product with benzoyl chloride, water, and sodium hydroxide under the conditions of the Schotten-Baumann reaction.[13] The aqueous mixture was extracted with ether, the ether solution extracted with 10% hydrochloric acid, the acid extracts made alkaline with 20% sodium hydroxide, and the resultant oil extracted into ether. Drying of the ethereal solution over anhydrous magnesium sulfate followed by removal of the solvent and distillation of the residue afforded *N*-ethyldibutylamine, b.p. 72–76° (26 mm.), n_D^{23} 1.4197.

Reaction of 1,6-diaminohexane with 1,4-butanediol. A mixture of 263 g. (2.26 moles) of 1,6-diaminohexane, 204 g. (2.26 moles) of 1,4-butanediol, 1000 ml. of anhydrous toluene and 50 g. of Raney nickel (washed with toluene) was stirred and refluxed 23 hr. under a condenser fitted with a Dean-Stark water trap. During this time a large amount of ammonia was evolved. Filtration of the mixture and fractionation of the filtrate yielded 109.6 g. of slightly amber colored, crude *N*-(4-hydroxybutyl)hexahydroazepine (I), b.p. 106–143° (4.5 mm.), n_D^{23} 1.4806, and 213 g. of a dark, viscous oil which decomposed during attempts at distillation under reduced pressure. Two further distillations of the crude I gave 25.75 g. (15% yield) of colorless I, b.p. 111–115° (2.8 mm.), n_D^{22} 1.4831, d_{20}^{20} 0.9487

Anal. Calcd. for $C_{10}H_{21}NO$: C, 70.12; H, 12.36; N, 8.18. Found: C, 69.46, 69.49; H, 12.62, 12.67; N, 8.20, 8.31.

The results of the carbon and hydrogen analyses indicated that the product was still impure even after the third distillation. The methiodide melted at 147.5–148.5° when recrystallized from absolute ethanol; the benzoate boiled at 168–170° (2.8 mm.), n_D^{22} 1.5132.

The molecular weight as determined by acidification of a sample of I with standard hydrochloric acid followed by titration of the excess acid with standard base using phenolphthalein indicator was 171.3; the Rast method using camphor gave a value of 161.4. The calculated molecular weight of I is 171.28.

The molar refraction determined from the density and refractive index data is 51.56 ml.; the value calculated from the data of Vogel[14] is 51.41 ml. In this calculation the increment due to the steric effect of the hexahydroazepine ring was assumed to be the same as that of cycloheptane.

Independent synthesis of I. The procedure of Moffett[6] was followed using 4-aminobutanol-1 and 1,6-dibromohexane, except that the nitrous acid treatment of the crude product was omitted. From 7.0 g. (0.0785 mole) of 4-aminobutanol-1 and 19.16 g. (0.0785 mole) of redistilled 1,6-dibromohexane there was obtained 0.43 g. (3.2% yield) of *N*-(4-hydroxybutyl)hexahydroazepine (I), b.p. 92.5–93.5° (0.02 mm.), n_D^{23} 1.4813. The infrared spectrum in the range 2–15μ was identical with that of the sample of I obtained from the diamine-diol reaction. The methiodide melted at 147.5–148.5°, after recrystallization from absolute ethanol.

N-(6-Hydroxyhexyl)pyrrolidine (II). *N*-(ω-bromohexyl)-phthalimide was prepared in 92% yield by the method of Kremer.[15] Hydrolysis of this compound with 20% KOH[15] gave a 36% yield of crude 6-aminohexanol-1. When this aminoalcohol was treated with redistilled 1,4-dibromobutane, according to the procedure of Moffett,[6] a 28% yield of II was obtained, b.p. 132–134° (9 mm.). n_D^{22} 1.4739.

WASHINGTON, D. C.

(12) K. N. Campbell, A. H. Sommers, and B. K. Campbell, *J. Am. Chem. Soc.*, 66, 83 (1944).

(13) R. L. Shriner and R. C. Fuson, *The Systematic Identification of Organic Compounds*, Third Ed., John Wiley & Sons, Inc., New York, 1948.

(14) A. I. Vogel, *J. Chem. Soc.* 1811, 1842 (1948).

(15) C. B. Kremer, *J. Am. Chem. Soc.*, 61, 1322 (1939).

[CONTRIBUTION FROM THE ROHM & HAAS CO.]

Transesterification of Methyl Methacrylate with Amino Alcohols. Preparation of a Primary Aminoalkyl Methacrylate and 2-Isopropenyl-4,4-dimethyloxazoline[1]

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The transesterification of 7-amino-3,7-dimethyloctanol (I) and methyl methacrylate, catalyzed by aluminum isopropoxide, gave 7-amino-3,7-dimethyloctyl methacrylate (II). The reaction of 2-amino-2-methylpropanol (III) with the ester, also catalyzed by heavy metal alkoxides, gave 2-isopropenyl-4,4-dimethyloxazoline (IV). The assigned structure was established by analyses, spectroscopy, and reduction to the 2-isopropyl analog (V) which was identical with an authentic sample. The oxazoline (IV) was also obtained by heating the methacrylic acid salt of III and by the acid-catalyzed cyclization of *N*-(1,1 dimethyl-2-β-hydroxyethyl)methacrylamide (VI).

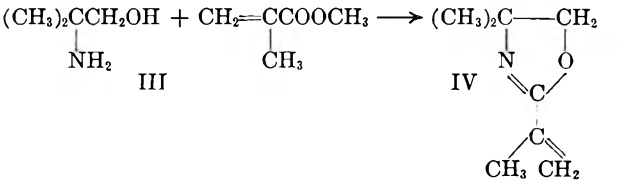
In a recent study of the reaction of 2-monoalkylaminoethanols with acrylic esters, the structure of the alkyl substituent was shown to be the factor which determined the nature of the product.[2] Usually, a complex mixture was obtained. Analyses of products indicated the predominance of amide formation, accompanied by transesterification of the hydroxyamide with methacrylate and addition of amine to the double bond. However, when the group in which the carbon atom bearing the nitrogen was fully substituted (*t*-butyl, 1,1,3,3-tetramethylbutyl), a clean transesterification occurred and the desired alkylaminoethyl methacrylates or acrylates were obtained in high yield.

This selectivity which favors the transesterification reaction stems from the slowness with which trialkylcarbinamines enter into aminolysis of esters[3] or addition to the double bonds of acrylic esters.[4] In this transesterification, the resulting absence of interfering side reactions engendered by the amino function leads to a single reaction product.

In order to investigate further the scope of this selectivity, the transesterification of methyl methacrylate with aminoalcohols was extended to those compounds containing primary amino groups attached to a fully substituted carbon atom.

One such compound, whose functional groups are widely separated, is 7-amino-3,7-dimethyloctanol (I). The reaction of this alcohol with methyl methacrylate in the presence of aluminum isopropoxide gave a single product, the primary amino ester, 7-amino-3,7-dimethyloctyl methacrylate (II). This was a distillable, colorless oil with the correct analysis and neutralization equivalent. One mole of hydrogen was absorbed in a quantitative hydrogenation in the presence of palladium. The infrared spectrum was very similar to that of *t*-butylaminoethyl methacrylate, but with an additional peak attributed to the primary amino group. It could be polymerized by heating with azo initiators to give a hard, clear, somewhat tacky polymer.

The application of this reaction to primary amino alcohols in which the functional groups were on proximate carbon atoms did not produce the expected amino esters, but instead led to new heterocyclic monomers. The main attention was given to the reaction of 2-amino-2-methylpropanol (III) with methyl methacrylate, from which 4,4-dimethyl-2-isopropenyloxazoline (IV) was obtained:



The catalysts used were aluminum isopropoxide, tetraalkyl titanates, and other alkoxides of metals of the middle groups in the periodic table. Since these materials should be destroyed by the presence of water, which would be one of the reaction products, it is considered that the intermediate aminoalkyl ester may have formed and then cyclized during the distillation. The crude product was obtained in about 65% yield and contained small amounts of water and starting amine. It could be purified by treatment with metallic sodium or isocyanates, followed by distillation.

The new olefinic oxazoline is a colorless liquid with a characteristic, pyridine-like odor, distillable under atmospheric pressure. It is partially miscible with water and soluble in typical organic solvents. Its composition was indicated by elemental analysis, neutral equivalent, and hydrogenation, in which one mole of hydrogen was absorbed. The reduction product, 4,4-dimethyl-2-isopropyloxazoline (V), was identical with the product obtained by the reaction of isobutyric acid with the amino alcohol.

(1) Presented at the 2nd Delaware Valley Regional Meeting of the American Chemical Society, Philadelphia, Pa., February 5, 1958.

(2) H. J. Sims, P. L. de Benneville, and A. J. Kresge, *J. Org. Chem.*, **22**, 787 (1957).

(3) L. M. Arnett, J. G. Miller, and A. R. Day, *J. Am. Chem. Soc.*, **72**, 5635 (1950).

(4) L. S. Luskin, M. J. Culver, G. E. Gantert, W. E. Craig, and R. S. Cook, *J. Am. Chem. Soc.*, **78**, 4042 (1956).

Each preparation of V gave the same picrate, which differed from the picrate of the olefinic oxazoline IV. The infrared spectra of both samples of V were superimposable and showed only one band at 1665 cm.$^{-1}$, attributed to the imine group.

The oxazoline IV showed two bands at 1658 and 1613 cm.$^{-1}$. These values are similar to the positions of the bands of α,β-unsaturated Schiff bases,[5] while the position of the single absorption band of the reduced oxazoline V is similar to the imine band of ordinary Schiff bases.[6] The data do not permit distinction in the assignment of imine and olefin to the two peaks of the oxazoline IV.

The conjugated structure was further indicated by the ultraviolet absorption spectrum in iso-octane (point of inflection at 225 mμ, log ϵ = 3.79). By contrast, the reduced oxazoline (V) showed only end absorption.

The oxazoline IV was obtained by two other methods. 2-Alkyloxazolines have been prepared in poor yields by heating ethanolamine salts of carboxylic acids above 250°.[7] These drastic conditions would not be desirable in the preparation of the new oxazoline. However, the salt of 2-amino-2-methylpropanol with methacrylic acid was rapidly dehydrated at 190° to give the oxazoline in 43% yield. Similar low temperatures sufficed in the preparation of the reduced oxazoline V from the amino alcohol and isobutyric acid. The olefinic oxazoline was contaminated by a small amount of an unknown impurity. This was indicated by a shoulder at 1662 cm.$^{-1}$ in the infrared spectrum, which was otherwise similar to that of the transesterification product. The contaminant might be 2-ethyl-4,4-dimethyloxazoline resulting from acid-catalyzed cleavage of the methylene group.

The dehydration of *N*-(1,1-dimethyl-2-hydroxyethyl)methacrylamide (VI), obtained by the reaction of the amino alcohol with methacryloyl chloride, was also studied. The intermediate amide was a viscous, colorless oil, distillable at low pressures. Its preparation required the addition of the chloride to an excess of amine; the reverse procedure gave a mixture of the hydroxyamide VI with its methacrylate ester.

When the pure amide VI was heated under atmospheric pressure at 175–180°, water and the oxazoline IV co-distilled. This amide is therefore another possible intermediate in the formation of the oxazoline in the transesterification method. The reaction was accelerated by the addition of a few drops of sulfuric acid. The acid-catalyzed cyclization gave the product in 60% yield and in a state of high purity, as indicated by the infrared spectrum.

The pyrolysis of the isomeric amide, *N*-(2-hydroxy - 2 - methyl)propylmethacrylamide (VIII), gave a small amount of distillate, but most of the product was a polymeric residue. This result further established the structural features needed for easy preparation of an oxazoline.

4,4-Dimethyl-4-isopropenyloxazoline was polymerized in bulk or in solution by heating in the presence of azo initiators. The resulting polymer was hard, clear resin, with inverse solubility in water, that is, soluble in the cold, precipitated by heating. Its infrared spectrum showed a single band at 1660 cm.$^{-1}$ indicating the survival of the oxazoline ring.

EXPERIMENTAL[8]

7-Amino-3,7-dimethyloctyl methacrylate (II). A mixture of 7-amino-3,7-dimethyloctanol[9] (57.6 g., 0.33 mole), methyl methacrylate (66.6 g., 0.67 mole), aluminum isopropoxide (2 g.), and di-β-naphthol (7.2 g.) was heated under a Vigreux column, 20 cm. long, and total reflux distillation head for 10 hr. Distillate (23 g.) was collected, about half between 65 and 70°, and the remainder as the temperature slowly rose to 98°. After removal of excess methyl methacrylate, the crude product (74 g., 92%), b.p. 119–146° (0.9 mm.), was obtained. Redistillation gave pure II, b.p. 115–120° (0.8 mm.), n_D^{25} 1.4570, d_{25}^{25} 0.9215, strong infrared peaks at 1724 (ester), 1641 (C = C) and 1565 cm.$^{-1}$ (NH_2).

Anal. Calcd. for $C_{14}H_{26}NO_2$: N, 5.8; neut. and hydrogenation equiv., 241. Found: N, 5.7; neut. equiv. 250; hydrogenation equiv. 255.

When II was heated with 1% by weight of dimethyl azoisobutyrate at 70° for about 16 hr., a clear, somewhat tacky polymer was obtained.

4,4-Dimethyl-2-isopropenyloxazoline (IV). *a. Transesterification of methyl methacrylate with 2-amino-2-methylpropanol* (III). A mixture of III (89 g., 1 mole), methyl methacrylate (220 g., 2.2 moles), and di-β-naphthol (10 g.) was heated under a short column (Cannon packing) and reflux head for 1 hr. to remove a small amount of water. Tetraisopropyl titanate (1 g.) was then added and distillation was continued for 15 hr. More catalyst was added after 4 and 11 hr. The pot temperature was carefully adjusted to keep the overhead temperature below 70° as long as possible. From the refractive indices of the distillates, the total collection of methanol was about 81% of the calculated amount. Distillation then gave 59 g. of recovered methyl methacrylate, 19.5 g. and 82.3 g. of product cuts, b.p. 61–56° (22 mm.) and 56–88° (21 mm.), respectively, 7.3 g. of higher boiling liquid, b.p. 83–103° (20 mm.) and 22 g. of residue.

The crude product fractions were combined and treated with ethyl isocyanate (25 g.) in pentane (200 cc.) to remove unreacted III and water. Two layers formed. The upper layer was distilled twice to give 52.3 g. of pure IV, b.p. 62–63° (30 mm.), while the lower layer gave 11 g., b.p. 65–66° (36 mm.); the total yield was 45%, n_D^{25} 1.4535–1.4540, d_{25}^{25} 0.9181, neut. equiv. calcd., 139; found, 142.

In a run of similar size, the pot temperature was held below 110° by operation at 400 mm. The yield of crude IV was then 89.5 g., b.p. 59–62° (34 mm.), which, after drying over sodium, was redistilled to give a 60% yield of pure IV, b.p. 149°.

(5) E. P. Goldberg and H. R. Nace, *J. Am. Chem. Soc.*, **75**, 3646 (1953); **77**, 359 (1955).

(6) W. D. Emmons, *J. Am. Chem. Soc.*, **79**, 5739 (1957); M. Carmack and L. S. Luskin, unpublished data.

(7) H. Wenker, *J. Am. Chem. Soc.*, **57**, 1079 (1935).

(8) The assistance of A. J. McFaull and Rita Cerruti in the performance of some of the experimental work, James D. Stroupe and Helen Miklas for determination and interpretation of some of the infrared data, and C. W. Nash for analyses is gratefully acknowledged.

(9) R. A. LaForge, C. R. Whitehead, R. B. Keller, and C. B. Hummel, *J. Org. Chem.*, **17**, 457 (1952).

Anal. Calcd. for $C_8H_{13}NO$: N, 10.1; neut. and hydrog. equiv., 139. Found: N, 10.0; neut. equiv., 142; hydrog. equiv., 153.

The solubility of IV in water at 25° was found to be 9.15%, while the solubility of water in IV at 25° was 10.2%.

Infrared analysis showed two strong peaks at 1658 and 1613 cm.$^{-1}$ The ultraviolet absorption spectrum of a solution in isooctane showed a point of inflection at 225 mμ (log $\epsilon = 3.79$).

4,4-Dimethyl-2-isopropenyloxazoline picrate. A slight excess of a saturated aqueous solution of sodium picrate was added to a solution of IV (1.39 g., 0.01 mole) in 0.5*N* hydrochloric acid (20 ml.). The colorless needles were collected and dried at 50°, 2.6 g., m.p. 115–116°.

Anal. Calcd. for $C_{14}H_{16}N_4O_8$: C, 45.7; H, 4.4; N, 15.2. Found: C, 45.5; H, 4.4; N, 15.1.

4,4-Dimethyl-2-isopropyloxazoline (V). *a. By Hydrogenation of 4,4-dimethyl-2-isopropenyloxazoline.* IV (28 g., 0.2 mole) was shaken for 48 hr. with Adams catalyst and hydrogen under 50 lbs. pressure in a Parr hydrogenation apparatus. After addition of fresh catalyst, shaking was continued for 24 hr. Distillation of the filtered oil gave 17.4 g. (62%), b.p. 50–52° (29 mm.). After drying over sodium, it was redistilled, b.p. 56° (35 mm.), n_D^{25} 1.4218, d_{25}^{25} 0.8797; strong infrared absorption at 1665 cm.$^{-1}$ (C =N), with a very weak peak at 1612 cm.$^{-1}$ indicating some residual unreduced IV.

Anal. Calcd. for $C_8H_{15}NO$: N, 9.95; neut. equiv., 141. Found: N, 9.75; neut. equiv., 141.

b. From 2-amino-2-methylpropanol and isobutyric acid. III (89 g., 1 mole) was added to isobutyric acid (89 g., 1 mole). The salt was heated under a distillation head for 5 hr. At first, only water was obtained, but as the overhead temperature increased from 106 to 142°, a two-phased distillate was formed. The separated wet product layer (112 g.) was dried over sodium and distilled, 93 g. (66%), b.p. 50–53° (28 mm.), n_D^{25} 1.4210, d_{25}^{25} 0.8770; infrared absorption at 1665 cm.$^{-1}$; ultraviolet end absorption below 245 mμ.

Anal. Found: N, 9.87.

The picrates of each preparation were obtained as above, m.p. and mixture m.p., 190–191°.

Anal. Calcd. for $C_{14}H_{18}N_4O_8$: C, 45.4; H, 4.9; N, 15.1. Found: C, 45.4; H, 4.8; N, 15.0.

4,4-Dimethyl-2-isopropenyloxazoline (IV). *b. From 2-amino-2-methylpropanol and methacrylic acid.* This reaction was carried out in a manner similar to the preparation of V on a 1-mole scale to give 60 g. (43%) of IV, b.p. 64–67° (35 mm.), n_D^{25} 1.4492, neut. equiv. 143. The product thus obtained seemed to be less pure than obtained by other methods, since the infrared spectrum had a shoulder at 1665 cm.$^{-1}$ No attempt was made to identify the contaminant. The yield of IV was not improved by the addition of a few drops of sulfuric acid.

N-(1,1-Dimethyl-2-β-hydroxyethyl)methacrylamide (VI). A solution of methacryloyl chloride (104.5 g., 1 mole) in benzene (50 ml.) was added to a stirred solution of III (185 g., 2.1 moles) in benzene (100 ml.) at 10–15° in 2.5 hr. Stirring was continued for 3 hr. and the mixture was refrigerated overnight. It was then filtered and the solids washed with benzene. The combined filtrates were evaporated to give a pale yellow residual oil (169 g.) which was distilled in the presence of *p*-hydroxydiphenylamine. The yield of viscous amide was 140 g. (89%), b.p. 97° (0.15 mm.), n_D^{25} 1.4785, infrared peaks at 1660 and 1621 cm.$^{-1}$

Anal. Calcd. for $C_8H_{15}NO_2$: N, 8.9. Found: N, 8.9.

4,4-Dimethyl-2-isopropenyloxazoline (IV). *c. By dehydration of 1,1-dimethyl-2-hydroxyethylmethacrylamide* (VI). VI (32 g., 0.2 mole) was heated at 175–180° for 4 hr. Water and IV co-distilled. The crude product was separated and weighed 24.3 g. (86%), n_D^{25} 1.4545.

In the presence of a few drops of concentrated sulfuric acid, the distillation was completed in 1.5 hr. at 180–190°. The yield of IV was 24.5 g. (87%), n_D^{25} 1.4543. After drying over sodium, redistillation gave a 67% yield of pure oxazoline. The infrared spectrum of this material was identical with the product obtained by transesterification.

N-(2-Hydroxy-2-methylpropyl)methacrylamide (VII) was prepared by the reaction of 1-amino-2-methylpropanol-2[10] with methacryloyl chloride as above. The product was largely insoluble in benzene and was recovered from the solids by solution in 100 ml. of water and extraction with two 50-ml. portions of chloroform. Evaporation of the extract, finally under reduced pressure, gave 34.5 g. (75%) of a crystalline solid, m.p. 70–75°, to which a small amount of polymerization inhibitor was added. The solid could not be distilled.

Anal. Calcd. for $C_8H_{15}NO_2$: N, 8.9. Found: N, 8.6.

When the hydroxyamide VII (33 g., 0.2 mole) was heated with 5 drops of concentrated sulfuric acid at 180–250°, only 2.5 g. of water and 1.5 g. of an oil, n_D^{25} 1.4532, was obtained. The oil was not examined further. The remainder of the material (27 g.) in the pot had resinified.

Polymerization of 4,4-dimethyl-4-isopropenyloxazoline. IV (1 g.) containing 0.01 g. of dimethylazoisobutyrate was heated at 75° for 24 hr. There was formed a hard, clear, colorless polymer which was soluble in water and benzene. The benzene solution was poured into 200 ml. of pentane to give a dry fluffy powder. Infrared examination of the benzene solution showed an imine peak at 1660 cm.$^{-1}$

PHILADELPHIA, PA.

(10) T. L. Cairns and J. H. Fletcher, *J. Am. Chem. Soc.*, 63, 1034 (1941).

[CONTRIBUTION FROM THE RESEARCH LABORATORIES OF TENNESSEE EASTMAN CO., DIVISION OF EASTMAN KODAK CO.]

Cyclization of 2-Aminopyridine Derivatives. III. Reaction of Some 2-Aminopyridines with Alkyl Acrylates and Alkyl 3-Halopropionates

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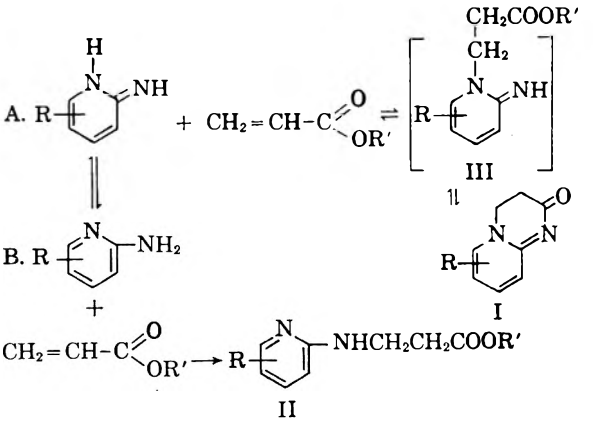
The reaction of 2-aminopyridine with alkyl acrylates gave not only the previously reported 3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidin-2-one but also a noncyclic product, an alkyl ester of *N*-(2 pyridyl)-β-alanine. The cyclic product was converted to the noncyclic adduct by alcoholysis. 4-Methyl-2-aminopyridine and 5-methyl-2-aminopyridine reacted with methyl acrylate in a similar manner. 6-Methyl-2-aminopyridine gave only the noncyclic product. 3-Methyl-2-aminopyridine gave only the cyclic product. Alkyl 3-halopropionates reacted with 2-aminopyridine and all of the methyl-2-aminopyridines, except 6-methyl-2-aminopyridine, to give not only the previously reported 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one hydrohalide but also the aminopyridine hydrohalide and alkyl acrylate. Only dehydrohalogenation occurred when 6-methyl-2-aminopyridine reacted with alkyl 3-halopropionates.

The reaction of 2-aminopyridine with ethyl acrylate has been reported to give a 53% yield of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (I, R = H), the product of the attack at the ring nitrogen of the imino form of 2-aminopyridine.[1] In the course of the synthesis of certain pyridopyrimidines this reaction was studied in detail and was found to follow a more complex course than that proposed by the original investigators.

When the reaction of ethyl acrylate with 2-aminopyridine was carried out as described by Adams and Pachter, that is, by heating the mixture on the steam bath for 12 hr., 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one (I, R = H) was obtained, although the conversion was lower than these authors reported. Distillation of the liquid portion of the reaction mixture gave, in an almost equal amount, a second, low-melting, product as well as some unreacted 2-aminopyridine. This low-melting product gave the correct analysis for a noncyclic adduct of ethyl acrylate and 2-aminopyridine. Hydrolysis of this product gave an acid, $C_9H_{10}N_2O_2$, (m.p. 144–145° without decomposition) isomeric with, but different from, 2-imino-1(2*H*)-pyridinepropionic acid (m.p. 178° with decomposition), reported by Adams and Pachter[1] as being formed by hydrolysis of I (R = H) or by addition of acrylic acid to 2-aminopyridine. This new acid must then be *N*-(2-pyridyl)-β-alanine and the noncyclic adduct is, therefore, the ethyl ester of *N*-(2-pyridyl)-β-alanine (II, R = H, R′ = C_2H_5) rather than ethyl 2-imino-1-(2*H*)-pyridinepropionate (III R = H, R′ = C_2H_5). This appears to be the first reported example of a single reaction of 2-aminopyridine giving derivatives of the imino and amino forms. Similar results were obtained with methyl acrylate except that the over-all conversion was higher. For this reason, the further investigation of the reaction was made with this ester.

It was found that a shorter heating time, 6 hr., gave a ratio of cyclic to noncyclic product of about



8, although the total conversion was decreased. A longer heating time, 100 hr., gave almost no cyclic product but a 74% yield of the methyl ester of *N*-(2-pyridyl)-β-alanine. Thus it was evident that the effect of long heating was to convert I to II; that is, reaction A must be reversible under these conditions, whereas reaction B is not. This conclusion was confirmed when the methyl ester of *N*-(2-pyridyl)-β-alanine together with some 2-aminopyridine was obtained by heating 3,4-dihydro-2*H*-pyrido[1,2-*a*]-pyrimidin-2-one with a small excess of methanol. Further confirmation was obtained from the results of adding methanol to the reaction mixture after 4 hr. and then heating for an additional 16 hr. The yield of I, as compared to a similar experiment in which no methanol was added, was decreased from 45% to 12%, while the yield of II was increased from 42% to 71%.

Although an effort was made to obtain evidence for the formation of the other noncyclic adduct, methyl 2-imino-1(2*H*)pyridinepropionate (III, R = H, R′ = CH_3—), none was found. It is interesting to note that 2-aminopyridine has been found to give products derived directly from the imino form only in those amine reactions which give either a cyclic derivative such as I in which the bonds are constrained in the imino structure or a salt which can be written also as a quarternary salt in which the aromaticity of the pyridine ring is preserved. In all

(1) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 5491 (1952).

cases in which neither of these types of product can be formed, 2-aminopyridine gives derivatives of the amino form.

The 4- and 5 methyl-2-aminopyridines reacted with methyl acrylate to give both methyl-3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one and the methyl ester of *N*-(*X*-methyl-2-pyridyl)-β-alanine. The relative proportion of the cyclic product was again found to decrease with an increase in time and at a somewhat faster rate than in the case of 2-aminopyridine.

Only methyl ester of *N*-(6-methyl-1-pyridyl)-β-alanine was formed in the reaction with 6-methyl-2-aminopyridine. The failure of 6-substituted-2-aminopyridines to form cyclic derivatives by reaction at the ring nitrogen has been observed previously[2,3] and has been attributed to steric hindrance.

In the reaction of 3-methyl-2-aminopyridine with methyl acrylate, a high yield of cyclic product was obtained but no β-alanine derivative could be isolated. Whether the failure to give a noncyclic product was due to steric hindrance or to stabilization of the imino form in some manner is not known.

The results obtained in these reactions with methyl-2-aminopyridines are summarized in Table I.

TABLE I

REACTION OF AMINOPYRIDINES WITH METHYL ACRYLATE

Substituent in 2-Amino-Pyridine	Reaction Time, Hr.	Amino-pyridine Recovered, %	Yield Type I, %	Yield Type II, %
H	6	25	72	9
H	20	17	45	42
H	20[a]	15	12	71
H	100	12	ca. 2	75
6-CH_3—	2[b]	—	0	—
	8[b]	—	0	—
	24[b]	—	0	—
	48	39	0	87
5-CH_3—	2	44	67	10
	18	20	14	73
4-CH_3—	3[c]	30	82	10
	48	20	0	70
3-CH_3—	8	60	21	0
	60	5	83	0

[a] Twenty g. (0.62 mole) methanol added after 4 hr. [b] Small samples withdrawn, diluted with benzene, and chilled. [c] No solid separated from the reaction mixture before addition of benzene.

The reaction of 2-aminopyridine with ethyl 3-chloropropionate has also been reported to give a high yield of the hydrochloride of I (R = H).[4] This result was confirmed. However, it was also found that a small amount of ethyl acrylate was present in the volatile product from the reaction. When this reaction was applied to the various methyl-2-aminopyridines, the extent of the dehydrohalogenation increased. Only dehydrohalogenation occurred when 6-methyl-2-aminopyridine reacted with alkyl 3-halopropionate; no cyclic product was formed. The results of this investigation are summarized in Table II. It may be seen that the extent of dehydrohalogenation increases with the expected order of increasing basicity of the aminopyridine.

TABLE II

REACTION OF AMINOPYRIDINES WITH ALKYL 3-HALOPROPIONATES

Amino-pyridine Substituent	Alkyl 3-Halopropionate Alkyl	Halogen	Mole Fraction[a] Cycliz-ation	Dehydro-halogenation
None	C_2H_5	Cl	0.90	0.10
None	CH_3	Br	0.85	0.15
6-CH_3—	C_2H_5	Cl	0.00	1.00[b]
6-CH_3—	CH_3	Br	0.00	1.00[b]
5-CH_3—	CH_3	Br	0.80	0.20
4-CH_3—	C_2H_5	Cl	0.55	0.45
4-CH_3—	CH_3	Br	0.40	0.60
3-CH_3—	CH_3	Br	0.45	0.55

[a] Average of value obtained by infrared analysis of liquid product and the value obtained by elemental analysis of the solid product. [b] No methanol detected. Solid product was analytically pure 6-methyl-2-aminopyridine hydrohalide.

EXPERIMENTAL

Reaction of 2-aminopyridine with ethyl acrylate. The reaction of 47 g. (0.50 mole) of 2-aminopyridine with 55 g. (0.55 mole) of ethyl acrylate was carried out under the conditions described by Adams and Pachter[1] (heating the mixture for 12 hr. on the steam bath). The reaction mixture was diluted with 500 ml. of ether, chilled, and filtered to give 22 g. (30% conversion, 56% yield) of 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-one, m.p. 185–187° (reported 187–188°). The ether was removed from the filtrate, and the residue was distilled under vacuum through a 6-in. Vigreux column to give 22 g. of recovered 2-aminopyridine, b.p. 80–85° (0.5 mm.) and 19 g. (21% conversion, 36% yield) of ethyl ester of *N*-(2-pyridyl)-β-alanine, b.p. 122–125° (0.2 mm.), m.p. after recrystallization from benzene-hexane mixture, 45–46°.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.85; H, 7.22; N, 14.43. Found: C, 61.93; H, 7.18; N, 14.55.

Reaction of aminopyridines with methyl acrylate. A mixture of 0.50 mole of the selected aminopyridine, 0.55 mole of methyl acrylate, and 0.5 g. of 2,5-di-*tert*-butylhydroquinone (to prevent polymerization of the acrylate) was refluxed on the steam bath for the desired length of time. The mixture was then diluted with 500 ml. of benzene and chilled at 10° for about 6 hr. The 3,4-dihydro-2*H*-pyrido[1,2-*a*]pyrimidine was removed by filtration and purified by crystallization from chloroform-hexane mixture. The benzene was removed from the filtrate under reduced pressure, and the residue was distilled through a 6-in. Vigreux at 0.5 mm. pressure to give the recovered aminopyridine and the methyl ester of *N*-pyridyl-β-alanine.

Methyl ester of N-(2-pyridyl)-β-alanine. Boiling point 122–125° at 0.5 mm., m.p. 50–51° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 59.9; H, 6.67; N, 15.57. Found: C, 60.0; H, 6.72; N, 15.68.

Methyl ester of N-(6-methyl-2-pyridyl)-β-alanine. Boiling point 128–132° at 0.5 mm.

(2) G. Lappin, *J. Am. Chem. Soc.*, **70**, 3348 (1948).

(3) G. Lappin, Q. B. Petersen, and C. Wheeler, *J. Org. Chem.*, **15**, 377 (1950).

(4) R. Adams and I. Pachter, *J. Am. Chem. Soc.*, **74**, 4906 (1952).

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.8; H, 7.18; N, 14.53.

Methyl ester of N-(5-methyl-2-pyridyl)-β-alanine. Boiling point 130–135° at 0.5 mm., m.p. 34–35° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.6; H, 7.28; N, 14.61.

Methyl ester of N-(4-methyl-2-pyridyl)-β-alanine. Boiling point 140–145° (0.5 mm.), m.p. 43–44° after recrystallization from benzene-hexane mixture.

Anal. Calcd. for $C_{10}H_{14}N_2O_2$: C, 61.7; H, 7.22; N, 14.45. Found: C, 61.7; H, 7.26; N, 14.40.

6-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 195–196° after recrystallization from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.7; H, 6.13; N, 17.36.

7-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 167–169° after recrystallizztion from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.5; H, 6.23; N, 17.33.

8-Methyl-3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Melting point 230–232° after recrystallization from chloroform-hexane mixture.

Anal. Calcd. for $C_9H_{10}N_2O$: C, 66.8; H, 6.17; N, 17.28. Found: C, 66.8; H, 6.10; N, 17.39.

Methanolysis of 3,4-dihydro-2H-pyrido[1,2-a]pyrimidin-2-one. Fifty g. (0.338 mole) of I (R = H) and 16 g. (0.50 mole) of absolute methanol was heated on the steam bath for 20 hr. The excess methanol was removed under vacuum. The residue was diluted with 150 ml. of benzene and chilled at 10° for 6 hr. Filtration gave 7.0 g. of recovered pyrimidinone, m.p. 184–187°. The filtrate was distilled under vacuum through a 6-in. Vigreux column to give 6.5 g. (23% yield) of 2-aminopyridine, b.p. 80–85° (0.5 mm.), m.p. 55–56°, and 34 g. (63% yield) of methyl ester of N-(2-pyridyl)-β-alanine, b.p. 120–125° (0.4 mm.), m.p. 49–50°, m.p. of mixture with authentic sample 50–51°.

N-(2-pyridyl)-β-alanines. The methyl ester of *N*-(2-pyridyl)-β-alanine (5.0 g.) was refluxed with 50 ml. of water for 16–20 hr. The water was then removed by evaporation on the steam bath and the residue was recrystallized from ethyl alcohol. The amino acid was obtained in nearly quantitative yield. The following new compounds were prepared in this manner.

N-(2-pyridyl)-β-alanine. Melting point 144–145°.

Anal. Calcd. for $C_8H_{10}N_2O_2$: C, 57.8; H, 6.03; N, 16.86. Found: C, 57.8, H, 5.94; N, 16.89.

N-(6-methyl-2-pyridyl)-β-alanine. Melting point 155–156°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.9: H, 6.72; N, 15.61.

N-(5-methyl-2-pyridyl)-β-alanine. Meling point 198–200°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.8; H, 6.80; N, 15.42.

N-(4-methyl-2-pyridyl)-β-alanine. Meling point 134–136°.

Anal. Calcd. for $C_9H_{12}N_2O_2$: C, 60.0; H, 6.67; N, 15.56. Found: C, 59.8, H, 6.77; N, 15.46.

Reaction of aminopyridines with alkyl 3-halopropionates. A mixture of 0.25 mole of the aminopyridine and 0.25 mole of the alkyl 3-halopropionate was heated on the steam bath in a flask fitted with a short Vigreux column topped by a Dry Ice-cooled trap to collect the volatile products. In every case a vigorous reaction occurred within a few minutes, and the reaction mixture solidified. Heating was continued for 4 hr. The solid residue was then pulverized and heated at 100° and 0.5 mm. pressure for 4 hr. The volatile material removed during this heating was collected in a Dry Ice-cooled trap and was added to the volatile products collected during the reaction. The relative proportion of methanol and alkyl acrylate in this liquid product was determined by infrared analysis. The ratio of pyrido[1,2-*a*]pyrimidin-2-one hydrohalide to aminopyridine hydrohalide in the solid product was calculated from its elemental analysis. In all cases the ratios given by the two methods were in good agreement.

Repeated crystallization of the crude solid product from ethyl alcohol gave relatively pure 3,4-dihydro-2*H*-pyrido-[1,2-*a*]pyrimidin-2-one hydrohalides in 50–80% recovery of the amount calculated from elemental analysis to be in the crude product. These hydrohalides were all white, crystalline solids that decomposed above 300°. These salts were converted to the free bases in 70–80% yield by dissolving them in excess cold, saturated, aqueous potassium carbonate solution, then extracting the mixture with chloroform. The dihydro-2*H*-pyrido[1,2-*a*]pyrimidin-2-ones were shown by mixture melting point to be identical with the cyclic products obtained by the reaction of the aminopyridine with methyl acrylate.

KINGSPORT, TENN.

[CONTRIBUTION FROM THE RESEARCH DIVISION, BRISTOL LABORATORIES, INC.]

Basic Ethers Derived from β-Hydroxyphenethylamines

WILLIAM B. WHEATLEY, WILLIAM E. FITZGIBBON, JR.,[1] WILLIAM F. MINOR, RICHARD R. SMITH, AND LEE C. CHENEY

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A series of basic ethers represented by the general formula I has been prepared. Several of these compounds, which are derivatives of *N,N*-disubstituted β-hydroxyphenethylamines, have local anesthetic activity.

Derivatives of β-hydroxyphenethylamine have long been known to possess marked physiological activity, the nature of this activity being dependent on the type and number of substituents present. Many of the sympathomimetic amines contain this fundamental structure; other derivatives are central nervous system stimulants or local anesthetics.[2]

Some years ago we began the investigation of some compounds derived from β-hydroxyphenethylamine, and selected a series of aryl and aralkyl ethers of *N,N*-disubstituted β-hydroxyphenethylamines as a starting point. This series had at that

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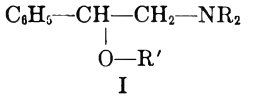
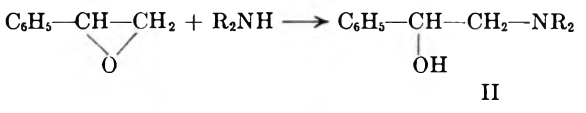
(2) W. H. Hartung, *Ind. Eng. Chem.*, **37**, 126 (1945).

time not been described,[3] and the commercial availablity of styrene oxide made the synthesis of the intermediate amino alcohols much simpler than before.[4] The compounds to be described are depicted by the general formula I, in which NR_2 represents a dialkyamino group, either cyclic or acyclic, and R′ may be aryl or aralkyl.

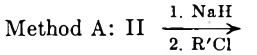


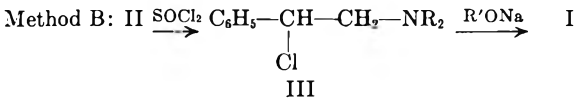
I

Styrene oxide and the secondary amines reacted smoothly to give the amino alcohols (II) in high yields.[4] From these amino alcohols, *via* the Williamson synthesis, were obtained the basic ethers (I) as described in Method A. This route proved quite satisfactory when the halide was an aralkyl halide, or a reactive aryl halide such as 2-choro-



II

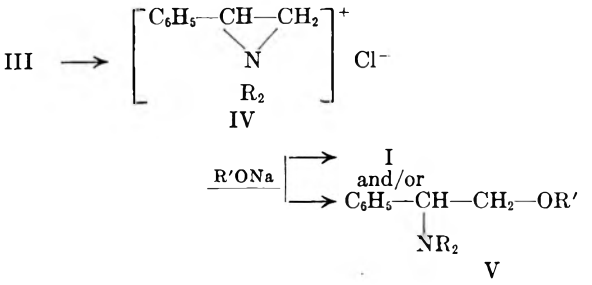




III

pyridine. For the preparation of a phenyl ether Method B was used, wherein II was converted to the chloride (III) with thionyl chloride and then caused to react with sodium phenoxide. This procedure was also used for the preparation of the benzylthio ether, using the sodium salt of benzyl mercaptan.

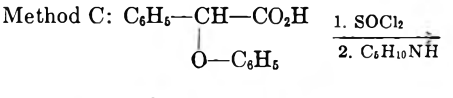
In this connection, the question arose as to the structure of the basic ether obtained by Method B. If it is assumed that during the reaction of III with sodium phenoxide, the cyclic imonium ion (IV) is formed, and there are indeed anlaogous cases in the literature,[5] then the product could be either I or V,

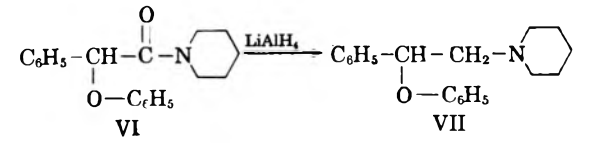


IV

V

or a mixture of the two. The fact that homogenous material was obtained in high yield from β-chloro-β-phenethylpiperidine and sodium phenoxide indicates that one isomer is formed almost exclusively. The proof of structure of this ether is outlined in Method C: α-phenoxyphenylacetic acid was converted to the piperidide (VI) through standard





VI VII

procedures with thionyl chloride and then piperidine; lithium aluminum hydride reduction of VI gave authentic β-phenoxy-β-phenethylpiperidine (VII). The identity of VII and the basic ether I (R′ = phenyl; NR_2 = piperidino) prepared by Method B was established by the absence of a depression in melting point of a mixture of their hydrochlorides and the superimposition of their infrared spectra. Our experimental data do not allow a decision as to whether a direct replacement of chloride by the phenoxide ion occurs or the intermediate ethylenimonium ion is involved, or both. If the cyclic ion is involved, the attack of the phenoxide ion obviously must be at the carbon atom bearing the phenyl group. In any event, the over-all course of the reaction from III to I has been established.

Pharmacology. A number of these basic ethers (Table I) show local anesthetic activity, β-benzyloxy-β-phenethylpiperidine being one of the more potent. Assayed by means of the rabbit cornea test, it is more active than procaine.

EXPERIMENTAL[6]

N,N-Disubstituted β-hydroxyphenethylamines (II). The general procedure used was to add styrene oxide dropwise to a 10–50% excess of the amine at reflux temperature, and continue refluxing for a total of 7–8 hr. The product was then isolated directly by distillation. With dimethylamine, a benzene solution of the amine and styrene oxide was allowed to stand at room temperature for three days; with diisopropylamine, the reaction mixture was refluxed for 7 days. The specific amino alcohols made are listed below.

N,N-Dimethyl-β-hydroxyphenethylamine. B.p. 90–91° at 1 mm. (84% yield).[7]

N,N-Diisopropyl-β-hydroxyphenethylamine. B.p. 102–105° at 1 mm., n_D^{25} 1.5004 (81% yield).

Anal. Calcd. for $C_{14}H_{23}NO$: C, 76.0; H, 10.5. Found: C, 75.9; H, 10.5.

(3) Since this work was completed, references to a few basic ethers of this type have come to our attention: (a) B. F. Hoffert, *Iowa State Coll. J. Sci.*, **26**, 219 (1952) [*Chem. Abstr.*, **47**, 8672 (1953)]; (b) J. O. Jilek and M. Protiva, *Chem. Listy*, **47**, 1814 (1953) [*Chem. Abstr.*, **49**, 249 (1955)]; (c) J. W. Cusic, U. S. Patent 2,683,742 (1954); (d) I. A. Kaye and I. C. Kogon, *J. Am. Chem. Soc.*, **73**, 4893 (1951).

(4) W. S. Emerson, *J. Am. Chem. Soc.*, **67**, 516 (1945).

(5) *cf.* W. R. Brode and M. W. Hill, *J. Am. Chem. Soc.*, **69**, 724 (1947); E. M. Schultz, C. M. Robb, and J. M. Sprague, *J. Am. Chem. Soc.*, **69**, 2454 (1947).

(6) Melting points and boiling points are uncorrected. We are indebted to Mr. Richard M. Downing for the analytical data and to Dr. Frank M. Palermiti for infrared spectra.

(7) Prepared by F. E. King and D. Holmes [*J. Chem. Soc.*, 164 (1947)] by reduction of $C_6H_5—CO—CH_2—N(CH_3)_2$.

TABLE I

$C_6H_5—CH(OR')—CH_2—NR_2$

R'	NR_2[a]	Method	Yield, %	B.P., °C./Mm.	Formula	Analyses: Carbon Calcd.	Carbon Found	Hydrogen Calcd.	Hydrogen Found
$C_6H_5CH_2$	NC_4H_8	A	59	170–172/1	$C_{19}H_{23}NO$	81.1	81.1	8.2	8.2
C_6H_5	NC_5H_{10}	B	74	146–147/0.8	$C_{19}H_{23}NO$[b]	81.1	80.9	8.2	8.3
C_5H_4N[c]	NC_5H_{10}	A	87	164–166/1.1	$C_{18}H_{22}N_2O$	76.6	76.6	7.8	7.8
$C_6H_5CH_2$	NC_5H_{10}	A	49	178–180/2	$C_{20}H_{26}NO·HCl$[d]	72.4	72.6	7.9	7.9
$C_6H_5CH_2$[e]	NC_5H_{10}	B	50	180–187/1	$C_{20}H_{25}NS$[f]	77.1	77.2	8.1	8.1
$4\text{-}ClC_6H_4CH_2$	NC_5H_{10}	A	80	174–180/1	$C_{20}H_{24}ClNO·HCl$[g]	65.6	65.6	6.9	7.0
$4\text{-}CH_3OC_6H_4CH_2$	NC_5H_{10}	A	65	177–184/0.2	$C_{21}H_{27}NO_2$	77.5	77.3	8.4	8.1
$3,4\text{-}(CH_3O)_2C_6H_3CH_2$	NC_5H_{10}	A	30[h]	220–230/2	$C_{22}H_{29}NO_3$	74.3	74.6	8.2	8.2
$3,4,5\text{-}(CH_3O)_3C_6H_2CH_2$	NC_5H_{10}	A	68	223–226/1	$C_{23}H_{31}NO_4$	71.7	72.0	8.1	8.4
$C_4H_3SCH_2$[i]	NC_5H_{10}	A	47	181–185/2.5	$C_{18}H_{23}NOS$[j]	71.7	72.2	7.7	8.0
$C_6H_5CH_2$	NC_6H_{12}	A	76	168–169/0.9	$C_{21}H_{27}NO·HCl$[k]	72.9	72.9	8.2	8.3
$C_6H_5CH_2$	NC_7H_{14}	A	85	[l]	$C_{22}H_{29}NO·HCl$[m]	73.5	73.5	8.4	8.5
C_5H_4N[c]	NC_4H_8O	A	56	169–173/1.5	$C_{17}H_{20}N_2O_2$	71.8	71.9	7.1	6.8
$C_6H_5CH_2$	NC_4H_8O	A	80	153–156/0.6	$C_{19}H_{23}NO_2·HCl$[n]	68.4	68.3	7.3	7.4
$2\text{-}ClC_6H_4CH_2$	NC_4H_8O	A	59	191–195/1.5	$C_{19}H_{22}ClNO_2·HCl$[o]	62.0	61.6	6.3	6.2
$2,4\text{-}Cl_2C_6H_3CH_2$	NC_4H_8O	A	82	[l]	$C_{19}H_{21}Cl_2NO_2·HCl$[p]	56.6	56.7	5.5	5.6
$C_4H_3SCH_2$[i]	NC_4H_8O	A	43	178–180/2	$C_{17}H_{21}NO_2S$[q]	67.3	66.7	7.0	6.7
$C_6H_5CH_2$	$NC_6H_{12}O$	A	73	[l]	$C_{21}H_{27}NO_2·HCl$[r]	69.7	69.8	7.8	7.9
C_6H_5	$N(CH_3)_2$	B	55	175–177/0.7	$C_{16}H_{19}NO$[s]	79.6	79.5	7.9	8.3
$4\text{-}CH_3OC_6H_4CH_2$	$N(i\text{-}C_3H_7)_2$	A	77	191–197/1.3	$C_{22}H_{31}NO_2$	77.4	77.3	9.2	8.9

[a] NC_4H_8 = 1-pyrrolidino; NC_5H_{10} = 1-piperidino; NC_6H_{12} = 2-methyl-1-piperidino; NC_7H_{14} = 2,6-dimethyl-1-piperidino; NC_4H_8O = 4-morpholino; $NC_6H_{12}O$ = 2,6-dimethyl-4-morpholino. [b] Hydrochloride: m.p. 196.0–197.5° (isopropyl alcohol–ether). *Anal.* Calcd. for $C_{19}H_{23}NO·HCl$: C, 71.8; H, 7.6. Found: C, 71.6; H, 7.6. [c] C_5H_4N = 2-pyridyl. [d] Hydrochloride: m.p. 184.5–186.5° [methyl isobutyl ketone (MIBK)]. [e] O replaced by S. [f] Hydrochloride: m.p. 158.5–160.0° (MIBK). *Anal.* Calcd. for $C_{20}H_{25}NS·HCl$: C, 69.0; H, 7.5. Found: C, 69.3; H, 7.5. [g] Hydrochloride: m.p. 194.0–196.0° (isopropyl alcohol). [h] The low yield may be due in part to the use of crude 3,4-dimethoxybenzyl chloride. [i] $C_4H_3SCH_2$ = 2-thenyl. [j] Hydrochloride: m.p. 163.5–165.5° (MIBK). *Anal.* Calcd. for $C_{18}H_{23}NOS·HCl$: C, 64.0; H, 7.2. Found: C, 64.0; H, 7.3. [k] Hydrochloride: m.p. 171.5–173.5° (isopropyl alcohol–ether). [l] The hydrochloride of the basic ether crystallized on attempted extraction with dilute hydrochloric acid on working up the reaction mixture. The yield represents unrecrystallized hydrochloride. [m] Hydrochloride: m.p. 236.0–237.5° (methanol-ether). [n] Hydrochloride: m.p. 173.0–175.5° (isopropyl alcohol–petroleum ether, 60–71°). [o] Hydrochloride: m.p. 156.5–157.5° (MIBK). [p] Hydrochloride: m.p. 182.5–183.5° (MIBK). [q] Hydrochloride: m.p. 185.0–186.0° (acetonitrile). *Anal.* Calcd. for $C_{17}H_{21}NO_2S·HCl$: C, 60.1; H, 6.5. Found: C, 60.2; H, 6.8. [r] Hydrochloride: m.p. 184.0–186.0° (MIBK). [s] Hydrochloride: m.p. 201.0–202.0° (isopropyl alcohol–ether). *Anal.* Calcd. for $C_{16}H_{19}NO·HCl$: C, 69.2; H, 7.3. Found: C, 68.9; H, 7.5.

1-(β-Hydroxyphenethyl)pyrrolidine. M.p. 57.5–59.5° (petroleum ether, 28–38°) (73% yield).[8]

1-(β-Hydroxyphenethyl)piperidine. B.p. 125–127° at 1 mm., m.p. 71.0–72.5° (petroleum ether, 60–71°) (93% yield).[9]

1-(β-Hydroxyphenethyl)-2-methylpiperidine. B.p. 123–125° at 1 mm. (90% yield).

Anal. Calcd. for $C_{14}H_{21}NO$: C, 76.7; H, 9.6. Found: C, 76.7; H, 9.7.

2,6-Dimethyl-1-(β-hydroxyphenethyl)piperidine. M.p. 76.5–78.5° (petroleum ether, 60–71°) (55% yield).

Anal. Calcd. for $C_{15}H_{23}NO$: C, 77.2; H, 10.0. Found: C, 77.4; H, 9.9.

Hydrochloride: m.p. 245.5–246.5° (ethanol).

Anal. Calcd. for $C_{15}H_{23}NO·HCl$: C, 66.8; H, 9.0. Found: C, 66.9; H, 8.9.

4-(β-Hydroxyphenethyl)morpholine. M.p. 83.0–84.0° (petroleum ether, 60–71°) (90% yield).[4]

2,6-Dimethyl-4-(β-hydroxyphenethyl)morpholine. B.p. 148–151° at 2 mm. (91% yield).

Anal. Calcd. for $C_{14}H_{21}NO_2$: C, 71.4; H, 9.0. Found: C, 71.1; H, 8.9.

Hydrochloride: m.p. 197.5–199.5° (isopropyl alcohol–ethyl acetate).

Anal. Calcd. for $C_{14}H_{21}NO_2·HCl$: C, 61.9; H, 8.1. Found: C, 62.2; H, 8.2.

N,N-Dialkyl-β-chlorophenethylamines (III). Treatment of the amino alcohols with thionyl chloride as described by Cheney[10] yielded the basic chloride hydrochlorides.

N,N-Dimethyl-β-chlorophenethylamine hydrochloride. M.p. 202–205° (isopropyl alcohol).

Anal. Calcd. for $C_{10}H_{14}ClN·HCl$: C, 54.6; H, 6.9. Found: C, 54.7; H, 6.9.

Basic ethers (I). One example will be given to illustrate each method of preparation; the individual compounds prepared are listed in Table I.

Method A. A solution of 0.25 mole of II in 100 ml. of toluene was added dropwise to a stirred suspension of 0.25 mole of sodium hydride in 100 ml. of toluene. After 5 hr. refluxing, all of the sodium hydride had dissolved; to this clear solution, stirred and maintained at reflux, was added a solution of 0.25 mole of the aralkyl chloride in 50 ml. of toluene. After refluxing overnight, the reaction mixture was cooled and water added to dissolve the inorganic salt. The toluene layer was extracted three times with dilute hydrochloric acid; the acid extracts were combined and made strongly basic with potassium hydroxide. Extraction of the liberated organic base with several portions of ether, followed by drying of the extracts over anhydrous potassium carbonate and distillation *in vacuo* yielded the basic ether I. This

(8) C. T. Bahner, M. Fielden, L. M. Rives, and M. D. Pickens, *J. Am. Chem. Soc.*, **73**, 4455 (1951).

(9) Prepared by R. E. Lutz, R. H. Jordan, and W. L. Truett [*J. Am. Chem. Soc.*, **72**, 4085 (1950)] by reduction of $C_6H_5—CO—CH_2—NC_5H_{10}$ in 60% yield.

(10) L. C. Cheney, U. S. Patent 2,548,652 (1951) [*Chem. Abstr.*, **45**, 8039 (1951)].

procedure was used in cases where R′ = aralkyl and 2-pyridyl; 2-chloropyridine is sufficiently reactive to participate in the Williamson synthesis. In certain cases, as noted in Table I, the hydrochloride of the product precipitated on extraction of the toluene solution with acid; the salt was collected by filtration and purified by recrystallization.

Method B. β-Chlorophenethylpiperidine hydrochloride[10] (72.0 g., 0.28 mole) was stirred at room temperature with an equivalent amount of 56% potassium hydroxide and the liberated base extracted with two portions of toluene. The combined extracts (150 ml.) were dried by shaking for 2 hr. with anhydrous potassium carbonate. The filtered toluene solution was then added dropwise to a hot, stirred, suspension of sodium phenoxide. This suspension had been prepared by adding 26.0 g. (0.28 mole) of phenol to 6.7 g. (0.28 mole) of sodium hydride in 150 ml. of toluene. After the reaction mixture had been refluxed for 16 hr., it was cooled and shaken with 10% hydrochloric acid. The aqueous layer was made strongly basic and extracted several times with benzene. The benzene extracts were dried and distilled to give 57.3 g. of I (R′ = phenyl, NR_2 = piperidino).

α-Phenoxy-α-phenylacetopiperidide (VI). A solution of 44.0 g. (0.19 mole) of α-phenoxyphenylacetic acid[11] and 34.5 g. (0.29 mole) of thionyl chloride in 150 ml. of ether to which 3 drops of pyridine had been added was stirred at reflux for 4 hr. The residue which remained on evaporation of the solvent was taken up in 150 ml. of Skellysolve B. A solid separated, and was collected by filtration. This solid was identified as recovered acid; 18.8 g., 43% recovery. The solvent was evaporated from the filtrate, leaving a residue of 28.7 g. which failed to crystallize. This crude acid chloride was taken up in 100 ml. of benzene and added dropwise to a stirred solution of 25.5 g. of piperidine in 100 ml. of benzene. Heat was evolved, and a white solid formed. After the addition had been completed, the reaction mixture was stirred at reflux for 1 hr., then allowed to stand overnight at room temperature. The mixture was then poured in water (solid dissolved); the benzene layer was separated and extracted twice with saturated sodium bicarbonate solution. Evaporation of the solvent from the dried benzene solution left a residue which spontaneously solidified. Two recrystallizations from dilute methanol gave 25.7 g. of VI, m.p. 115.0–117.0°. An analytical sample melted at 116.0–117.0°.

Anal. Calcd. for $C_{19}H_{21}NO_2$: C, 77.3; H, 7.2. Found: C, 77.2; H, 7.2.

1-(β-Phenoxyphenethyl)piperidine (VII). A suspension of 5.9 g. (0.02 mole) of VI and 3.7 g. (0.1 mole) of lithium aluminum hydride in 300 ml. of ether was stirred at reflux for 2 hr., then allowed to stand overnight at room temperature. The mixture was hydrolyzed by cautious addition of ice; the white solid which formed was collected by filtration and washed several times on the filter with fresh ether. The filtrate and washings were combined and the solvent evaporated. Distillation at 0.8 mm. gave 4.8 g. of colorless liquid, b.p. 158–159° (86% yield).

Anal. Calcd. for $C_{19}H_{23}NO$: C, 81.1; H, 8.2. Found: C, 81.3; H, 8.3.

Hydrochloride: melting point alone and when mixed with a sample prepared by the alternate route (Method B), 196.5–198.0°.

Anal. Calcd. for $C_{19}H_{23}NO{\cdot}HCl$: C, 71.8; H, 7.6. Found: C, 71.8; H, 7.6.

Further evidence for the identity of the basic ethers prepared by the two routes was afforded by the infrared spectra, which were indistinguishable.

(11) C. O. Guss, *J. Am. Chem. Soc.*, **71**, 3460 (1949).

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, IOWA STATE COLLEGE]

Some Organosilicon Compounds Derived from Phenyl Ether

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This article reports the preparation of several organosilicon compounds derived from either *o*- or *p*-phenoxyphenyllithium, or from (oxydi-*o*- or oxydi-*p*-phenylene)dilithium. These compounds are of interest as synthetic lubricants or hydraulic fluids because of their low melting points and relatively high volatilization points.

The preparation in this laboratory of several organosilicon compounds derived from aryl ethers has already been reported.[1-3] These compounds were prepared, as a part of a current research problem, for the purpose of finding thermally stable organosilicon compounds for possible use as synthetic lubricants or hydraulic fluids. A second aim of this research is to develop such thermally stable compounds which are also low-melting, preferably being liquids at room temperature.

Among the phenyl ether derivatives previously reported are two complete series of compounds of the general formula $(C_6H_5)_xSiR_{(4-x)}$; where x is 0, 1, 2 or 3, and R is either *o*-phenyloxyphenyl[1] or *p*-phenoxyphenyl[2] except for the compound where x is 3 and R is *p*-phenoxyphenyl. In addition, *n*-dodecyltris(*p*-phenoxyphenyl)silane was prepared.[2] The compounds were prepared by reaction of organolithium compounds with chlorosilanes. The preparations of the organolithium compounds were carried out by either halogen-metal interconversion or metalation reactions using *n*-butyllithium[4,5] as the metalating agent.

In another study, dimetalation of phenyl ether using slightly more than two equivalents of *n*-butyllithium to one equivalent of phenyl ether was

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(2) H. Gilman and J. J. Goodman, *J. Org. Chem.*, **22**, 45 (1957).

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found to yield (oxydi-*o*-phenylene)dilithium.[3] This reagent further reacted with dichlorodimethyl- and dichlorodiphenyl silane to give the cyclic compounds 10,10-dimethyl- and 10,10-diphenyl-phenoxasilin and with silicon tetrachloride to form 10,-10′-spirobiphenoxasilin.

All of the compounds previously reported,[1-3] with the exceptions of *n*-dodecyltris(*p*-phenoxy phenyl)silane (a liquid) and 10,10-dimethylphenoxasilin (m.p. 78.5–79.0°), were solids melting above 140°. Since it was desired to prepare low-melting compounds having high thermal stability, attempts have now been made to incorporate either long-chained *n*-alkyl groups or benzyl groups into organosilicon compounds derived from phenyl ether.

Reactions of (oxydi-*o*-phenylene)dilithium with dibenzyldichloro- and dichlorodi-*n*-dodecylsilane have given 10,10-dibenzyl- and 10,10-di-*n*-dodecylphenoxasilin. Attempts to prepare 10-benzyl-10-chloro- and 10-chloro-10-*n*-dodecylphenoxasilin by reactions of (oxydi-*o*-phenylene)dilithium with benzyltrichloro- and trichloro-*n*-dodecylsilane have yielded materials containing little or no hydrolyzable chloride ion, although careful precautions were taken to avoid contact with moisture.

Chlorotri-*n*-hexadecylsilane[6] was treated with *p*-phenoxyphenyllithium to give tri-*n*-hexadecyl-*p*-phenoxyphenylsilane. Reaction of *p*-phenoxyphenyllithium with tri-*n*-hexadecylsilane, $(C_{16}H_{33})_3SiH$, apparently yielded a small amount of tri-*n*-hexadecyl-*p*-phenoxyphenylsilane since the infrared spectra of several fractions were similar to that of the pure compound. The spectra, however, showed the presence of the Si-H bond (4.75 μ) indicating that unreacted tri-*n*-hexadecylsilane was still present. Dichlorodi-*n*-dodecylsilane yielded upon reaction, in separate experiments, with 2 equivalents each of *o*- and *p*-phenoxyphenyllithium, the compounds di-*n*-dodecylbis(*o*- and *p*-phenoxyphenyl)-silane.

Since (oxydi-*p*-phenylene)bis[triphenylsilane][7] had shown good thermal stability, but was a high-melting solid, the corresponding benzyl compound, (oxydi-*p*-phenylene)bis[tribenzylsilane], and methyl compound, (oxydi-*p*-phenylene)bis[trimethylsilane], were prepared. The methyl compound was found to melt near room temperature (45.0–45.5°); therefore its somewhat less symmetrical isomer, (oxydi-*o*-phenylene)bis[trimethylsilane], was prepared by reaction of two equivalents of chlorotrimethylsilane with (oxdi-*o*-phenylene)dilithium. The *p,p′*-disubstituted phenyl ether compounds were made by reaction of two equivalents of tribenzylsilane and chlorotrimethylsilane, in separate experiments, with (oxydi-*p*-phenylene)dilithium.

All of the new compounds, with the exceptions of (oxydi-*p*-phenylene)bis[trimethylsilane] and (oxydi-*p*-phenylene)bis[tribenzylsilane] (a glass), and 10,10-dibenzylphenoxasilin (melting near room temperature), were liquids. The two (oxydiphenylene)bis[trimethylsilane] compounds have good thermal stability, but boil around 320° at atmospheric pressure. The (oxydi-*p*-phenylene)bis[tribenzylsilane] volatilizes at 540–550° with only slight decomposition; this compares favorably with the corresponding bis[triphenylsilane] compound (m.p. 306–307°) which volatilizes at 557–560°.[7] The other compounds all volatilize in the range from 440–480°, which is comparable to the mono- and di-(*o*-phenoxyphenyl)phenylsilanes[1] and to 10,10-diphenylphenoxasilin,[3] but is somewhat lower than the other compounds prepared previously.[1-3] Thus far no compound containing a long-chained *n*-alkyl group has been found to be stable above 480°.

EXPERIMENTAL[8]

10,10-Dibenzylphenoxasilin. A four-necked flask was equipped with a reflux condenser, Trubore mechanical stirrer, and two dropping funnels. Into one funnel was placed a solution of 28 g. (0.1 mole) of dibenzyldichlorosilane[9] in 300 ml. of ether; into the other was placed a solution of *ca.* 0.1 mole of (oxydi-*o*-phenylene)dilithium[3] in 500 ml. of ether. The two reagents then were added slowly to a stirred mixture of 50 ml. of benzene and 100 ml. of ether at a rate to avoid excess of either reagent. The addition required 2 hr. The mixture was then stirred 72 hr. after which time Color Test I[10] was negative. Hydrolysis of the mixture was accomplished by the addition of 100 ml. of water. The layers were separated and the water layer was extracted with 100 ml. of ether. The ethereal layers were combined, dried over sodium sulfate, and filtered, and the ether was distilled. The benzene solution was then placed on a column of alumina and eluted with 500 ml. of benzene. The benzene was distilled to leave 33 g. of a crude oil. Distillation of this oil at reduced pressure gave two liquid fractions: 8.5 g. (27%), boiling at 188–194° (0.003 mm.), n_D^{20} 1.6305; and 7.8 g. (25%), b.p. 194–195° (0.003 mm.), n_D^{20} 1.6322. Both fractions gave identical infrared spectra and the spectra indicated them to be the desired compound. The fraction boiling at 194–195° (0.003 mm.) was analyzed. *Volatilization point:* Microbubbles begin at 400°, and the compound volatilizes at 470–480°. Some decomposition is noted.

Anal.[11] Calcd. for $C_{26}H_{22}OSi$: Si, 7.44. Found: Si, 7.21, 7.30.

10,10-Di-n-dodecylphenoxasilin. By essentially the same procedure described for 10,10-dibenzylphenoxasilin, except using 0.05 mole quantities, 10,10-di-*n*-dodecylphenoxasilin was prepared from (oxydi-*o*-phenylene)dilithium and dichlorodi-*n*-dodecylsilane. The main product, 4.3 g. (16.5%)

(6) This compound has been prepared by two different methods and has been shown to decompose, if the distillation temperature exceeds 300°, into hexadecene-1 and an organosilicon residue. Results of this investigation will be published later.

(7) Unpublished studies, J. J. Goodman, doctoral dissertation, Iowa State College, 1955.

(8) All melting points are uncorrected. Reactions were carried out under dry, oxygen-free nitrogen when involving organolithium reagents or chlorosilanes. Volatilization points were determined by heating the compounds in a capillary tube mounted in a flame-heated copper block.

(9) Prepared by Mr. E. A. Zuech of this Laboratory.

(10) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **27**, 2002 (1925).

(11) Silicon analyses of most compounds were by the method of H. Gilman, B. Hofferth, H. W. Melvin, and G. E. Dunn, *J. Am. Chem. Soc.*, **72**, 5767 (1950).

of an oil, boiled at 247–255° (0.009 mm.), n_D^{20} 1.5135, d_4^{20} 0.9359. *Volatilization point:* Microbubbles form at 355°, the compound volatilizes at 460–470° with some decomposition.

Anal. Calcd. for $C_{36}H_{58}OSi$: Si, 5.25; MR_D,[12] 171.98. Found: Si, 4.98, 4.90, 4.89; MR_D, 171.93.

(Oxydi-o-phenylene)bis[trimethylsilane]. (Oxydi-*o*-phenylene)dilithium (0.073 mole) in 140 ml. of ether was prepared by a published procedure.[3] To the stirred organodilithium compound in solution was added 19 ml. (16.2 g., 0.15 mole) of chlorotrimethylsilane. After refluxing overnight Color Test I[10] was negative. The mixture was hydrolyzed and worked up as in the previous experiments to leave 19.2 g. (87%) of a crude oil. This oil was distilled at reduced pressure to give 13.7 g. (59.7%) of product, boiling at 117–120° (0.001 mm.), n_D^{20} 1.5415, d_4^{20} 1.432. *Volatilization point:* Microbubbles form at 300°, the compound volatilizes at 315–320° leaving no residue.

Anal.[13] Calcd. for $C_{18}H_{26}OSi_2$: Si, 17.86; MR_D,[12] 99.92. Found: Si, 17.56, 17.60; MR_D, 100.35.

(Oxydi-p-phenylene)bis[trimethylsilane]. (Oxydi-*p*-phenylene)dilithium was prepared by the reaction[14] of 23 g. (0.1 mole) of bis(*p*-bromophenyl) ether in 200 ml. of benzene and 244 ml. of a 1.23*N* ethereal solution of *n*-butyllithium. To the resulting mixture was added slowly 30 g. (0.277 mole) of chlorotrimethylsilane. After two days at reflux temperature, the reaction mixture was hydrolyzed and then worked up in the usual manner. There was obtained 24.2 g. (77.3%) of an oil, boiling at 124–130° (0.02 mm.), n_D^{20} 1.5372, d_4^{20} 0.993.

Anal.[13] Calcd. for $C_{18}H_{26}OSi_2$: Si, 17.86; MR_D,[12] 99.92. Found: Si, 17.7, 17.5; MR_D, 98.84.

Following distillation of part of the product under a nitrogen atmosphere at slightly greater than atmospheric pressure, the product obtained was found to crystallize into large rhombohedral crystals. These melted at 44.5–46.5° and were used to seed the material which was not distilled and which gave finer crystals melting at 44.5–46.5°. Recrystallization of the crystals gave 6.3 g. (20%) of product, m.p. 45.0–45.6°.

J. J. Goodman[15] also prepared this compound by the same method, but found the index of refraction to be n_D^{20} 1.5430, and the density to be d_{20}^{20} 1.0251 giving an MR_D value of 96.2 which does not agree with the calculated value[12] of 99.92. The authors checked the density and index of refraction and found them to be n_D^{20} 1.5420 and d_4^{20} 1.013 giving an MR_D value of 97.7, which is still quite low.

During the nitrogen atmosphere distillation mentioned previously, no decomposition of the material prepared by the authors was noted. *Volatilization point:* Microbubbles begin at 300°, the compound distils at 315–320° and no decomposition is noted.

(Oxydi-p-phenylene)bis[tribenzylsilane]. (Oxydi-*p*-phenylene)dilithium was prepared as in the previous experiment (0.025 mole) and allowed to react with 15 g. (0.05 mole) of tribenzylsilane.[9] After the reaction mixture had stirred for 1 hr., Color Test I[10] was weak and the reaction mixture was hydrolyzed and worked up in the usual manner to leave 8.0 g. (41.3%) of an oil, b.p. 320–322° (0.001 mm.). This oil is very viscous and glassy. *Volatilization point:* Microbubbles are formed at 420°, the compound volatilizes at 540–550° with very little decomposition.

Anal. Calcd. for $C_{54}H_{60}OSi_2$: Si, 7.29. Found: Si, 7.40, 7.35.

Tri-n-hexadecyl-p-phenoxyphenylsilane. p-Phenoxyphenyllithium (0.045 mole) was prepared from *n*-butyllithium and *p*-bromophenyl phenyl ether[4] and then was added to 10 g. (0.035 mole) of chlorotri-*n*-hexadecylsilane. Color Test I was negative within 15 min. and the mixture was hydrolyzed and worked up in the usual fashion. There was obtained 6.9 g. (58.5%) of an oil, boiling over the range 305–315° (0.005 mm.), n_D^{20} 1.4960, d_4^{20} 0.8971. *Volatilization point:* Microbubbles form at 340°, the compound volatilizes at 450–460°.

Anal. Calcd. for $C_{60}H_{108}OSi$: Si, 3.22; MR_D,[12] 285.18. Found: Si, 3.39, 3.28; MR_D, 284.61.

A slightly impure sample was made by the same method using somewhat impure chlorotri-*n*-hexadecylsilane. When tri-*n*-hexadecylsilane was allowed to react with *p*-phenoxyphenyllithium at reflux for 12 hr., no pure product was obtained, but a crude fraction was obtained whose infrared spectrum was similar to that of the authentic material prepared as previously described. However, complete reaction did not occur as evidenced by the presence of the Si-H band at 4.75 μ in the infrared spectrum.

Di-n-dodecylbis(o-phenoxyphenyl)silane. To 13.6 g. (0.08 mole) of phenyl ether in 100 ml. of ethyl ether was added 63 ml. (0.084 mole) of 1.34 *N* *n*-butyllithium. After stirring at room temperature for 24 hr., Color Test II[16] was negative. To the resulting solution was added 17.5 g. (0.04 mole) of dichlorodi-*n*-dodecylsilane. After refluxing overnight, Color Test I[10] was negative. Hydrolysis and work-up in the usual manner yielded 8 g. (28.8%) of product, boiling over the range 260–270° (0.001 mm.), n_D^{20} 1.5290, d_4^{20} 0.9680. Another 7 g. (25.2%) of crude product also was obtained. *Volatilization point:* Microbubbles form at 370°, the compound volatilizes at 460–470° leaving no residue.

Anal. Calcd. for $C_{48}H_{68}O_2Si$: Si, 3.98; MR_D,[12] 224.19. Found: Si, 4.14, 4.12; MR_D, 224.67.

Di-n-dodecylbis(p-phenoxyphenyl)silane. To *p*-bromophenyl phenyl ether (14.98) g., 0.06 mole in 100 ml. of ether was added 50 ml. (0.061 mole) of a 1.22*N* ethereal solution of *n*-butyllithium. When Color Test II[16] was negative, the mixture was treated with 13.1 g. (0.03 mole) of dichlorodi-*n*-dodecylsilane. As soon as Color Test I was negative, the mixture was hydrolyzed and worked up as usual to give 21 g. of an oil. Reduced pressure distillation of the oil gave 5.0 g. (25%) of product, boiling at 275–280° (0.001 mm.), n_D^{20} 1.5380, d_4^{20} 0.9776, as well as a slightly impure sample amounting to 6.5 g. *Volatilization point:* Microbubbles form at 400°, the compound volatilizes at 450–470°.

Anal. Calcd. for $C_{48}H_{68}O_2Si$: Si, 3.98; MR_D,[12] 224.10. Found: Si, 4.00, 3.83; MR_D, 225.6.

Infrared spectra of the compounds. Infrared spectra of each of the above compounds were run and compared to those of related compounds. Except where otherwise noted, the spectra indicated the compound obtained to be the desired product.

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[CONTRIBUTION FROM THE DEPARTMENT OF CHEMISTRY, DREXEL INSTITUTE OF TECHNOLOGY]

Reactions of Tetra-*n*-propyltin and Tetraisopropyltin with Organic Acids[1]

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The cleavage of tetra-*n*-propyltin and tetraisopropyltin by halo acids and mercaptans was studied. With tetra-*n*-propyltin one alkyl group was cleaved and the corresponding trialkyltin ester or mercaptide was formed. Mercaptans also cleaved one alkyl group from tetraisopropyltin, but with the halo acids two alkyl groups were cleaved and the corresponding dialkyl diesters were formed. The relative rate of cleavage of tetraalkyltin by acidic compounds is in the order: halo acids > arylthiols > alkane thiols. Eleven previously unreported organotin compounds were prepared.

This paper reports the cleavage of *n*-propyl and isopropyl groups from the tetra-*n*-propyltin and tetraisopropyltin by organic acids whose ionization constants range between 10^{-1} and 10^{-10}. This investigation is a continuation of work previously carried out in this laboratory.[2]

Previous to this study, a cleavage reaction of tetra-*n*-propyltin was reported with stannic chloride.[3] Apparently no cleavage reactions of tetraisopropyltin have been reported in the literature.

One propyl group was cleaved from tetra-*n*-propyltin and tetraisopropyltin with the gradual addition of mercaptans to form the corresponding tripropyltin mercaptides. As in the case of tetraethyltin, aryl mercaptans reacted more readily than aliphatic mercaptans. Reaction of tetra-*n*-propyltin with chloroacetic and dichloroacetic acids also cleaved one propyl group and formed the corresponding tri-*n*-propyltin ester. The halo acids

$$(C_3H_7)_4Sn + RSH \longrightarrow (C_3H_7)_3SnSR + C_3H_8\uparrow$$

$$(n\text{-}C_3H_7)_4Sn + ClCH_2COOH \longrightarrow (n\text{-}C_3H_7)_3SnO_2CCH_2Cl + C_3H_8\uparrow$$

reacted more readily than the mercaptan probably because they are stronger acids.

A comparison of the yields (Table I) shows that the halo acids reacted most readily, followed by the aryl mercaptans, and the aliphatic mercaptans gave the lowest yields. Actually, the results obtained cannot be used in an absolute sense, but must be used as comparative values.

Chloroacetic and dichloroacetic acids cleaved two propyl groups from tetraisopropyltin to form the corresponding diisopropyltin diesters. A possible explanation for the cleavage of two propyl groups lies in the difference in the inductive effects of the alkyl groups. It is generally agreed that the inductive effects of alkyl groups decrease in the following order:

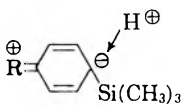
$$\begin{matrix} H_3C \\ \searrow \\ \quad CH \longrightarrow > CH_3 \longrightarrow CH_2 \longrightarrow CH_2 \longrightarrow > \\ \nearrow \\ H_3C \end{matrix}$$

$$CH_3 \longrightarrow CH_2 \longrightarrow > CH_3 \longrightarrow$$

$$(i\text{-}C_3H_7)_4Sn + ClCH_2COOH \longrightarrow (i\text{-}C_3H_7)_2Sn(O_2CCH_2Cl)_2 + 2C_3H_{8}$$

Since the isopropyl groups exert a stronger inductive effect than the *n*-propyl groups, there is a higher electron density on the carbon atom of the carbon-tin bond in tetraisopropyltin than in tetra-*n*-propyltin. Only one propyl group is cleaved by halo acids in the tetra-*n*-propyltin because the electron release effect of the three remaining *n*-propyl groups is balanced by the electron withdrawing effect of the haloacyloxy group. On the other hand, the isopropyl groups exert a stronger electron release effect than the *n*-propyl groups and two haloacyloxy groups are necessary to prevent further cleavage in tetraisopropyltin.

A very similar reaction scheme was proposed by Benkeser and Krysiak[4] for the hydrogen chloride cleavage of a series of trimethylarylsilanes. They assumed a proton attack on the carbon atom of the carbon-silicon bond and concluded that the cleavage of an aryl group from silicon is facilitated by the introduction of a substituent capable of furnishing a high electron density at the aromatic carbon-silicon bond.



A similar electrophilic attack has been proposed for the cleavage of trialkylphenyltin compounds with silver nitrate.[5] In this case, the inductive effect of the alkyl groups exerts a high electron density on the carbon atom of the phenyl group which is attached to the tin atom and thus promotes the approach of the silver ion.

(1) From a thesis submitted by Alan L. Borror to the Department of Chemistry of the Drexel Institute of Technology in partial fulfillment of the requirements for the degree of Bachelor of Science.

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TABLE I
CLEAVAGE REACTIONS

Reagent	Product	Time, Hr.	Yield, %
	Tetra-*n*-Propyltin		
CH_2ClCO_2H	*n*-$Pr_3SnO_2CCH_2Cl$	0.5	35
$CHCl_2CO_2H$	*n*-$Pr_3SnO_2CCHCl_2$	0.5	39
C_6H_5SH	*n*-$Pr_3SnSC_6H_5$	3	30
p-$CH_3C_6H_4SH$	*n*-$Pr_3SnS(p\text{-}C_6H_4CH_3)$	3	34
o-$CH_3C_6H_4SH$	*n*-$Pr_3SnS(o\text{-}C_6H_4CH_3)$	3	30
$C_6H_5CH_2SH$	*n*-$Pr_3SnSCH_2C_6H_5$	3	22
$CH_3(CH_2)_6SH$	*n*-$Pr_3SnS(CH_2)_6CH_3$	4	13
$CH_3(CH_2)_9SH$	*n*-$Pr_3SnS(CH_2)_9CH_3$	4	12
	Tetra-*i*-Propyltin		
CH_2ClCO_2H	*i*-$Pr_2Sn(O_2CCH_2Cl)_2$	0.5	47
$CHCl_2CO_2H$	*i*-$Pr_2Sn(O_2CCHCl_2)_2$	0.5	51
C_6H_5SH	*i*-$Pr_3SnSC_6H_5$	3	31
p-$CH_3C_6H_4SH$	*i*-$Pr_3SnS(p\text{-}C_6H_4CH_3)$	3	45
$C_6H_5CH_2SH$	*i*-$Pr_3SnSCH_2C_6H_5$	3	33
$CH_3(CH_2)_6SH$	*i*-$Pr_3SnS(CH_2)_6CH_3$	4	16
$CH_3(CH_2)_9SH$	*i*-$Pr_3SnS(CH_2)_9CH_3$	4	12

The cleavage reactions of tetra-*n*-propyltin and tetraisopropyltin, the yields obtained, and the length of time of heating are listed in Table I. The physical constants and analyses of the trialkyltin esters and mercaptides and the dialkyltin diesters are summarized in Table II.

with 400 ml. of 3*M* sodium hydroxide solution. The ether-benzene layer was separated from the aqueous layer, and the aqueous layer was extracted with 400 ml. of hexane. The combined extracts were dried over anhydrous sodium sulfate and the solvent was removed by distillation. The residue on distillation under diminished pressure yielded 104 g. (24%) of tetra-*n*-propyltin boiling at 110–111° at 10 mm. Luijten and Van Der Kerk report a boiling point of 108–109° at 11 mm.[3] The yield of tetraisopropyltin, boiling at 103–104° at 10 mm. was 98 g. or 22.6% of the theoretical amount. The reported boiling point of this compound is 106° at 12 mm.[3]

Cleavage reactions. Tri-n-propyltin phenyl mercaptide, benzyl mercaptide, p-tolyl mercaptide, heptyl mercaptide, and decyl mercaptide. Triisopropyltin phenyl mercaptide, benzyl mercaptide, p-tolyl mercaptide, heptyl mercaptide, and decyl mercaptide. A *one-molar* proportion of the appropriate mercaptan was added to 5.8 g. (0.02 mole) of tetra-*n*-propyltin or tetraisopropyltin in approximately three equal portions over a period of 2 hr. with intermittent reflux. The reaction mixture then was boiled under gentle reflux for an additional 1 or 2 hr. (Table I). After removal of the unchanged reactants by distillation, the mercaptides were distilled under diminished pressure.

Tri-n-propyltin monochloroacetate. To 5.8 g. (0.02 mole) of tetra-*n*-propyltin was added 1.71 g. (0.02 mole) chloroacetic acid in approximately three equal portions over a period of 15 min. The unchanged reactants were removed by distillation under diminished pressure and the ester then was distilled under diminished pressure. The resulting solid was found to melt at 69–70°. By repeated recrystallization from petroleum ether, the melting point was raised to 69.5–70.5°.

Tri-n-propyltin dichloroacetate, diisopropyltin di-monochloroacetate, and diisopropyltin di-dichloroacetate. To 5.8 g (0.02 mole) of tetra-*n*-propyltin or tetraisopropyltin was added a one-*molar* proportion of the appropriate acid in approximately three equal portions over a period of 15 min. with intermittent reflux. The reaction mixture then was boiled under gentle reflux for an additional 15 min. The solid which resulted on cooling was crystallized repeatedly from petroleum ether until there was no increase in the melting point.

TABLE II

Compound	B.P. (1 Mm.)	M.P., °C.	d_4^{20}	n^{20}	Analyses: Mol. Wt.[a] Calcd.	Mol. Wt.[a] Found	Sulfur Calcd.	Sulfur Found	Tin Calcd.	Tin Found
				n-Propyltin Esters and Mercaptides						
n-$Pr_3SnO_2CCH_2Cl$[b]	135–140	78–79	—	—	341	326	—	—	34.7	34.8
n-$Pr_3SnO_2CCHCl_2$[c]	—	83–84	—	—	375	357	—	—	31.6	31.3
n-$Pr_3SnS(pC_6H_4CH_3)$	159–160	—	1.2127	1.5602	371	394	8.64	8.52	—	—
n-$Pr_3SnSCH_2C_6H_5$	165–167	—	1.2318	1.5558	371	364	8.64	8.68	—	—
n-$Pr_3SnS(CH_2)_6CH_3$	158–160	—	1.1033	1.4981	379	368	8.46	8.52	—	—
n-$Pr_3SnS(CH_2)_9CH_3$	180–183	—	1.0688	1.4998	421	436	7.61	7.39	—	—
				iso-Propyltin Esters and Mercaptides						
i-$Pr_2Sn(O_2CCH_2Cl)_2$	—	54–55	—	—	389	396	—	—	30.4	30.0
i-$Pr_2Sn(O_2CCHCl_2)_2$	—	69–71	—	—	461	467	—	—	25.4	26.6
i-$Pr_3SnSC_6H_5$	138–139	—	1.2327	1.5676	357	366	8.96	8.85	—	—
i-$Pr_3SnS(pC_6H_4CH_3)$	157–158	—	1.2191	1.5648	371	363	8.64	8.76	—	—
i-$Pr_3SnSCH_2C_6H_5$	167–170	—	1.2053	1.5497	371	386	8.64	8.58	—	—
i-$Pr_3SnS(CH_2)_6CH_3$	155–157	—	1.0940	1.5045	379	388	8.46	8.37	—	—
i-$Pr_3SnS(CH_2)_9CH_3$	192–195	—	1.0494	1.5010	421	452	7.61	7.58	—	—

[a] Molecular weights in camphor solution. [b,c] Ref. [6] reports m.p. 78–80° and 84–85°, respectively.

EXPERIMENTAL

All melting points are uncorrected.

Tetra-n-propyltin and tetraisopropyltin. To 390 g. (1.5 moles) of stannic chloride dissolved in 500 ml. of dry benzene immersed in an ice water bath were added over a period of 3 hr., with occasional shaking, 3 liters of 1.5 *molar* *n*-propyl- or isopropyl-magnesium chloride. The reaction mixture was allowed to stand overnight and the unchanged Grignard reagent was decomposed by the gradual addition of water. The organotin layer was separated and shaken

(6) A. Saitow, E. G. Rochow, and D. Seyferth, *J. Org. Chem.*, **23**, 116 (1958).

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Notes

A department for short papers of immediate interest.

Synthesis and Properties of Triiodoacetic Acid and Its Salts

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Received October 30, 1957

In 1893, Angeli reported[1] that the reaction between iodic acid and malonic acid gave triiodoacetic acid and diiodoacetic acid in unspecified amounts. The same method was used in 1938 to prepare the triiodo compound, but no experimental details were given.[2] Recently it was reported that nitrogen triiodide and acetoacetic ester yielded a material thought to be a mixture of diiodoacetamide and triiodoacetamide.[3] In connection with the preparation of triiodoacetic acid for use in another investigation, the reaction of malonic acid with iodic acid has been reexamined, and attempts have been made to determine the conditions which will give optimum yields of triiodoacetic acid.

Under the conditions specified by Angeli,[1] the predominant product is diiodoacetic acid. We have found that the ratio of products (diiodoacetic and triiodoacetic acids) is dependent on the initial ratio of iodic acid to malonic acid. Triiodoacetic acid can be obtained as the major product, in yields of 50–60% based on iodic acid, if an iodic to malonic acid weight ratio of 1.5 is used. Diiodoacetic acid was the major product with reactant weight ratios of less than about 1.2, and the only product isolated when a ratio of 0.6 was used. With reactant weight ratios higher than 1.5, crystallization of triiodoacetic acid from the reaction mixture was accompanied by precipitation of increasingly larger amounts of free iodine. A reactant ratio of 2.0 gave a heavy precipitate of free iodine, and no triiodoacetic acid was isolated. The stability of triiodoacetic acid is involved here, since it was found that it decomposes to free iodine in the presence of concentrated aqueous iodic acid.

The steps in the reaction that lead to the observed products have not been clearly defined. Angeli[1] assumed that the first step in the reaction was formation of diiodomalonic acid, which could react further by simple decarboxylation to yield diiodoacetic acid or by decarboxylation and iodination to give triiodoacetic acid. Willstätter[4] has prepared diiodomalonic acid by the reaction of malonic acid with iodic acid and iodine in anhydrous formic acid as a solvent and noted that it is unstable in water. We obtained a 30% yield of triiodoacetic acid from the reaction of diiodomalonic acid with a suspension of iodine in aqueous idoic acid using charge weights based on Equation 1. The possibility that the use of

$$5CI_2(CO_2H)_2 + 2I_2 + HIO_3 \longrightarrow 5CI_3CO_2H + 5CO_2 + 3H_2O \quad (1)$$

free iodine in the reaction of malonic acid with aqueous iodic acid (Equation 2) would lead to higher yields of triiodoacetic acid was also explored. Good

$$5CH_2(CO_2H)_2 + 6I_2 + 3HIO_3 \longrightarrow 5CI_3CO_2H + 5CO_2 + 9H_2O \quad (2)$$

yields of triiodoacetic acid were obtained by this method, but the product was contaminated by large amounts of unreacted iodine.

Crystalline triiodoacetic acid was found to be quite stable at room temperature, in contrast to a report[2] that decomposition is rapid. The acid decomposes rapidly at higher temperatures, however. Triiodoacetic acid is very soluble in polar organic solvents, but the solutions as a rule are extremely unstable, rapidly developing an iodine coloration. In certain solvents as noted in the experimental section, the acid is stable enough to permit further work, if done rapidly. Triiodoacetic acid is insoluble in water, but aqueous suspensions are quite stable. It is soluble, with rapid decomposition, in dilute (4%) sodium hydroxide, but in more concentrated sodium hydroxide (10–40%) the acid is insoluble and little decomposition is observed. The acid may be partially recovered by rapidly neutralizing a freshly prepared bicarbonate solution.

The lead and sodium salts of triiodoacetic acid were prepared and isolated. Attempts to isolate a calcium salt were unsuccessful, although the calcium salt of diiodacetic acid was prepared.

EXPERIMENTAL[5]

Triiodoacetic acid. A solution of 20 g. of malonic acid in 30 cc. of water was added to an almost boiling solution of 30 g. of iodic acid in 80 cc. of water. The resulting solution was cautiously heated until the evolution of carbon dioxide was vigorous and then cooled immediately by plunging the flask into an ice bath; several small pieces of ice were added to the solution to help moderate the reaction.[6] After the reaction had subsided, the yellow reaction mixture was allowed to stand at room temperature. There was a mildly exothermic reaction, the temperature rising to about 45° with a steady evolution of gas; in about 1.5 hr., the reaction solution was a

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(2) R. A. Fairclough, *J. Chem. Soc.*, 1186 (1938).
(3) J. F. Fellman, S. H. Wilen, and C. A. VanderWerf, *J. Org. Chem.*, **29**, 713 (1956).
(4) R. Willstätter, *Ber.*, **35**, 1374 (1902).
(5) All melting points are uncorrected.
(6) Particular care must be taken in the heating step, as the reaction may very easily get out of hand and become uncontrollably violent.

bright yellow-orange color. Triiodoacetic acid as golden yellow crystals settled out and was filtered after another hour. Air drying the product served also to remove a small amount of free iodine which was present. Weight 14.3 g. (57.6%), m.p. 135–140° (dec.); reported m.p. 150° (dec.).[1] Other samples of triiodoacetic acid prepared in this manner gave m.p.'s as high as 150–154° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: I, 86.97%; eq. wt. 438. Found: I, 87.5%; eq. wt.[7] 449.

After removal of the triiodoacetic acid, the mother liquor became a dark color and deposited 1.2 g. of iodine; this was removed. By concentration of the solution, a total of 5.4 g. (20.3%) of diiodoacetic acid was isolated as pale yellow needles, m.p. 110–111°; reported[1] m.p. 110°. It was recrystallized from chloroform. Data obtained by varying the reactant ratio were as follows:

Weight Ratio HIO_3/Malonic Acid	Yield, Wt. % Based on Iodine in HIO_3	
	CI_3COOH	CHI_2COOH
0.60	0	58.6
1.00	19.2	51.8
1.00[a]	39.6	—
1.00[a]	26.4	—
1.26	37.2	30.4
1.50	46.8	28.2
1.50	57.6	20.3
1.50[a]	51.6	28.2
1.75	22.8	21.4
2.00[a,b]	0	14.7

[a] Reaction mixture was kept cold after the initial reaction. [b] A trace of a white solid, m.p. 300°, was isolated.

Diiodomalonic acid. Diiodomalonic acid was prepared by the method of Willstätter.[4] A mixture of 10 g. (0.167 mole) of malonic acid, 6.8 g. (0.10 mole) of iodic acid, and 19.6 g. (0.20 mole) of finely divided iodine in 50 cc. of 90% formic acid was stirred at room temperature 3 hr. The reaction mixture was allowed to stand overnight in a refrigerator and then filtered while cold. The product was dried on a clay plate to allow excess iodine to evaporate, giving 20 g. (58%) of diiodomalonic acid as pale yellow crystals, m.p. 110° (dec.); reported m.p. 119–120° (dec.).[4]

Conversion of diiodomalonic acid to triiodoacetic acid. Ten g. of diiodomalonic acid was added to 20 cc. of water containing 1.0 g. of iodic acid and 2.85 g. of pulverized iodine. The mixture was allowed to stand at room temperature with frequent shaking for 3 hr. A pale yellow solid appeared almost immediately. After standing overnight, the mixture was filtered and the product air-dried 6 days to remove free iodine, giving 3.7 g. (30%) of triiodoacetic acid, m.p. 140–142° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: eq. wt. 438. Found: eq. wt. 450, 439.

Reaction of malonic acid with iodine and iodic acid. A mixture of 10.0 g. (0.096 mole) of malonic acid, 29.3 g. (0.115 mole) of pulverized iodine, and 10.2 g. (0.058 mole) of iodic acid in 250 cc. of water was stirred vigorously. After about 20 min., a yellow solid appeared; in another 15–20 min., evolution of carbon dioxide started with considerable foaming. The reaction was slightly exothermic; the temperature was not allowed to exceed 45° by using a water bath when necessary. A heavy yellow solid appeared after 3.5 hr. After standing overnight in a refrigerator, stirring was resumed for 3 hr. at room temperature. The mixture was filtered and the yellow solid dried on a clay plate in the air to remove excess iodine, giving 17.5 g. (42%, based on malonic acid) of the triiodoacetic acid, m.p. 131–132° (dec.). Other samples of the acid prepared in this manner had m.p. as high as 154–155° (dec.).

Anal. Calcd. for $C_2HO_2I_3$: I, 86.9%. Found: I, 86.4%.

After removal of the triiodoacetic acid, concentration of the mother liquors gave about 7 g. (16%) of diiodoacetic acid, m.p. 108–109° after recrystallization from chloroform.

Preparation of salts of triiodoacetic acid. Calcium salt: A solution of 0.25 g. of calcium acetate in 2–3 cc. of water was added to a freshly prepared solution of 1.00 g. of triiodoacetic acid in 5 cc. of dimethylformamide. Immediately a golden orange solid appeared, accompanied by evolution of a gas. After cooling in an ice bath, the solid was filtered. It decomposed on the filter paper. Similar results were obtained with acetic acid and with a carefully neutralized bicarbonate solution.

Lead salt: A solution of 2.0 g. of lead acetate in 10 cc. of water was added to a freshly prepared solution of 5.0 g. of triiodoacetic acid in 20 cc. of dioxane. After an induction period of a few seconds, a heavy bright yellow solid appeared. This was filtered and washed well with cold water. Drying on the filter in the air for 2 hr. did not change the color of the product. The salt was dried *in vacuo* over phosphorus pentoxide for 4 hr.; 5.1 g. of a light yellow tan product was obtained. On heating in a capillary tube, the product liberated iodine above 90° particularly at 130–140° to 180°, yielding a yellow solid which was stable at 260°.

Sodium salt: Two grams of triiodoacetic acid was dissolved in a solution of 0.4 g. of sodium bicarbonate in 10 cc. of water. Immediately 4 g. of sodium acetate was added to salt out the product and beautiful golden yellow, glistening leaves settled out. These were filtered and air dried, wt. 2.1 g. Upon heating in a melting point tube, the solid started losing iodine at 90°, darkened gradually from 170–180°, and became quite dark colored at 230°. The salt appeared to be relatively stable to air at room temperature.

Preparation of calcium diiodoacetate. Treatment of diiodoacetic acid solution in the same manner as afforded the calcium salts of triiodoacetic acid gave none of the desired salt. It was observed that the salts were more water soluble than the parent acid. Calcium diiodoacetate was obtained as a pale yellow solid in the following manner. Six g. of the acid in 10 cc. of warm water gave a two-phase liquid system. This was neutralized with 1 g. of calcium carbonate. The two layers disappeared and a clear solution resulted until the neutralization point was almost reached, then the calcium salt started crystallizing. Water was added and excess carbonate was filtered off. The solution was concentrated under reduced pressure to 5–10 cc. and cooled to give 4.9 g. of the calcium diiodoacetate, dec. above 200° with liberation of iodine.

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(7) After allowing a sample of the acid to stand several weeks at room temperature, the eq. wt. was redetermined and found to be 451.

Infrared Analysis of a Cyclopropane Polymer

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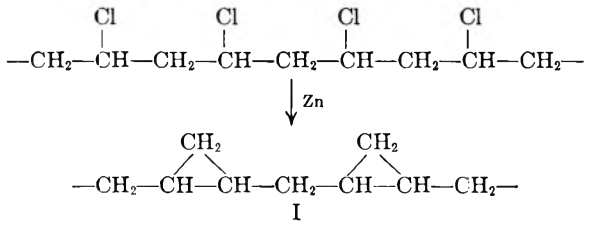
In 1939, C. S. Marvel and co-workers reported[2] the preparation of a polymer containing cyclopropane rings by dehalogenation of polyvinyl chloride with zinc.

(1) Present address: Department of Chemistry, Texas Christian University, Fort Worth, Tex.

(2) C. S. Marvel, J. H. Sample, and M. F. Roy, *J. Am. Chem. Soc.*, 61, 3241 (1939).



I

The dehalogenated polymer (I) was shown to be resistant to ozone and permanganate but added chlorine on chlorination. On vigorous nitric acid oxidation, no products could be isolated that would have been characteristic of a dehydrohalogenated polymer.

The preparation of I was repeated in order to obtain additional evidence for the original structure designation and to investigate the position of characteristic cyclopropane bands in a polymer environment. Only 60% of the total chlorine was removed in our experiments, compared to 85% obtained in the previous work; but this seems sufficient for infrared analysis. Films of I were cast directly on salt plates from dioxane solution, dried *in vacuo*, and compared to films of polyvinyl chloride prepared in a like manner. The spectrophotometer was a Perkin-Elmer Model 21 with sodium chloride optics.

Two new bands appeared in I in positions expected from prior band assignments in nonpolymeric cylopropane structures. A band at 9.83μ, characteristic of the nonsymmetrical ring deformations of cyclopropanes[3,4] and a band at 3.2μ, characteristic of the methylene hydrogens of a cyclopropane ring[4,5] confirm the original assignment. Bands associated with carbon-carbon double bonds were either not present or obscured by carbon-chlorine overtone bands between 6.0 and 6.5μ and past 10μ by various skeletal vibrations.

It was not possible to obtain interpretable nuclear magnetic resonance spectra of I because of its low solubility in organic solvents.

Research Division Contribution No. 258
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Metalation of Cyclopropane by Amylsodium[1]

Edward J. Lanpher, Leslie M. Redman, and Avery A. Morton

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Metalation of hydrocarbons has been observed only when some unsaturation was present, a previous success with decalin[2] having been found due to some impurity.[3] The first experiments with cyclopropane were carried out about ten years ago in the presence of isopropoxide with the expectation that the ring would open to give allylsodium. Thereby an alternative method for the preparation of an Alfin catalyst[4,5] would be provided. The product of this reaction, however, did not cause Alfin polymerization of butadiene. Carbonation yielded an acid which did not resemble vinylacetic but was similar to cyclopropanecarboxylic acid.

Recently cyclopropane was again metalated, but in the absence of an alkoxide, in order to study the absorption spectrum for the cyclopropyl anion. The infrared spectrum showed bands not far from those of cyclopropane itself and entirely distinct from those for allylsodium or amylsodium. Carbonation produced cyclopropanecarboxylic acid which was converted to the known amide for identification.

Although cyclopropane has a formula in which all four valencies for each carbon appear saturated, it still possesses a fair degree of olefinic character according to Coulson and Moffit[6] and Vogel.[7] Accordingly the statements previously made to the effect that some unsaturated system was necessary[8] for metalation of a hydrocarbon and that no indiscriminate removal of hydrogen by a supposedly all-powerful anion[9] took place are still valid.

EXPERIMENTAL

Metalation in the presence of isopropoxide. Amylsodium was prepared[10] from 1 g.-atom of sodium and 0.5 mole of amyl chloride in the usual manner. Isopropyl alcohol (15 ml.) was added and 15 min. later the mixture was saturated with cyclopropane. All operations were under an atmosphere of dry nitrogen and the mixture was continuously stirred at 5000 r.p.m. After a total time of 6.5 hr. the reaction mixture was transferred to a bottle and stored under nitrogen. A portion (20 ml. of suspension) was tested as a polymerizing agent for 30 ml. of butadiene in 180 ml. of pentane, but did not produce the thick gel characteristic for Alfin polybuta-

(1) This work was performed as a part of research projects sponsored by the Reconstruction Finance Corp., Office of Synthetic Rubber, and by the National Science Foundation.
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diene. No marked polymerization took place within 1 hr. The remainder of the blue-black mixture was carbonated. The carboxylic acid therefrom distilled at 69–86°/1 mm. The neutralization equivalent was 76 and the refractive index was 1.4362. The yield was 1.3 g.

Metalation in the absence of alkoxide. A suspension (250 ml.) of amylsodium was prepared in the usual way[10] from 0.5 g.-atoms of sodium sand and 0.25 mole of amyl chloride, and, next, was saturated with cyclopropane and allowed to stand. The disappearance of amylsodium was followed by infrared measurements[11,12] of a Nujol mull. After one week the bands at 919 and 755 cm.$^{-1}$ characteristic for the amyl anion had become very much weaker. Meanwhile strong absorption bands had appeared at 1155, 1055, 1030, 860, and 810 cm.$^{-1}$, a moderate one at 1570 cm.$^{-1}$ and a weak band at 745 cm.$^{-1}$ These bands are not far from some of those for cyclopropane itself which were very strong at 1434, 1024, and 866, moderate at 1510 and 1188, and very weak at 745 cm.$^{-1}$ The bands are different from those for the allyl ion[12] which are very strong at 1525, 1247, and 600 cm.$^{-1}$

From this reaction mixture a 25-ml. aliquot was evaporated to dryness under reduced pressure. Then the dried residue was heated to 100° for 1 hr. The condensate caught in a nitrogen cooled trap showed an absorption curve identical with that for cyclopropane itself except for contamination from the pyrolysis of some amylsodium which was still present.

The remainder of the reaction mixture was carbonated and the recovered acids fractionated. The fraction of impure acid (4.4 g.), collected at 90°/30 mm., had $n^{26.5}$ 1.4355. The recorded[13] refractive index for cyclopropanecarboxylic acid is n^{25} 1.4359, and boiling point is 105°/48 mm. The amide from the acid chloride and ammonia melted at 124–127° (recorded[14] 124.5–126°).

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(11) E. J. Lanpher, *J. Org. Chem.*, **21**, 830 (1956); *J. Am. Chem. Soc.*, **79**, 5578 (1957).
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A Synthesis of Fluorene-3-carboxylic Acid[1]

D. C. Morrison

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Alder[2] and coworkers have shown that the sulfuric acid cyclization of phenyl terephthalic acid (diphenyl 2-5-dicarboxylic acid) gives fluorenone-3-carboxylic acid. Their synthesis of the diphenyl dicarboxylic acid, however, presents several difficulties and it was thought that if this acid were more readily available, a convenient route to 3-substituted fluorenes would be at hand. In the present work, the ester of phenyl terephthalic acid was prepared by a one-step process from diethyl terephthalate, though in mediocre yield.

Hey[3] has demonstrated that the free radical decomposition of dibenzoyl peroxide in ethyl benzoate yields a mixture of esters of phenyl benzoic acids. In a similar reaction with diethyl terephthalate, only one isomer is possible due to the symmetry of para di-substituted benzenes. This operation has now been carried out yielding the ester of the desired phenyl terephthalic acid in about 12% yield. The poor yields (expected in this type of reaction) are compensated for by the economy of starting materials. The ester was hydrolyzed under alkaline conditions to the phenyl terephthalic acid which was cyclized by sulfuric acid to the fluorenone-3-carboxylic acid.[2] The latter was purified through its methyl ester as was done by Campbell and Stafford.[4] Reaction of the methyl ester with red phosphorus and hydriodic acid in glacial acetic acid caused reduction and hydrolysis to give fluorene-3-carboxylic acid. This acid was further characterized by its methyl ester.

The route to fluorenone-3-carboxylic acid by oxidation of 3-methyl fluorene by permanganate[5] or by chromic acid[6] gave poor yields of material which was difficult to purify due to its contamination with acids probably produced by further oxidation of the desired acid (with cleavage of the fluorene ring).

EXPERIMENTAL

Melting points are uncorrected.

The better known dimethyl terephthalate was not employed in the reaction as it is a solid at steam bath temperatures. The diethyl terephthalate was made by two days refluxing of the acid with sulfuric acid and ethanol, followed by conventional purification.

Diethyl phenylterephthalate. Diethyl terephthalate (260 g.) was melted and kept at 60–70° while 50 g. of dibenzoyl peroxide were added in portions. The solution was immersed in a bath of boiling water for 4 hr. and then excess diethyl terephthalate was distilled under vacuum directly from the flask. If the temperature during the first hour of the reaction should rise above 100°, the decomposition may become violent. The distillation was carried out at 5 mm. and a forerun of diphenyl was discarded. This was followed by a large amount of recovered terephthalate which could be used again in another run. A similar reaction was done using 357 g. of diethyl terephthalate and 60 g. of dibenzoyl peroxide, and the distillation residues combined with those from the first run. These were now dissolved in ether and the solution extracted with aqueous sodium carbonate and then washed with sodium chloride solution (if water is used, a stable emulsion results). The ether was distilled and the product taken at 140–195°/3 mm. It was redistilled at about 160°/3 mm. The yield was 31.76 g. of a light yellow viscous oil. This is 11.73% based on the peroxide. The yield may perhaps be improved by reaction at higher dilution or by better temperature control. A resinous residue is left in the distillation flask.

Phenyl terephthalic acid. The 31.76 g. of ester was refluxed for 32 hr. with 40 g. of potassium hydroxide in 50% ethanol and the acid isolated as usual, by acidification with hydro-

(1) The work described in this paper was carried out under a research grant (No. C-327) to Prof. D. M. Greenberg, from the National Cancer Institute, U. S. Public Health Service.
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chloric acid after removing ethanol. The yield of precipitated acid was 24.29 g. or 94.2%. It was very sparingly soluble in water. After one recrystallization from ether, the acid sintered above 200° and melted at 268–275° and after an additional recrystallization it melted at 277–280° (lit.[2] 277–278°).

Fluorenone-3-carboxylic acid. Alder *et al.*[2] give few details so these were worked out again. The cyclization in sulfuric acid gives yields of 79–87%. It was found to be temperature sensitive and should not be heated over 45° or further reaction occurs. Twenty g. of finely powdered phenyl terephthalic acid was stirred with 180 ml. of concentrated sulfuric acid at 25–30° until all was dissolved. The resulting dark solution was then kept at 40° (internal temp.) for 20–30 min. It was poured into ice water, and the precipitated acid filtered, washed, and dried. A yield of 15.17 g. or 81.9% of acid was obtained which sintered at 265° with melting 270–300°. Hydrolysis of the purified methyl ester and recrystallization from aqueous acetone gave a product of m.p. 299–304° with previous sintering (lit.[4] 304°).

Methyl fluorenone-3-carboxylate. The acid was esterified by refluxing for 1 day a mixture of 8.0 g. acid with 5 ml. concentrated sulfuric acid and 750 ml. of methanol. After the usual isolation, a yield of 7.66 g. or 90% was obtained. Four recrystallizations from aqueous acetone gave a product sintering at 133° and melting at 146–147° (lit.[4] 145°). Recrystallization eliminates any phenyl terephthalate or other impurities. The ester is decomposed by hot concentrated potassium hydroxide solution, giving a dark brown solution, and for hydrolysis, short contact with warm alkali is necessary.

Fluorene-3-carboxylic acid. A solution of 8.24 g. of methyl fluorenone-3-carboxylate in 300 ml. of acetic acid was mixed with 9 g. of red phosphorus and 10 ml. of 47–50% hydriodic acid and the liquid refluxed 45 hr. Most of the solvent was distilled and the residue diluted with 450 ml. of water and ice cooled several hours. The solids were filtered and then extracted with an excess of dilute potassium carbonate solution. The carbonate extract was filtered and acidified and the precipitated acid filtered off, washed, and dried. It weighed 7.18 g. or 98.7%. This preparation melted at 220–230° with previous sintering. Three recrystallizations from acetone-water with a minimum of heating gave a product of m.p. 229.5–231.5° with sintering at 222° (lit.[4] 230 and 231°).

Methyl fluorene-3-carboxylate. 10 g. of the above acid with 8 ml. of concentrated sulfuric acid and 350 ml. of methanol were refluxed 24 hr. and the ester isolated as usual. The light brownish ester was washed with alkali and dried. It was then distilled from a small short-path still at 1 mm. and the solid distillate recrystallized from acetone-water and dried. The yield of white product was 10.1 g. or 94.7%. After four recrystallizations from aqueous acetone, the ester had m.p. 79–80°.

Anal. Calcd. for $C_{15}H_{10}O_2$: C, 80.36; H, 5.36. Found: C, 80.13; H, 5.32.

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Preparation of Diethyl 4-Phosphonovalero-4-lactone

J. A. Cade

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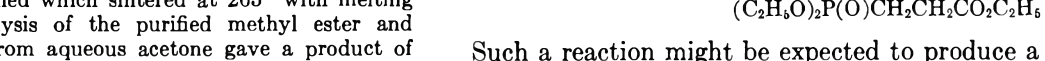
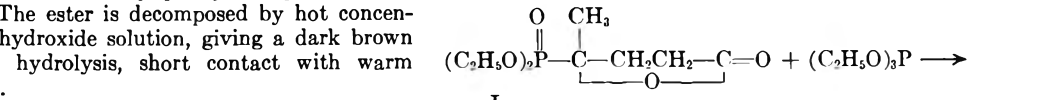
The preparation of esters of 1-hydroxyalkanephosphonic acids by the base-catalyzed interaction of carbonyl compounds with dialkyl hydrogen-phosphonates is well known,[1] but the behavior of 1-ketocarboxylic acids in this reaction does not appear to have been examined hitherto. Interest in such a reaction was provoked during a search for new methods of obtaining methanediphosphonates and related derivatives, *i.e.*, compounds containing a P-C-P bridge.[2]

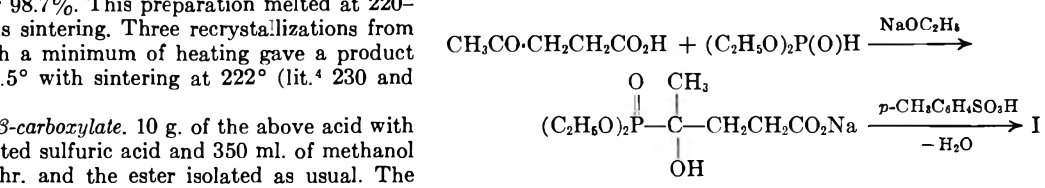
It had been shown,[3] that trialkyl phosphite reacts with a lactone to give predominantly the trialkyl ester of a phosphonocarboxylic acid, *e.g.*:



Such a reaction might be expected to produce a *gem*-bis(dialkyl phosphono)carboxylic ester, II, from a dialkyl phosphonolactone in which the phosphorus atom is joined to the same carbon atom as the oxygen bridge; especially since the presence of the dialkyl phosphono group should enhance the electrophilic power of this atom:



This aspect of the investigations had to be suspended before it was brought to satisfactory completion, but an example of the type of lactone required *viz.* diethyl 4-phosphonovalero-4-lactone, I, was made from levulinic acid by the reactions:



Because of competition from the carboxyl group for the base, more than one equivalent of the latter is necessary to effect interaction, whereas with ordinary ketones a trace suffices. The product, I, is very sensitive to water and alcohols, and could not be isolated in a sufficiently pure condition to warrant quoting a value for the molecular refraction, even after repeated redistillation. It is acknowledged that most 1-hydroxyalkanephosphonates are not stable and easily revert to equilibrium with the components from which they are derived,[4] but one would have expected ring formation in the lactone to prevent this. The triethyl ester obtained by in-

(1) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4450 (1956) and references.

(2) Atomic Energy Research Establishment reports C/R 2011; C/R 2012 (1957).

(3) R. L. McConnell and H. W. Coover, Jr., *J. Am. Chem. Soc.*, **78**, 4453 (1956).

(4) V. S. Abramov and N. A. Ilyina, *J. Gen. Chem.* (*U.S.S.R.*) (Consultants Bureau English Translation), **24**, 121 (1956).

teraction of I with absolute ethanol was even less stable to distillation, but its composition, refractive index, and infrared spectrum were substantially the same as those of the substance produced by the reaction between diethyl hydrogenphosphonate and ethyl levulinate in the presence of a trace of sodium ethoxide.

Two other keto acids were examined. No identifiable product was obtained when pyruvic acid was used in place of levulinic acid although reaction took place; the dimer $[(C_2H_5O)_2P(O)C(CH_3)\text{-}O\text{-}CO]_2$ was sought.

Benzoylformic acid (0.1 mole) in ether reacted readily with dimethyl, diethyl, diallyl, diisopropyl, di-*n*-butyl, di(3,3,5-trimethyl)hexyl, or di-2-phenylethyl hydrogen phosphonates (0.12 mole) in the presence of pyridine (0.12 mole). Subsequent addition of cyclohexylamine (0.1 mole) to the reactions precipitated white crystalline solids with ill-defined melting points, which approximated in composition to the salts with this base of the corresponding phenyl(dialkyl phosphono)glycollic acids, $(RO)_2P(O)C(OH)(C_6H_5)CO_2^-$ $C_6H_{11}NH_3^+$, and which were obtained in yields of 95, 75, 49, 61, 50, 42, and 45%, respectively. Recrystallization from a variety of solvents only had the effect of increasing the melting range and lowering its upper limit.

EXPERIMENTAL

Diethyl 4-phosphonovalero-4-lactone. Sodium (7.9 g., 0.345 mole) was dissolved in ethanol (180 cc.) contained in a 1 liter 3-necked flask fitted with a reflux condenser, a dropping funnel, and a mechanical stirrer. To the cooled solution, diethyl hydrogen phosphonate (45.2 g., 0.328 mole) was added, followed by levulinic acid (38 g., 0.328 mole) in alcohol (50 cc.). The mixture was heated under reflux for 1 hr., the bulk of the alcohol was distilled (180 cc.), and the residue was sucked dry for several hours at the water-pump. Toluene (250 cc.) was then added to the dry product which was dispersed by means of the stirrer and the mixture was heated while toluene (*ca.* 75 cc.) distilled until the boiling point indicated the absence of alcohol.[5] At this stage, *p*-toluenesulphonic acid (59 g., 0.343 mole) in toluene (500 cc.) was added by means of a dropping funnel. The distillation of solvent was continued, while the suspension was stirred to prevent serious bumping, until the boiling point indicated the complete removal of water. The mixture was allowed to cool, was then filtered, and the filtrate was distilled, first at atmospheric pressure to remove toluene and then at low pressure, the fraction b.p. 90–140° (0.1–0.2 mm.) being collected. Redistillation gave 50 g. of almost pure lactone, b.p. 100–104° (0.2 mm.), n_D^{20} 1.442. Yield 64%.

Anal. Calcd. for $C_9H_{17}O_5P$: C, 45.77; H, 7.25; P, 13.11. Found: C, 45.63; H, 7.44; P, 13.00.

Acknowledgment. Thanks are due to Mr. P. J. Fydelor for recording the infrared spectrum of the product which is shown in Fig. 1. It was obtained from a cap layer between rock salt plates in a Hilger H 800 double beam instrument. The absence of an absorption peak in the 2410 cm.$^{-1}$ region characteristic of P-H bond stretching is noteworthy.

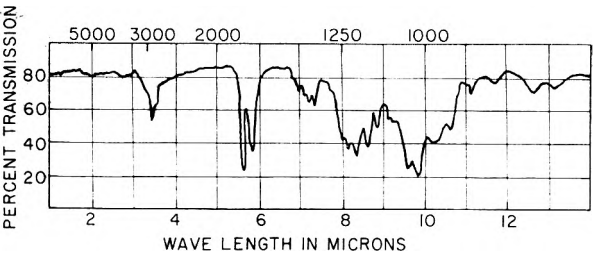


Fig. 1. Infrared absorption spectrum of diethyl 4-phosphonovalero-4-lactone

TABLE I

PRINCIPAL ABSORPTION PEAK ASSIGNMENTS

Cm.$^{-1}$	Assignment
763	P—C
856, 900	C—C=O or C—O—C
1020, 1045	P—O—C
1134	C—O—C
1203	P=O
1252	Epoxy in C—O—C=O
1368, 1393	Multiple —CH_3
1445	Assymetric C—CH_3
1721, 1786	C=O
2900, 2950	Aliphatic C—H

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(5) It is imperative to remove the alcohol completely, otherwise that remaining reacts with the lactone to give triethyl 4-phosphono-4-hydroxyvalerate.

Polar, Resonance, and Steric Effects of the 2:3-Benzo Substituent

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We have determined the rate constants of (1) acid-catalyzed esterification, in methanol, of benzoic and 1-naphthoic acids, and (2) alkaline hydrolysis(with sodium hydroxide) of methyl and ethyl benzoates and 1-naphthoates in 56% (w/w) acetone-water. Kinetics of esterification, with hydrogen chloride as catalyst, were followed by a method similar to that of Hartman and Borders,[1] a correction for the effect of product water being applied to the rate equation. Tommila and Hinshelwood's[2] method was used in following ester hydrolysis. Results are given in Tables I and II together

(1) R. J. Hartman and A. M. Borders, *J. Am. Chem. Soc.*, 59, 2107 (1937).

(2) E. Tommila and C. N. Hinshelwood, *J. Chem. Soc.*, 1801 (1938).

TABLE I

RATE CONSTANTS FOR THE ESTERIFICATION OF ACIDS IN METHANOL

Acid	$k \times 10^4$ (L. mole^{-1} sec.$^{-1}$)				Derived Data	
	25°	40°	50°	60°	E (kcal. mole^{-1})	$\log_{10}B$
Benzoic	2.10	7.05	14.82	30.0	15.01 ± 0.03	7.33 ± 0.02
	2.13	7.06	15.00	30.7		
		7.08	15.12			
		7.13				
1-Naphthoic	0.859	2.78	6.05	12.43	15.15 ± 0.11	7.03 ± 0.07
			6.25	12.55		

TABLE II

RATE CONSTANTS FOR THE ALKALINE HYDROLYSIS OF ESTERS IN 56% (W/W) ACETONE-WATER

Ester	$k \times 10^3$ (L. mole^{-1} sec.$^{-1}$)				Derived Data	
	15°	25°	40°	50°	E	$\log_{10}B$
Ethyl benzoate	1.303	2.98	9.75	19.87	14.44 ± 0.03	8.07 ± 0.02
	1.311	2.99	9.90	19.87		
		3.00				
		3.03				
Ethyl 1-naphthoate	0.436	1.000	3.20	6.73	14.46 ± 0.05	7.61 ± 0.03
		1.005	3.20	6.73		
Methyl benzoate	4.17	9.62	30.6	63.0	14.33 ± 0.01	8.49 ± 0.01
	4.20	9.67	30.8	63.1		
Methyl 1-naphthoate	1.52	3.46	11.33	22.87	14.44 ± 0.04	8.13 ± 0.03
		3.47		23.33		

with the derived values of the Arrhenius parameters E and $\log_{10}B$. Rate constants are accurate to 1%.

Taft[3] has shown that the polar substituent constant (σ^*) of ortho groups in o-substituted benzoates may be evaluated from the equation

$$\log (k/k_0)_B - \log (k/k_0)_A = \sigma^*(\rho_B^* - \rho_A^*)$$

Using the data of Tables I and II and Jaffé's[4] values of ρ for the unhindered m- and p- derivatives, the σ^* value for the 2:3-benzo group relative to hydrogen (the relevant k_0 refers to the reaction of the corresponding unsubstituted benzoic ester) has been evaluated. With this σ^* value, the nonpolar contribution (E_s) to the relative rate, has been evaluated (again relative to hydrogen) using the equation

$$E_s = \log k/k_0 - \sigma^*\rho^*$$

Values for both parameters are given in Table III. These figures are derived using log k values obtained from Arrhenius plots of the data in Tables I and II. It should be noted that Taft's σ^* and E_s values for ortho substituents are relative to the methyl group.

Table IV gives energy factors for the formation and hydrolysis of 1-naphthoic esters at 25°. The values of σ^* and E_s (25°) used are the mean values −0.026 and −0.402, respectively.

(3) R. W. Taft in M. S. Newman *Steric Effects in Organic Chemistry*, John Wiley & Sons, Inc., New York, 1956, Chapter 13.

(4) H. H. Jaffé, *Chem. Revs.*, **53**, 191 (1953).

TABLE III

POLAR AND NONPOLAR CONTRIBUTIONS TO RELATIVE RATE

	σ^{*ac}	$E_s{}^a$	σ^{*bc}	$E_s{}^b$
25°	−0.018	−0.401	−0.033	−0.404
40°	−0.019	−0.396	−0.036	−0.399
50°	−0.022	−0.393		

[a] From formation and hydrolysis of methyl 1-naphthoate; [b] from formation of methyl 1-naphthoate and hydrolysis of ethyl 1-naphthoate; [c] mean value and median deviation of the five σ^* values are −0.026 ± 0.004.

At first sight, it would appear, from Table IV, that (1) the polar and nonpolar contributions to the relative heats of activation are both very small and (2) kinetic energy steric effects ($T\Delta\Delta S^\ddagger$) constitute the dominant factor in reducing the rates of reaction of the 1-naphthyl derivatives. However, the nonpolar contribution to the relative heat of activation is a composite of two terms, one due to resonance effects ($\Delta\Delta E\psi^\ddagger$) and the other due to steric strain ($\Delta\Delta E_R^\ddagger$). It seems likely that these two effects are of approximately equal magnitude but of opposing sign, so that the total nonpolar contribution is zero. (The steric requirements of the ester transition state would be expected to be at least comparable with those of the transition state for the Menschutkin reaction of quinoline and methyl iodide, for which $\Delta\Delta E_R^\ddagger = 1$ kcal.[5]) Upper and lower limits for the rate-increasing resonance effect and hence for the rate-retarding steric strain term may be readily estimated. The loss of resonance energy in passing from ground to

(5) J. Packer, J. Vaughan, and E. Wong, *J. Am. Chem. Soc.*, **80**, 905 (1958).

TABLE IV

ENERGY TERMS (RELATIVE TO BENZOIC ESTERS) FOR 1-NAPHTHOIC ESTER FORMATION AND HYDROLYSIS

Reaction	$\Delta\Delta H\ddagger$[a]	$-2.303\ RT\ \sigma^*\rho^*$[b]	$-T\Delta\Delta S\ddagger$[c]	$-2.303\ RT\ E_s$[d]	$\Delta\Delta H\ddagger + 2.303\ RT\sigma^*\rho^*$[e]
Formation of methyl ester	0.14 ± 0.11	-0.01	0.41	0.54	0.15
Hydrolysis of methyl ester	0.11 ± 0.04	0.06	0.49	0.54	0.05
Hydrolysis of ethyl ester	0.02 ± 0.06	0.06	0.62	0.54	-0.04

[a] Relative heat of activation (ΔE). [b] Relative polar energy of activation ($\Delta\Delta E_0\ddagger$). [c] $2.303\ RT\ \Delta \log B$. [d] Nonpolar contribution to the relative free energy of activation. [e] Nonpolar contribution to the relative heat of activation ($\Delta\Delta H\ddagger - \Delta\Delta E_\sigma\ddagger$).

transition state in the hydrolysis of ethyl benzoate, relative to a simple aliphatic ester, is 6 *k*cal. mole^{-1}.[6] If resonance between the ring and side-chain in a 1-naphthoic ester were completely inhibited owing to the steric effect of the fused ring, then the 1-naphthoate would resemble an aliphatic ester in giving a $\Delta\Delta E\psi\ddagger$ value of -6 *k*cal. mole^{-1}. A lower limit for $\Delta\Delta E\psi\ddagger$ may be estimated from relative pK$_a$ values for benzoic (4.20) and 1-naphthoic (3.69) acids. Resonance interaction between ring and side chain is less in the anion than in the parent acid. Some steric inhibition of such resonance in the case of naphthoic acid leads to a smaller decrease in resonance energy for 1-naphthoic acid ionization than for benzoic acid ionization. If this were the sole reason why 1-naphthoic acid is a stronger acid than benzoic acid, then $\Delta\Delta E\psi\ddagger$ for the ionization of 1-naphthoic acid (relative to benzoic) would be -0.7 *k*cal. mole^{-1} (*cf.* ref. 7). This may be accepted as a lower limit for $\Delta\Delta E\psi\ddagger$ for the ester hydrolysis because in this reaction all resonance interaction is frozen out in the transition state. Thus, the strain in the transition states, for hydrolysis and esterification involving simple 1-naphthoic esters, lies between 0.7 and 6 *k*cal. mole^{-1}.

In view of the small value for σ^* (Table III) it would appear that the relative reactivities of 1-naphthyl and phenyl derivatives will usually be governed more by steric than by polar factors.

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(6) M. M. Kreevoy and R. W. Taft, *J. Am. Chem. Soc.*, 79, 4016 (1957).
(7) Ref. 3, p. 581.

Synthesis of Some New 8,8′-Disubstituted 2,2′-Biquinolines

FRANCIS H. CASE AND JOHN J. LAFFERTY

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It has been shown[1] that when 2,2′-biquinoline is substituted in the 3-position with a methyl or ethyl group the molar absorptivity of the copper (I) complex is greatly reduced. However, substitution of a phenyl group in this position increases the value of the molar absorptivity. It has been proposed that the molar absorptivity and the stability of the complex are a function of the planarity of the biquinoline molecule and the electron density about the nitrogen atoms of the quinoline nuclei. Substitution of any of these substituents in the 3-position introduces a steric factor that causes distortion from planarity of the 2,2′-biquinoline molecule by rotation of the quinoline moieties about the bond between the 2,2′-positions. The stability of the complex and the molar absorptivity should then decrease. The anomalous behavior of 3-phenyl-2,2′-biquinoline was attributed to increased electron density about the nitrogen atoms of the quinoline nuclei by electron donation of the phenyl group. The resulting increased stability of the copper (I) complex would account for the increase in the value of the molar absorptivity of the complex.

To further test this proposal it was decided to prepare 2,2′-biquinolines substituted in the 8,8′-positions with the methyl, ethyl, and phenyl groups. Spatial models of these compounds indicate that formation of the copper (I) complex would require a similar rotation of the quinoline moieties about the bond between the 2,2′-positions of the biquinoline.

The preparation of 8,8′-dimethyl-2,2′-biquinoline from the reaction of 8-methylquinoline with sodium is claimed in the literature.[2] However, it has since been shown[3] that the application of this method to quinoline yields 2,3′-biquinoline and not the expected 2,2′-biquinoline. Although the yields vary widely when the method of Ueda[4] (reductive coupling using palladium and hydrazine) or the Ullmann reaction[5-7] is applied to the corresponding haloquinolines or haloisoquinolines for the preparation of biquinolines or biisoquinolines products of predictable structure are obtained. Application of the method of Ueda to 2-bromo-8-methylquinoline gave a product indicated by analysis to be 8,8′-

(1) G. F. Smith and D. H. Wilkins, *Anal. Chim. Acta*, 10, 139 (1954).
(2) E. Conolly, *J. Chem. Soc.*, 2083 (1925).
(3) K. Ueda, *J. Pharm. Soc. Japan*, 57, 817 (1937); *Chem. Abstr.*, 32, 1265 (1938).
(4) K. Ueda, *J. Pharm. Soc. Japan*, 57, 180 (1937); *Chem. Abstr.*, 33, 608 (1939).
(5) J. G. Breckenridge, *Can. J. Research B*, 28, 593 (1950).
(6) F. H. Case and G. Maerker, *J. Am. Chem. Soc.*, 75, 4920 (1953).
(7) F. H. Case, *J. Org. Chem.*, 17, 471 (1952).

TABLE I

INTERMEDIATE SUBSTITUTED QUINOLINES

	M.P., °C.	B.P., °C.	MM.	Yield, %	Calcd. C	Calcd. H	Calcd. Br	Found C	Found H	Found Br
2-Amino-8-methyl-[a]	84–85	150–155	0.1	41	—	—	—	—	—	—
2-Amino-8-ethyl-	118–119	100–105	0.15	66	76.71	7.02	—	76.90	6.89	—
2-Amino-8-phenyl-[a]	167–168	—	—	63	—	—	—	—	—	—
2-Hydroxy-8-methyl-[a]	218–219	—	—	79	—	—	—	—	—	—
2-Hydroxy-8-ethyl-	137–137.5	—	—	44	76.27	6.40	—	76.25	6.35	—
2-Hydroxy-8-phenyl	127–128	—	—	33	81.45	5.01	—	81.51	5.06	—
2-Bromo-8-methyl-	78–79	140–143	0.3	65	54.08	3.63	—	53.87	3.57	—
2-Bromo-8-ethyl-	26–27	172–175	0.2	80	—	—	33.85	—	—	33.36
2-Bromo-8-phenyl-	—	172–175	0.2	81	63.40	3.55	—	63.40	3.31	—

[a] Preparation previously reported in literature by another method.

dimethyl-2,2′-biquinoline, which melts 56° higher than that reported previously.[2]

The preparation of 8-methyl,[8] 8-ethyl,[9] and 8-phenyl[10] quinolines was effected by variation of the Skraup reaction as described in the literature.

From these, the required 2-aminoquinolines were conveniently prepared by the action of sodamide on solutions of the quinolines in dimethylaniline. This method of preparation was found to be superior to those described in the literature for the methyl[11] and phenyl[12] aminoquinolines.

Attempts to prepare the bromoquinolines from the corresponding aminoquinolines by variations of the Sandmeyer or Craig[13] reaction failed. It was found that the 2-aminoquinolines can be easily diazotized by the methods of Schoutissen[14] or Hodgson and Walker[15] but attempts to prepare the bromo derivatives by the diazonium method were unsuccessful. For this reason the diazonium salts prepared as above were converted to the respective carbostyrils. Of these only the 8-methyl derivative has been previously reported.[16]

From the carbostyrils the three requisite bromoquinolines, previously unreported, were prepared by the method of Kaslow and Lawton.[17]

Application of the Ullmann reaction to 8-ethyl-2-bromoquinoline gave 8,8′-diethyl-2,2′-biquinoline when the copper catalyst was pretreated by the method of Kleider and Adams.[18] With an untreated catalyst none of the desired products could be isolated from the reaction mixture. Application of the Ullmann reaction to 2-bromo-8-methyl and 8-phenylquinoline failed to yield the desired biquinolines. These were obtained in very small yield by the method of Ueda.[4]

These compounds are now being tested and the results will appear in a later publication.

EXPERIMENTAL

2-Amino-8-alkyl and 8-phenylquinolines. A mixture of 0.5 mole of the quinoline, 0.6 mole of sodamide, and 500 ml. of dimethylaniline was stirred and heated at 120–125° for 8–10 hr. The mixture was cooled and treated with 300 ml. of water. The dimethylaniline layer was washed several times with 100-ml. portions of water. The 2-amino-8-phenylquinoline was precipitated by addition of excess petroleum ether (b.p. 30–60°). It was purified by crystallization from benzene.

The 2-amino-8-methyl and 2-amino-8-ethyl quinolines were isolated by vacuum distillation following the removal of the dimethylaniline *in vacuo*. Crystallization of the distillates from benzene-hexane mixtures yielded the pure amines.

8-Alkyl and 8-phenylcarbostyrils. A solution of 0.24 mole of the aminoquinoline in 900 ml. of 85% phosphoric acid was cooled to 0° and diazotized with nitrosylsulfuric acid prepared from 18.6 g. of sodium nitrite in 450 ml. of concentrated sulfuric acid. The temperature was kept below 5° during the addition of the nitrosylsulfuric acid. Stirring was continued for 30 min. after the addition. The diazonium solution was slowly poured into 8 l. of hot water. The solution was heated on the steam bath for 1 hr. and allowed to stand for 15 hr. The *p*H of the solution was adjusted to approximately 5 with aqueous sodium hydroxide solution. The crude carbostyrils separated as semisolid masses which were dissolved in benzene. The benzene solutions were washed with water and evaporated to dryness. The carbostyrils were purified by crystallization from benzene-hexane.

2-Bromo-8-alkyl and 8-phenylquinolines. A mixture of 0.07 mole of the respective carbostyril, 40 g. of phosphorus tribromide, and 26 g. of phosphorus oxybromide was heated at 150–155° for 4 hr. The reaction mixture was poured on ice, made alkaline with aqueous sodium hydroxide solution, and extracted with benzene. The benzene was evaporated and the residual oil distilled *in vacuo*. The final purification of the 8-methyl and 8-ethyl-2-bromoquinolines was accomplished by recrystallization from hexane.

8,8′-Dimethyl-2,2′-biquinoline. A mixture of 10 g. of 8-methyl-2-bromoquinoline, 39.6 g. of 85% hydrazine hydrate in water, 4.5 g. of Pd on calcium carbonate (5% Baker Catalyst), and 300 ml. of 5% ethanolic potassium hydroxide was stirred at reflux for 2 hr. The reaction mixture was

(8) R. Adams and J. Johnson, *Elementary Laboratory Experiments in Organic Chemistry*, Third Ed., Macmillan Co., New York (1945), 351.

(9) R. A. Glenn and J. R. Bailey, *J. Am. Chem. Soc.*, **63**, 640 (1941).

(10) C. E. Kaslow and M. Hayek, *J. Am. Chem. Soc.*, **73**, 4986 (1951).

(11) F. W. Bergstrom, *J. Org. Chem.*, **3**, 233 (1938).

(12) F. W. Bergstrom, *J. Org. Chem.*, **3**, 424 (1938).

(13) L. Craig, *J. Am. Chem. Soc.*, **56**, 231 (1934).

(14) H. A. Schoutissen, *J. Am. Chem. Soc.*, **55**, 4531 (1933).

(15) H. H. Hodgson and J. Walker, *J. Chem. Soc.*, 530 (1935).

(16) O. Fischer, *Ber.*, **35**, 3678 (1902).

(17) C. E. Kaslow and W. R. Lawton, *J. Am. Chem. Soc.*, **72**, 1723 (1950).

(18) E. C. Kleider and R. Adams, *J. Am. Chem. Soc.*, **55**, 4225 (1933).

filtered. The spent catalyst was boiled in benzene and the benzene solution added to the filtrate. After evaporation of the solvent the residue was crystallized from benzene. The yield was 52 mg. (0.8%), m.p. 203–204°.

Anal. Calcd. for $C_{20}H_{16}N_2$: C, 84.47; H, 5.67. Found: C, 84.12; H, 5.76.

8,8′-Diphenyl-2,2′-biquinoline. The method of preparation was similar to that used for 8,8′-dimethyl-2,2′-biquinoline. From 6 g. of 8-phenyl-2-bromoquinoline, 71 mg. (1.7%) of purified product was obtained. After crystallization from benzene it melted at 247–248°.

Anal. Calcd. for $C_{30}H_{20}N_2$: C, 88.21; H, 4.94. Found: C, 88.37; H, 4.94.

8,8′-Diethyl-2,2′-biquinoline. A mixture of 7.5 g. of 8-ethyl-2-bromoquinoline and 10 g. of copper powder pretreated by the method of Kleider and Adams[18] was heated for 3 hr. at 210–220°. The reaction mixture was pulverized and extracted with hot concentrated hydrochloric acid. The acid extracts were cautiously neutralized with aqueous sodium hydroxide and then made strongly alkaline with ammonium hydroxide. The mixture was extracted with benzene and the extracts were concentrated to a small volume. The solution was adsorbed on an alumina column. Hexane and hexane-chloroform mixtures were used as eluents with fractions taken at every 20 ml. The residue from evaporation of the solvents was crystallized from benzene yielding 0.156 g. (3.1%) melting at 122–123°.

Anal. Calcd. for $C_{22}H_{20}N_2$: C, 84.58; H, 6.45. Found: C, 84.51; H, 6.41.

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5-Bromoörotic Acid

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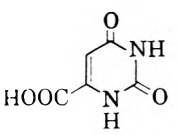
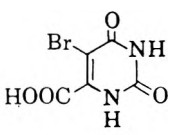
In the past few years, increased interest in the physiological properties of orotic acid (I) and its derivatives has been apparent. A variety of 5-substituted orotic acids have been investigated, including 5-halogenated derivatives; 5-chloroörotic acid was described by Johnson[1] in 1943, 5-iodoorotic acid has been synthesized and used to elucidate aspects of nucleic acid metabolism,[2] and the effect of 5-fluoroörotic acid on tumor growth has recently been studied.[3] However, no reliable synthesis or description of 5-bromoörotic acid (II) has been available.



(I)



(II)

Several reported attempts to brominate orotic acid directly in aqueous solution resulted in the formation of 5,5-dibromobarbituric acid.[4,5] Behrend[6] suggested that oxidation of 5-bromo-6-methyluracil with hot, fuming nitric acid gave 5-bromoörotic acid, but the yield was very poor and the product was not clearly described.

Although uracil[7] and 6-methyluracil[8] have been brominated in the 5-position in high yield by reaction with bromine in carbon disulfide, we recovered only unchanged starting material when orotic acid was treated with bromine in carbon tetrachloride at 70°. However, reaction with a mixture of aqueous hydrogen peroxide and hydrobromic acid led to a 73% yield of bromoörotic acid. The dihydrate crystallized from aqueous solution, and was converted to the anhydrous compound by heating at 80° *in vacuo* over phosphorus pentoxide. It was recovered unchanged after being boiled with aqueous sodium hydroxide solution, which indicates the stability of the C—Br bond and proves it to be at the 5-position as expected.

Potentiometric titration showed 5-bromoörotic acid to be dibasic, the $-\log$ of the apparent acidic ionization constants being 2.21 and 7.59. The corresponding values for orotic acid itself are 2.40[5,9] (2.8[10,11]) and 9.45,[10,11] while the value for o-bromobenzoic acid is 2.85.[9,12]

Upon heating above its melting point, the acid was smoothly decarboxylated to give a nearly quantitative yield of 5-bromouracil. Conversely, orotic acid itself has only recently been decarboxylated successfully, under drastic conditions, and the yield of the resulting uracil was low.[13]

EXPERIMENTAL[14]

Attempted direct bromination of orotic acid. Orotic acid monohydrate (25.0 g., 0.144 mole) was slurried with 100 ml. dry carbon tetrachloride, and bromine (23 g., 0.144 mole) was added dropwise with stirring. The red mixture was then boiled under reflux for several hours, cooled, and the solid filtered off and washed with carbon tetrachloride. After drying in air, the residue was recrystallized from water to give a quantitative recovery of orotic acid, m.p. 342° (decomp.) (immersed at 340°).

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(2) W. H. Prusoff, W. L. Holmes, and A. D. Welch, *Cancer Research*, **13**, 221 (1953).
(3) C. Heidelberger, N. K. Chadhuri, P. Danneberg, D. Mooren, L. Griesbach, R. Duschinsky, R. J. Schnitzer, E. Pleven, and J. Scheiner, *Nature*, **179**, 663 (1957); R. Duschinsky, E. Pleven, and C. Heidelberger, *J. Am. Chem. Soc.*, **79**, 4559 (1957).
(4) H. L. Wheeler, *Am. Chem. J.*, **38**, 358 (1908).
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(7) H. L. Wheeler and H. F. Merriam, *Am. Chem. J.*, **31**, 603 (1904).
(8) R. Behrend, *Ann.*, **231**, 248 (1885).
(9) Determined by conductivity.
(10) Determined spectrophotometrically.
(11) D. Shugar and J. J. Fox, *Biochim. et Biophys. Acta*, **9**, 199 (1952).
(12) J. F. J. Dippy, *Chem. Revs.*, **25**, 151 (1939).
(13) M. R. Atkinson, M. H. Maguire, R. K. Ralph, G. Shaw, and R. N. Warrener, *J. Chem. Soc.*, 2363 (1957).
(14) All melting points were measured in a Vanderkamp block, and are corrected.

Anal. Calcd. for $C_5H_4N_2O_4 \cdot H_2O$: C, 34.5; H, 3.47; N, 16.1. Found: C, 34.7; H, 3.54; N, 16.2.

5-Bromoörotic acid. Orotic acid monohydrate (52 g., 0.30 mole) was suspended in 30% aqueous hydrogen peroxide ("Superoxol") (63 ml., 0.80 mole) at about 0°, and 90 ml. (0.80 mole) 48% aqueous hydrobromic acid was added dropwise with mechanical stirring. The violent reaction was moderated by ice cooling to maintain the temperature below 35°. After addition of the hydrobromic acid was complete, the mixture was allowed to stand overnight. The precipitated solid was isolated by filtration, washed with cold water, and dried to give a 73% yield of crude product.

Recrystallization from water gave pale yellow needles of 5-bromoörotic acid dihydrate, m.p. 288° (dec.) (immersed at 280°).

Anal. Calcd. for $C_5H_3BrN_2O_4 \cdot 2H_2O$: C, 22.2; H, 2.60; N, 10.3. Found: C, 22.8; H, 2.57; N, 10.3.

The anhydrous acid was obtained by drying at 80° over phosphorus pentoxide.

Anal. Calcd. for $C_5H_3BrN_2O_4$: C, 25.6; H, 1.29; N, 11.9. Found: C, 25.6; H, 1.27; N, 12.1.

A sample of 5-bromoörotic acid was boiled for 1 hr. with 10% aqueous sodium hydroxide solution, and was recovered unchanged after acidification, isolation, and drying. Samples of the acid were titrated in approximately 0.01*M* aqueous solution with 0.100*M* sodium hydroxide solution. A Photovolt *p*H meter, equipped with standard glass and calomel electrodes, was employed for these measurements, and the usual precautions were observed. The *p*H of the solutions at 50% of the stoichiometric volume of alkali was taken as pK_a' for each ionizing group. The pK_a' calculated from eight other points on the titration curves was in reasonable agreement with these values. 5-Bromoörotic acid was found to have pK_{a1}' of 2.2[1] and a pK_{a2}' of 7.5[9].

The ultraviolet absorption spectrum of a $10^{-4}M$ solution of 5-bromoörotic acid in deionized water was measured with a Beckman Model DU spectrophotometer. At *p*H 5.6, λ_{max} 279.5 mμ ($\epsilon = 8.75 \times 10^3$), λ_{min} 243 mμ ($\epsilon = 1.02 \times 10^3$) were observed.

5-Bromouracil. A 2.0-g. sample of pure 5-bromoörotic acid was carefully heated to about 300° in a Wood's metal bath until gas evolution ceased. The cooled residue was recrystallized from water to give an almost quantitative yield of 5-bromouracil, m.p. 296° (dec.) (lit. 293°).[7]

Anal. Calcd. for $C_4H_3BrN_2O_2$: C, 25.2; H, 1.58. Found: C, 25.3; H, 1.64.

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Improved Syntheses of Certain Derivatives of 5,6-Dimethoxy-8-aminoquinoline[1]

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5,6-Dimethoxy-8-(4′-isopropylamino-1′-methylbutylamino)quinoline (SN-9972)[2] [5,6-dimethoxy-8-butylamino(1′-methyl-4′-diethylamino)quinoline and 5,6-dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)quinoline (SN-8233)[2] have recently provided encouraging data when examined against experimental tumors in animals.[3] It therefore became of interest to develop more efficient syntheses than those heretofore available for these substances.

In the preparation of SN-8233 previously reported[4] the key step involves alkylation of 5,6-dimethoxy-8-aminoquinoline with 1-diethylamino-4-bromopentane (as the hydrobromide) at *p*H 4.8.[5] However, even under the optimum conditions the yield of SN-8233, isolated as the oxalate, was only 21% largely because of cyclization of the bromoamine to 1,1-diethyl-2-methylpyrrolidinium bromide.

Shiho[6] has described the condensation of 1-diethylamino-4-ethoxy-3-pentene with 6-methoxy-8-aminoquinoline followed by reduction of the resulting anil to yield pamaquin. Barber and co-workers[7] have successfully condensed the aminoquinoline with 1-diethylamino-4,4-diethoxypentane to yield the same anil which was similarly reduced to pamaquin in high yield. This general method has been adapted, with some modifications, to the preparation of SN-8233 after attempts to effect the direct reductive alkylation of 5,6-dimethoxy-8-aminoquinoline or 5,6-dimethoxy-8-nitroquinoline with 1-diethylamino-4-pentanone as reported by Bergmann[8] failed. It should also be noted that Barber and co-workers[7] were also unable to obtain pamaquin by Bergmann's method.

In the preparation of the requisite intermediates, unexpected complications were encountered in the bromination of 6-methoxy-8-nitroquinoline. When the method described in detail by Elderfield and co-workers,[9] based on a Japanese report,[10] was followed, the expected 5-bromo-6-methoxy-8-nitroquinoline was not obtained. Rather, what appeared to be a perbromide of the desired compound was isolated. This could be readily converted to the 5-bromo compound by treatment with cyclohexene

(1) This work was supported by a Research Grant (CY-2951) from the National Cancer Institute to the University of Michigan.

(2) The prefix SN identifies a compound in F. Y. Wiselogle, *Survey of Antimalarial Drugs*, Edwards Brothers, Ann Arbor, Mich., 1946.

(3) Private communication from Dr. Ralph Jones, Jr., of the University of Miami Medical School.

(4) R. C. Elderfield, V. J. Gensler, J. D. Head, H. H. Hagerman, C. B. Kremer, J. B. Wright A. D. Holley, B. Williamson, J. Galbreath, L. Wiederhold III, R. Frohardt, S. M. Kupchan, T. A. Williamson, and O. Berstein, *J. Am. Chem. Soc.*, **68**, 1524 (1956).

(5) *cf.* R. C. Elderfield and L. E. Rubin, *J. Am. Chem. Soc.*, **75**, 2963 (1953).

(6) D. Shiho, *J. Chem. Soc. Japan*, **65**, 135 (1944).

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which underwent bromination as in the analogous reaction with pyridine perbromide.[11] Further, the iron and large excesses of bromine and calcium carbonate used in the earlier preparation[9] were found to be unnecessary, and a simpler procedure which gives the desired bromo compound directly has been worked out.

In the displacement of the bromine in 5-bromo-6-methoxy-8-nitroquinoline by methoxyl, the reaction time has been reduced from 4 days to 20 hr. by employing an excess of sodium methoxide instead of the equivalent amount previously used. Of the two methods for reducing the nitro group in 5,6-dimethoxy-8-nitroquinoline[9,12] catalytic reduction over palladium was manipulatively easier than the stannous chloride reduction, but the product from the latter reaction was easier to purify.

When the preparation of larger amounts of SN-9972 by the method used previously[4] was attempted, cyclization of the amino bromide, 1-isopropylamino-4-bromopentane, prior to alkylation of 5,6-dimethoxy-8-aminoquinoline, likewise was the cause of prohibitively low yields. Accordingly, SN-9972 has been prepared in acceptable yields by reductive alkylation of 5,6-dimethoxy-8-(4-amino-1-methylbutylamino)quinoline (CN-1104)[9] with acetone substantially according to Cope and co-workers.[13]

EXPERIMENTAL[14,15]

5-Bromo-6-methoxy-8-nitroquinoline and its perbromide. A. According to Elderfield et al.[9] To a suspension of 491 g. (2.4 moles) of 6-methoxy-8-nitroquinoline, 183 g. (1.83 moles) of calcium carbonate, and 9.6 g. of iron filings in a refluxing mixture of 2.4 l. of chloroform and 490 ml. of water, 480 ml. (9.4 moles) of bromine was added with stirring. After refluxing for 6 hr. and stirring for 15 hr. at room temperature, the precipitate was collected, washed successively with water and chloroform, and dried to yield 1075 g. of crude perbromide. Crystallization of a sample from benzene-nitrobenzene gave pale orange prisms of the perbromide, m.p. 155–157° (dec.).

Anal. Calcd. for $C_{10}H_7Br_3N_2O_3$: Br, 54.2. Found: Br, 54.2.

A mild exothermic reaction ensued when the crude perbromide was stirred for 15 hr. with 280 ml. of cyclohexene and 2.5 l. of benzene. After heating the mixture to the boiling point and cooling, the precipitate of crude bromo compound (734 g.) was collected. The main contaminant, calcium carbonate, was removed by hot filtration, and crystallization from pyridine gave pure 5-bromo-6-methoxy-8-nitroquinoline (362 g., 53%), m.p. 203.0–205.5°. Reported 204–205°.[9]

B. To a stirred suspension of 40.8 g. (0.2 mole) of 6-methoxy-8-nitroquinoline and 9 g. (0.09 mole) of calcium carbonate in 180 ml. of chloroform and 50 ml. of water, 12.2 ml. (0.24 mole) of bromine was added at such a rate as to maintain a gentle reflux. After refluxing for 1.75 hr., 40 ml. of cyclohexene was added followed, after 5 min., by 12 ml. of 28% ammonium hydroxide. After heating for a further 10 min., the mixture was diluted with 180 ml. of petroleum ether (40–60°) and 140 ml. of water. The product was collected, washed successively with 1:1 chloroform–petroleum ether and water, and dried to yield 49 g. (85%) of crude 5-bromo-6-methoxy-8-nitroquinoline, m.p. 170–195° (dec.). Crystallization from benzene-nitrobenzene gave pale yellow needles of the pure compound, m.p. 205–206°.

1-Diethylamino-4,4-diethoxypentane. A mixture of 222 ml. (1.21 moles) of 1-diethylamino-4-pentanone, 555 ml. of redistilled ethyl orthoformate, 240 g. (1.25 moles) of *p*-toluenesulfonic acid monohydrate, and 870 ml. of absolute ethanol was refluxed for 3 days. The alcohol (about one liter) was distilled off under reduced pressure. After addition of a solution of 61 g. of sodium hydroxide in 500 ml. of water, the mixture was extracted with ether. Removal of the ether from the dried extract and distillation under reduced pressure gave 197 g. (70%) of the ketal, b.p. 127–132° (27 mm.), n_D^{21} 1.433, d_4^{25} 0.86. Reported b.p. 121–122° (22 mm.).[16]

5,6-Dimethoxy-8-(4′-diethylamino-1′-methylbutylamino)-quinoline. (SN-8233). A mixture of 46 ml. (0.17 mole) of 1-diethylamino-4,4-diethoxypentane, 25 g. (0.12 mole) of 5,6-dimethoxy-8-aminoquinoline, and 0.17 g. of ammonium chloride was heated in an oil bath with stirring at 155° for 2 hr. during which the temperature was raised to 182°. Ethanol (16 ml., 81%) distilled. The residue was taken up in 300 ml. of absolute ethanol and shaken with 0.55 g. of prereduced Adams' platinum oxide catalyst at room temperature and 50 lb. hydrogen pressure. After 20 hr. 0.13 mole (77%) of hydrogen had been absorbed. The filtrate from the catalyst was added to a solution of 30 ml. of glacial acetic acid in 750 ml. of water and the resulting mixture was extracted three times with benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue gave 2.0 g. (8%) of unreacted 5,6-dimethoxy-8-aminoquinoline.

The aqueous suspension was made alkaline with sodium carbonate and extracted with four portions of benzene. Removal of the solvent from the dried benzene extracts and distillation of the residue *in vacuo* gave an oily fraction (2 g., 5%), b.p. up to 170° (0.1 mm.) followed by the drug base (28.9 g., 70%) as a yellow oil, b.p. 170–171° (0.1 mm.). Reported b.p. 179–185° (0.3 mm.).[4] The base was converted to the oxalate (96% yield) as previously described.[4] The salt formed yellow prisms, m.p. 132–136°, after recrystallization from absolute ethanol. Reported m.p. 126–128°.[4] When assayed by the Craig countercurrent procedure, the drug base showed an inhomogeneity of 4.6%[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{22}H_{33}N_3O_6$: C, 60.66; H, 7.64; N, 9.65; $(COOH)_2$, 20.69; drug base, 79.31. Found: C, 61.03; H, 7.34; N, 9.50; $(COOH)_2$, 21.18; drug base, 79.67.

5,6-Dimethoxy-8-(4′-isopropylamino-1-methylbutylamino)-quinoline. SN-9972. When 15 g. (0.045 mole) of 5,6-dimethoxy-8-(4′-amino-1-methylbutylamino)-quinoline[9] was reductively alkylated with acetone according to Cope and co-workers,[13] 13.9 g. (72%) of viscous yellow oil, b.p. 168–173° (0.2 mm.) was obtained. The reported b.p. is 190–195° (0.3 mm.).[4] From this the oxalate, m.p. 143–145° with sintering at 139°, was prepared in 73% yield. The reported m.p. is 138–141°. The drug base showed the presence of 5% inhomogeneity when assayed by the Craig method[17] (*cf.* Fig. 1).

Anal. Calcd. for $C_{21}H_{31}N_3O_6$: C, 59.84; H, 7.42; N, 9.97; $(COOH)_2$, 21.38; drug base, 78.62. Found: C, 59.97, 59.88;

(11) S. M. McElvain, and L. R. Morris, *J. Am. Chem. Soc.*, **73**, 206 (1951).

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(14) Melting points and boiling points are uncorrected unless stated otherwise.

(15) Microanalyses by Spang Microanalytical Laboratory, Ann Arbor, Michigan.

(16) Van Shelven, British Patent **388,087**, Example 32.

(17) Craig analyses, free base and oxalate determinations were done at Applied Science Laboratories, Inc., State College, Pa.

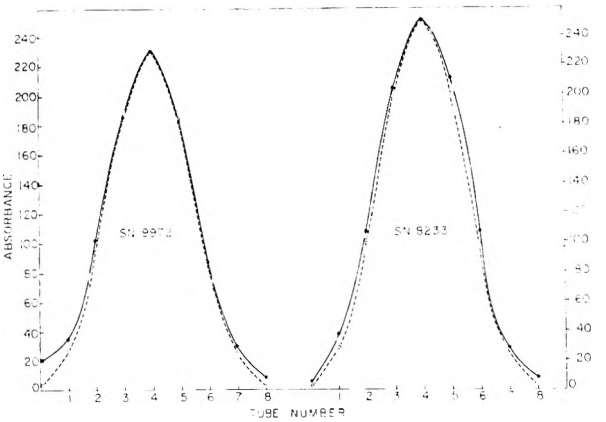

Fig. 1. SN-9972: system of isopropyl ether–*n*-butyl alcohol *vs.* 2*M* (total) citrate buffer at *p*H 3.86; concentration of base, 1.0 mg. per ml. of each phase. SN-8233: system of isopropyl ether–*n*-butyl alcohol *vs.* 2M (total) citrate buffer at *p*H 3.52; concentration of base 0.8 mg. per ml. of each phase. Concentrations determined by absorption at 390 mμ; dashed lines, theoretical; solid lines, experimental

H, 7.14, 7.19; N, 9.99, 10.04; $(COOH)_2$, 21.00; drug base, 79.88.

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Cyclic Sulfides. II. Ring Size and the Ultraviolet Absorption Spectra[1]

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The measurement of the ultraviolet absorption of ethylene sulfide[1] has now allowed a discussion of the effect of ring size upon the spectra of cyclic sulfides. The data are presented[2] in Fig. 1. Perusal shows that the four membered ring sulfide has the weak absorption band at the longest wave length. It is difficult to offer a complete explanation designating the energy levels and the transitions involved. However, an empirical relationship can be discerned between the electron density and basicity

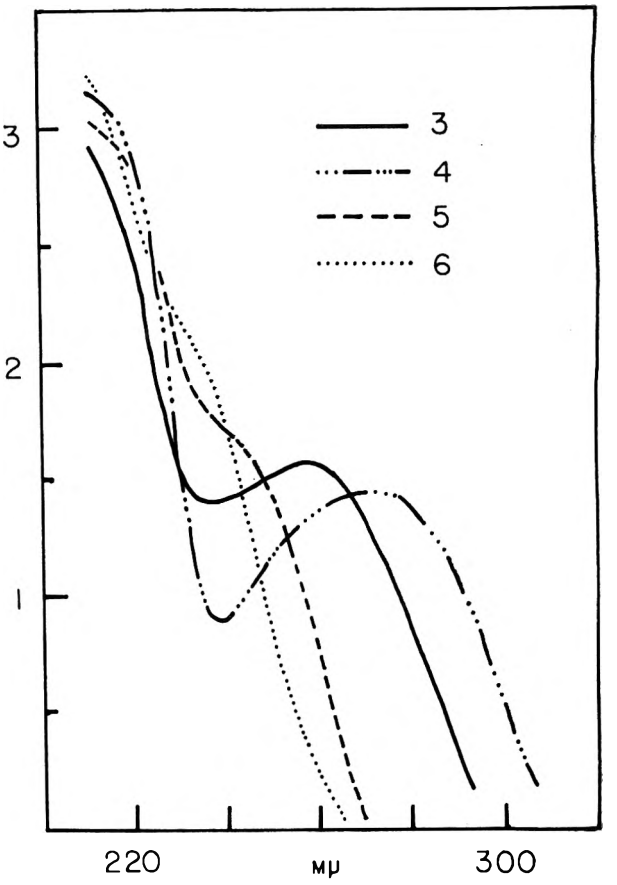

Fig. 1. Spectra of cyclic sulfides in absolute ethanol. Log ε *vs.* λ in mμ. 3 ethylene sulfide, 4 trimethylene sulfide, 5 tetramethylene sulfide, 6 pentamethylene sulfide

of the sulfur atom and the position of the transition in divalent sulfur compounds. The more the electron density on the sulfur, the further the absorption towards longer wave lengths. This can be seen in the following series.

The sulfur atom spectrum[6] serves as the basis for discussion. Hydrogen sulfide[7,8] (λ_{max} hexane 190 mμ log ε 3.2) can be compared with sodium sulfide[9] (λ_{max} 230 mμ log ε 3.8 in aqueous sodium hydroxide). Ethanethiol[7,8] has a band at 195 mμ (log ε 3.15) and an inflection at 225 mμ (log ε 2.2) in ethanol. The sodium salt of 1-*n*-butanethiol[9] in aqueous sodium hydroxide has a band at 240 mμ (log ε 3.7). The spectra of dialkyl sulfides[5] show strong bands in the region 210–215 mμ with inflections near 230 mμ (log about 2). Alkyl groups donate electrons to the sulfur. Unbonded pairs of electrons are needed in divalent sulfur compounds on the sulfur atom to have absorption above 200 mμ.

(1) Part I. R. E. Davis, *J. Org. Chem.*, **23**, 216 (1958).

(1a) National Science Foundation predoctoral fellow, 1955–1957.

(2) The experimental methods have been previously reported.[1] The sulfides were prepared by known procedures: 3 membered ring,[1] 4 membered,[3] 5 membered,[4] 6 membered.[5]

(3) G. M. Bennet and A. L. Hock, *J. Chem. Soc.*, 2496 (1927).

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(6) *Atomic Energy Levels*, Nat. Bur. Standards, Cir. No. 467, Vol. I, 1949, p. 181.

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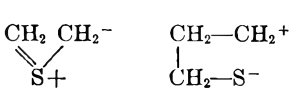
(9) L. H. Noda, S. A. Kuby, and H. A. Lardy, *J. Am. Chem. Soc.*, **75**, 913 (1953).

Dimethyl sulfone and triethyl sulfonium chloride[10,11] have no absorption above 200 mμ.

The electron donor abilities of the sulfur atom of cyclic sulfides have been observed to be in the order: 4>5>6>acyclic>3 by the complexing with boron trifluoride.[12] The order of NMR δ-values[13] was found to be 4>3>5>6 for the hydrogens on the carbon adjacent to the sulfur atom. The order of position of the weak band of cyclic sulfides (Fig. 1) is 4>3>5>6.

The explanation of these facts is based on the inherent electronic nature of the ring compounds rather than on steric considerations. The data favor formulas:



as the extreme forms. Each can be obtained as the excited state by consideration of the probable ground state and the geometric properties by molecular orbital treatment. Delocalization of p-electrons has also been used to explain other properties of small ring compounds.[14,15]

The author wishes to thank Profs. M. Carmack and E. A. Fehnel for communicating their unpublished spectral data which are in complete agreement with the data reported.

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(13) H. S. Gutowsky, R. L. Ritedge, M. Tamres, and S. Searles, *J. Am. Chem. Soc.*, 76, 4242 (1954).

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Further Reactions of Phenanthraquinone with Diaryldiazomethanes

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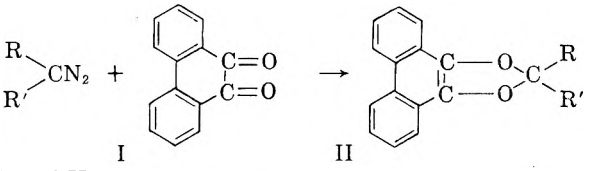
Schönberg and Mustafa[1] found that the action of diphenyldiazomethane on phenanthraquinone yields a methylenedioxy derivative of type II (R, R′ = C_6H_5) which gives phenanthraquinone when treated with sulfuric acid.

(1) A. Schönberg and A. Mustafa, *J. Chem. Soc.*, 746 (1946).

This reaction has now been extended using p,p′-dichlorodiphenyldiazomethane (Ia), o-chlorophenylphenyldiazomethane (Ib), p-nitrophenylphenyldiazomethane (Ic), and p-xenylphenyldiazomethane (Id).[2] The reactions led to the formation of the methylenedioxy derivatives IIa,b,c,d. The hydrolysis of IIa with concentrated sulfuric acid yielded phenanthraquinone.



I and II:
a, R = R′ = C_6H_4Cl-p
b, R = C_6H_5; R′ = C_6H_4Cl-o
c, R = C_6H_5; R′ = $C_6H_4NO_2$-p
d, R = C_6H_5; R′ = C_6H_4·C_6H_5-p

EXPERIMENTAL

9,10-(p,p′-Dichlorodiphenylmethylenedioxy)phenanthrene (IIa). To a suspension of phenanthraquinone (0.5 g.) in benzene (20 ml.) was added a benzene solution of p,p′-dichlorodiphenyldiazomethane (prepared from 0.8 g. of p,p′-dichlorobenzophenone hydrazone in 20 ml. of dry benzene). A mild evolution of nitrogen occurred and continued for 10 min. The quinone dissolved and the solution was kept at room temperature overnight. The red oily residue, obtained after evaporation of the benzene, solidified on washing with cold methyl alcohol and was crystallized from ethyl alcohol as yellow crystals, m.p. 185°. It gives, on treatment with concentrated sulfuric acid, a brown color which changes after some time to a green color; yield 0.7 g.

Anal. Calcd. for $C_{27}H_{16}Cl_2O_2$: C, 73.1; H, 3.6; Cl, 16.0. Found: C, 73.7; H, 3.7; Cl, 15.7.

9,10-(o-Chlorophenylphenylmethylenedioxy)phenanthrene (IIb) was obtained from phenanthraquinone (0.5 g.) and o-chlorophenylphenyldiazomethane (prepared from 0.7 g. of o-chlorobenzophenone hydrazone in 20 ml. of dry benzene). It was crystallized from petroleum ether (b.p. 60–80°) as almost colorless crystals, m.p. 207°; yield 0.6 g. It gives a brown then a green color with concentrated sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}ClO_2$: C, 79.3; H, 4.1; Cl, 8.7. Found: C, 79.4; H, 4.2; Cl, 8.4.

9,10(p-Nitrophenylphenylmethylenedioxy)phenanthrene (IIc) was obtained by treating phenanthraquinone (0.5 g.) with p-nitrophenylphenyldiazomethane (prepared from 0.8 g. of p-nitrobenzophenone hydrazone in 20 ml. of dry benzene). It was crystallized from petroleum ether (b.p. 80–100°) as orange crystals, m.p. 225; yield 0.7 g. It gives a brownish purple color with concentrated sulfuric acid.

Anal. Calcd. for $C_{27}H_{17}NO_4$: C, 77.3; H, 4.0; N, 3.3. Found: C, 77.4; H, 4.0; N, 3.5.

9,10-(p-Xenylphenylmethylenedioxy)phenanthrene (IId) was obtained as above, in 60% yield. It was crystallized from petroleum ether (b.p. 80–100°) as yellow crystals, m.p. 170°. It gives an orange color with concentrated sulfuric acid.

Anal. Calcd. for $C_{33}H_{22}O_2$: C, 88.0; H, 5.0. Found: C, 88.0; H, 5.5.

Hydrolysis of IIa. Half a gram of IIa was mixed with concentrated sulfuric acid (3 ml.) and left overnight, whereby a green solution was formed. The solution was poured onto ice,

(2) For the preparation of these diazomethane derivatives compare A. Schönberg, A. Fateen, and A. Sammour, *J. Am. Chem. Soc.*, 79, 6020 (1957).

neutralized with sodium carbonate, and extracted with ether. The residue, obtained after evaporation of the ether solution, was identified as phenanthraquinone (melting point and mixed melting point determinations).

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Synthesis of 2-Trifluoroacetylpyrrole[1]

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Received February 14, 1958

The reaction of pyrrole and trifluoroacetic anhydride in benzene at near zero temperatures occurred readily and 2-trifluoroacetylpyrrole was obtained in good yield. At higher temperatures a black tar formed rapidly. In contrast, the reaction of the weaker acid, acetic anhydride, and pyrrole was reported by Ciamician and Dennstedt[3] to require heating to give 2-acetylpyrrole.

2-Trifluoroacetylpyrrole was also prepared by treating pyrrole magnesium bromide with trifluoroacetyl chloride at low temperatures but the yield was low. This route was first reported by Oddo[4] who obtained 2-acetylpyrrole from the reaction of pyrrole magnesium bromide and acetyl chloride. More recently Portnoy and Gisser[5] prepared 2-heptafluorobutyrylthiophene by the reaction of thiophene magnesium bromide and heptafluorobutyryl chloride.

Although the fully fluorinated acyl chlorides have been reported to be acylating agents for aromatic compounds in a Friedel-Crafts type reaction,[6] when trifluoroacetyl chloride was added to pyrrole the characteristic "pyrrole red" color formed immediately, then a black tar separated. This occurred with and without aluminum chloride when near zero temperatures were used and either carbon tetrachloride or ether was used as diluent.

EXPERIMENTAL

2-Trifluoroacetylpyrrole. Method 1. A solution of 35 ml. trifluoroacetic anhydride in 300 ml. dry benzene was cooled to about 0°. While the anhydride solution was stirred vigorously, 15 g. pyrrole in 40 ml. benzene was added dropwise over a 2-hr. period. After the addition, the reaction mixture was maintained at about 0° for an additional 4 hr. The reaction mixture was washed with water then dried with anhydrous sodium sulfate. The benzene was removed by distillation and the residue was steam distilled. Trifluoroacetylpyrrole was recovered from the steam distillate by ether extraction: (24 g., 66 wt. % on pyrrole). The crude product was purified by vacuum sublimation and melted 46–47° (uncorr.).

Anal.[7] Calcd. for $C_6F_3H_4ON$: F, 35.9; N, 8.59; mol. wt., 163. Found: F, 34.3; N, 8.67; mol. wt., 163.

Method 2. A solution of 7 g. freshly distilled pyrrole in 50 ml. dry ether was cooled to 3–5° in a flask equipped with stirrer, thermometer, addition funnel, and Dewar-type condenser. Twenty-five ml. of 4*M* methyl magnesium bromide in ether (Arapahoe Special Products, Inc.) was added dropwise during a 1-hr. period while the reaction mixture was stirred and maintained at 3–5°. After the addition of the Grignard reagent, the stirred reaction mixture was maintained cold for 1 hr.

The condenser was filled with an acetone–Dry Ice mixture and the pyrrole magnesium bromide reaction mixture was gassed with 15 g. trifluoroacetyl chloride (10 wt. % excess). The acid chloride addition was completed within 30 min. and the reaction mixture was allowed to warm to room temperature. After the ether was distilled off, the residue was washed with 5 wt. % aqueous NaOH, then steam distilled. The product, recrystallized from ethyl alcohol–water, melted at 45–47° (uncorr.).

The product prepared by both methods was a white solid with a phenol-like odor and was soluble in benzene, ether, and carbon tetrachloride. An infrared spectrogram of a carbon tetrachloride solution of 2-trifluoroacetylpyrrole showed adsorptions at 2.91 microns (NH), 3.03 microns (CH), and 6.0 microns (CO). The phenylhydrazone, prepared by the standard procedure,[8] was a dark liquid which decomposed on heating.

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(1) This investigation was made at the Fluorine Research Center, University of Florida, Gainesville, Fla., under a grant from Minnesota Mining & Manufacturing Co., St. Paul, Minn.

(2) Present address: Celanese Corp. of America, Petroleum Chemicals Research and Development Dept., Clarkwood, Tex.

(3) G. Ciamician and M. Dennstedt, *Gazz. chim. ital.*, **13**, 445 (1883).

(4) B. Oddo, *Gazz. chim. ital.*, **39**, 649 (1910).

(5) S. Portnoy and H. Gisser, *J. Org. Chem.*, **22**, 1752 (1957).

(6) J. H. Simons, W. T. Black, and R. F. Clark, *J. Am. Chem. Soc.*, **75**, 5621 (1953).

(7) Micro-nitrogen determination by Peninsular Chemical Research, Gainesville, Fla. Mol. wt. determined by the melting point depression of *d*-camphor at one arbitrary dilution.

(8) R. L. Shriner and R. C. Fuson, *Identification of Organic Compounds*, 2nd ed., Wiley and Sons, New York, 1940, p. 139.

Preparation of Indazoles and Quinazolines by Catalytic Dehydrogenation

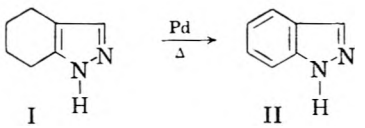
J. Paul Burnett, Jr., and C. Ainsworth

Received March 3, 1958

In a previous publication[1] it was reported that 4,5,6,7-tetrahydroindazole (I) was readily converted to indazole (II) by heating with palladium-on-carbon in decalin. A search of the literature revealed only a few other references[2] to this type of

(1) C. Ainsworth, *J. Am. Chem. Soc.*, **79**, 5242 (1957).

(2) E. C. Horning, M. G. Horning, and G. N. Walker, *J. Am. Chem. Soc.*, **70**, 3935 (1948); H. Adkins and L. G. Lundsted, *J. Am. Chem. Soc.*, **71**, 2964 (1949) and A. Treibs and D. Dinelli, *Ann.*, **517**, 152 (1935).



I II

reaction, namely, the transformation of a tetrahydrobenzo heteroaromatic compound to a benzo heterocyclic material. Two successful related dehydrogenations were recorded,[1] and we now report other examples.

It was found that 1-phenyl-4,5,6,7-tetrahydroindazole was converted in low yield to 1-phenylindazole. When the reaction was applied to the tetrahydroquinazoline system III, the transformation to IV took place in good yield where R was amino and in lower yield where R was aliphatic or aromatic.

III IV

The method was not successful when applied to 2-phenyl-4,5,6,7-tetrahydroindazole, 1-*p*-nitrophenyl-4,5,6,7-tetrahydro-indazole, and 4,5,6,7-tetrahydrobenzo isoxazole.

EXPERIMENTAL

Dehydrogenation—General Procedure. A mixture of 10 g. of the tetrahydro compound, 5 g. of 5% palladium-on-carbon, and 100 ml. of dry decalin was heated under reflux for 2 days. The catalyst was removed by filtration, and the filtrate was concentrated by heating under reduced pressure on a steam bath. The residue was recrystallized from alcohol or petroleum ether.

In this manner 1-phenyl-4,5,6,7-tetrahydroindazole[3] gave 1-phenylindazole,[4] m.p. 80°, yield 20%; 2-amino-5,6,7,8-tetrahydroquinazoline[5] yielded 2-aminoquinazoline,[6] m.p. 200°, yield 45%; 2-phenyl-5,6,7,8-tetrahydroquinazoline[7] formed 2-phenylquinazoline,[8] m.p. 100°, yield 30%; 2-methyl-5,6,7,8-tetrahydroquinazoline (prepared by the general method reported in ref. 7, picrate, m.p. 135°. *Anal.* Calcd. for $C_{15}H_{15}N_5O_7$: C, 47.75; H, 4.01; N, 18.56. Found: C, 47.42; H, 4.36; N, 18.77) gave 2-methylquinazoline,[8] m.p. 40°, yield 10%.

The dehydrogenation procedure was not successful when applied to 2-phenyl-4,5,6,7-tetrahydroindazole,[3] 1-*p*-nitrophenyl-4,5,6,7-tetrahydroindazole (prepared by the general method reported in ref. 3, m.p. 112°. *Anal.* Calcd. for $C_{13}H_{13}N_3O_2$: C, 64.18; H, 5.39; N, 17.28. Found: C, 64.38; H, 5.39; N, 17.34) and 4,5,6,7-tetrahydrobenzoisoxazole.[9]

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(3) K. von Auwers, W. Buschmann, and R. Heidenreich, *Ann.*, **435**, 277 (1924).
(4) W. Borsche and K. Diacont, *Ann.*, **510**, 287 (1934).
(5) E. Benary, *Ber.*, **63**, 2601 (1930).
(6) A. K. Macbeth and H. J. Rodda, *Nature*, **156**, 207 (1945).
(7) P. C. Mitter and A. Bhattacharya, *Quart. J. Indian Chem. Soc.*, **4**, 149 (1927); [*Chem. Abstr.*, **21**, 3198 (1927)].
(8) M. T. Bogert and F. P. Nabenhauer, *J. Am. Chem. Soc.*, **46**, 1932 (1924).
(9) K. von Auwers, T. Bahr, and E. Frese, *Ann.*, **441**, 54 (1925).

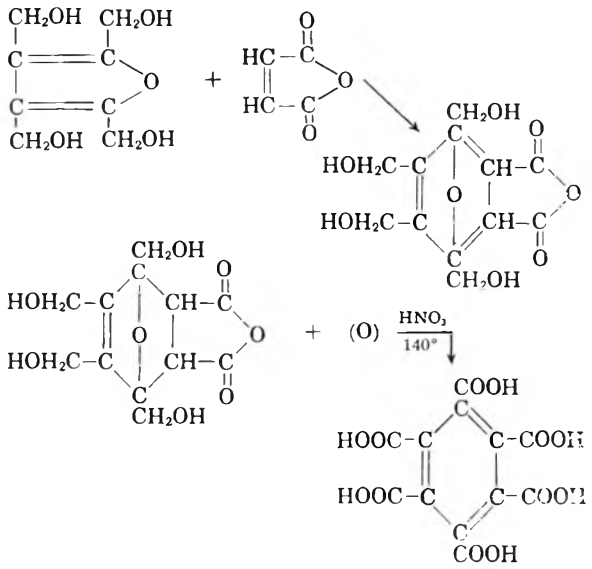
Heterocyclic Tetramethylol Derivatives in the Diene Synthesis

E. C. WINSLOW, J. E. MASTERSON, AND D. A. CAMPBELL

Received March 7, 1958

As a new approach to the laboratory preparation of mellitic acid by the diene synthesis, an attempt was made in this laboratory to add maleic anhydride as a dienophile to the diene system of tetraethyl furantetracarboxylate. The adduct of such a reaction could be hydrolyzed and oxidized to remove the oxygen bridge and produce mellitic acid. Accordingly tetraethyl furantetracarboxylate was prepared by the method of Sutter.[1] Several attempts to bring about the addition of maleic anhydride to this ester were unsuccessful. Attempts were also made to force tetraethyl furantetracarboxylate to react as a diene in the diene synthesis by using different dienophiles. Fumaronitrile, maleonitrile, and dimethylacetylenedicarboxylate were used as dienophiles but no reaction was observed. It was postulated that the dienic character of the tetraester was reduced by pi electron withdrawal from the diene structure of the ring because of the juxtaposition of four ester groupings. If such were the case, the replacement of the four ester groupings on the furan ring by four methylol groups should give some hope of enhancing the dienic character of the ring. The positive inductive effect of the four methylol groups could be relied upon to enhance the pi electron density of the diene system, thus improving its dienic character.

In order to test this theory tetraethyl furantetracarboxylate was reduced to tetramethylolfuran by the use of lithium aluminum hydride. The product, when purified, reacted with maleic anhydride in a



(1) H. Sutter, *Ann.*, **499**, 47 (1932).

typical diene synthesis. The adduct formed by this reaction was subjected to oxidation with concentrated nitric acid to produce mellitic acid.

Because thiophene and its simple derivatives do not react as dienes in a diene synthesis, an attempt was made to see if the positive inductive effect of four methylol groups on the thiophene ring could enhance the dienic character of thiophene sufficiently to enable it to react in a diene synthesis. Tetramethyl thiophenetetracarboxylate was prepared by a method employed by Michael.[2] This was reduced to tetramethylolthiophene by the use of lithium aluminum hydride. This compound failed to react with either maleic anhydride or dimethyl acetylenedicarboxylate in a diene synthesis.

EXPERIMENTAL[3]

Tetramethylolfuran. The tetraethyl ester of furan tetracarboxylic acid was reduced with lithium aluminum hydride to produce tetramethylolfuran. Eleven grams of lithium aluminum hydride were pulverized in a mortar and then suspended in 200 ml. of anhydrous ether in a 1000-ml., three-neck, round-bottom flask, fitted with a reflux condenser and a mechanical stirrer. Thirty-four grams of the tetraethyl ester of furan tetracarboxylic acid were warmed in a water bath to liquefy the ester and a few milliliters of ether were added to keep it in the liquid state. The ester was placed in a small separatory funnel and added drop-wise with caution to the hydride suspension which was cooled in an ice water bath. The rate of ester addition was adjusted to gentle reflux of the reaction mixture. After the ester had reacted, enough water was cautiously added to decompose the excess hydride, after which a large volume of water was added. The resulting aqueous layer contained a thick orange solid in suspension. The water layer was filtered to remove the aluminum and lithium salts and the filtrate, now strongly basic, was adjusted to a *p*H of approximately nine with phosphoric acid. The solution was again filtered, removing lithium and aluminum phosphates, and then evaporated on a steam bath to a volume of about 200 ml. The solution was allowed to go to virtual dryness at room temperature. The residue was treated with 95% ethyl alcohol to extract preferentially the organic portion. The ethyl alcohol was evaporated to 17 g. of a dark brown sirup, representing crude tetramethylol furan. Crystal formation occurred very slowly at a temperature of 0°. These crystals were removed mechanically and recrystallized from water using decolorizing charcoal to yield 8 g. (45%) of white crystals which melted at 123–124°.

Anal. Calcd. for $C_8H_{12}O_5$: C, 51.08%; H, 6.39%. Found: C, 50.93%; H, 6.46%.

Mellitic acid. Mellitic acid was prepared by addition of maleic anhydride to tetramethylol furan followed by oxidation of the adduct with nitric acid. About 5 g. of crude tetramethylol furan were placed in an 8-inch test tube. Four grams of finely ground maleic anhydride were added in the dry state to the test tube. About 5 ml. of dry benzene at a temperature of 23° was added and shaken gently to obtain a homogeneous mixture. During the next 5 min. the reaction temperature rose to 33°. The mixture was allowed to stand for 1 hr. after it returned to room temperature. The mixture was removed as a water suspension and added dropwise through a reflux condenser to 70 ml. of a boiling 1:1 by volume mixture of concentrated nitric and fuming nitric acid. Boiling was maintained for 1 hr. after addition and then the clear yellow solution was evaporated to dryness on a steam bath. The yellow residue was crystallized once from concentrated nitric acid and then from water using decolorizing carbon. White crystals melting at 284–286° were obtained. The yield was not determined because of subdivision of the diene adduct in other purification attempts.

Tetramethylolthiophene. A modification of the reduction technique for the production of tetramethylolfuran was required in the preparation of tetramethylolthiophene because the ester which was used as starting material is relatively insoluble in ether. Lithium aluminum hydride (2.75 g., 0.07 mole) was pulverized and suspended in 300 ml. of absolute ether in a 500-ml. round-bottom flask which was attached to a Soxhlet extraction tube containing tetramethyl thiophenetetracarboxylate (10.0 g., 0.03 mole). The reduction was run at reflux temperature for 12 hr. until no solid remained in the extraction thimble. Water was added to decompose the excess hydride. The reaction mixture was poured into ice water and the ether layer separated from the aqueous mixture. The aqueous portion was filtered with suction, the filtrate was evaporated on a steam bath to dryness, and the residue was extracted with 95% alcohol. The resulting brown solution was evaporated at room temperature to a viscous mass.

The product was isolated by use of Permutit Q cation exchange resin and Dowex 2 anion exchange resin.

Twenty ml. of an aqueous solution of the reaction mixture (5% by volume) was adjusted to a *p*H of approximately four with hydrochloric acid. This solution and the washes were allowed to run through the cation column at the rate of 2.5 ml./minute. After the solution had passed over the resin the column was washed with 50 ml. of distilled water, 20 ml. of 95% ethyl alcohol, and again with 150 ml. of distilled water. The filtrate obtained from the cation column was passed through the anion column at the rate of 2.5 ml./minute. The column was then washed, at the same rate of flow, with 20 ml. of distilled water and 100 ml. of distilled water saturated with carbon dioxide. The filtrate was colorless. The deionized filtrate was evaporated on a steam bath to a volume of 25 ml. and allowed to go to dryness at room temperature. The residue, two grams (33%), was a white substance which melted at 102–103°.

Anal. Calcd. for $C_8H_{12}O_4S$: C, 47.06; H, 5.88; S, 15.69. Found: C, 46.94; H, 5.97; S, 15.98.

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(2) Michael, *Ber.* **28**, 1633 (1895).

(3) All melting points are uncorrected.

Attempts to Copolymerize Pyrene with 1,3-Butadiene and with *p*-Chlorostyrene[1]

C. S. Marvel and B. D. Wilson

Received March 14, 1958

Some preliminary experiments on the copolymerization of pyrene with 1,3-butadiene in an emulsion system were reported by Marvel and Anderson.[2] The polymers obtained showed ultraviolet absorption maxima at 342, 301.5, and 260 mμ and on this basis it was concluded that copolymerization had occurred. In this further work on the problem with

(1) The work discussed herein was performed under contract number AF-33(616)-3772 with the Materials Laboratory of Wright Air Development Center, Wright-Patterson Air Force Base, Ohio; Lt. L. E. Coleman and Lt. Paul D. Shaw, project engineers.

(2) C. S. Marvel and W. S. Anderson, *J. Am. Chem. Soc.*, **76**, 5434 (1954).

a better grade of pyrene, the earlier experiments could not be duplicated.

Pure pyrene (m.p. 149.5–150°) was prepared by the zone melting technique[3] and was used in these emulsion copolymerization experiments with 1,3-butadiene and *p*-chlorostyrene. The purified polymers, when analyzed for carbon and hydrogen, proved to be only polybutadiene and poly-*p*-chlorostyrene, respectively. The butadiene polymers did show weak ultraviolet absorption, which appears to be due to small amounts of pyrene which were not removed in the purification. The pyrene contaminations are estimated at 0.031 ± 0.005% in these polymers.

EXPERIMENTAL

Pyrene. A 22-mm. diameter Pyrex tube *ca.* one meter in length was sealed off at one end and filled with 261.5 g. of crude pyrene (Gesellschaft für Teerverwurtung "pure" grade) by melting it to a solid plug *ca.* 81 cm. long. The tube was clamped vertically.

The heater was a 1-cm. long helix of nichrome wire attached to a five volt transformer. The transformer was attached over pulleys to a counterweight. The string connecting the two also was wrapped around a 0.5-inch diameter shaft, which was connected to a one revolution per hour synchronous motor.

The pyrene was heated at such a rate that a 3–5 cm. length was liquid at all times. It was necessary to shield the heater with aluminum foil to protect against air currents in the room. Moving at a rate of 1.6 inches down the tube per hour, the heater required between 19 and 20 hr. per pass. After fifteen passes had been made, the material was removed in fractions, starting from the top of the tube:

Fraction	Approximate Weight, G.	Color (When Melted)	M.P. (°C.) (Corr.)
1	15	Colorless	149.5–150
2	70	Very pale yellow	149 –150
3	90	Pale yellow	148.5–149.5
4	90	Dark	(Discarded)

Fraction 1 was used for all polymerization work.

p-Chlorostyrene. This compound was prepared from *p*-chloroacetophenone, using the procedure of Marvel and Schertz,[4] b.p. 40–41°/2.6 mm., n_D^{20} 1.5649.

Pyrene-butadiene copolymerizations. These copolymerizations were conducted in emulsion in 4-ounce screw-cap bottles sealed with acrylonitrile rubber gaskets. Each charge contained 28 ml. of a 2.86% solution of Office of Rubber Research soap (specification L.M. 2.3.0.5.2), 1.50 g. of pyrene, 7.5 ml. of benzene, 1.5 ml. of a 3% aqueous solution of potassium persulfate, and 13.5 g. of butadiene, in addition to a variable amount of technical lauryl mercaptan (Hooker Electrochemical Co.) as a modifier. The bottles were tumbled end-over-end at 29 revolutions per minute for a specified period in a constant temperature bath at 50 ± 1°. Table I lists the variables for these polymerizations. The polymers were isolated by addition of 5 ml. of a 4.2% solution of sulfuric acid saturated with sodium chloride after first protecting against air oxidation by the addition of 5 ml. of a saturated methanol solution of *N*-phenyl-β-naphthylamine. The polymers were purified by washing well with water, drying, and repeated precipitation (usually ten times) from benzene solution into methanol. The insoluble (cross-linked) material was separated out from the first solution before precipitation by filtration through 200-mesh wire screen. Only samples 10 and 11 showed complete solubility. The elemental analyses shown in Table II are the average of two values. The ultraviolet absorption spectra were obtained with a Cary recording spectrophotometer, Model 11, using solutions in tetrahydrofuran. The solvent was purified by passage through a column of Linde Molecular Sieves, Type 13X.

TABLE I

PYRENE-BUTADIENE POLYMERIZATION VARIABLES

Sample	Modifier, Mg.	Hours Tumbled	Conversion, %[a]	η (0.25% in Benzene)
5	45	88	87.5	[b]
6	45	36	33.1	1.21
7	45	48	46.3	1.65
8	60	37	44.3	1.13
9	60	43	52.6	1.03
10	90	30	42.6	0.350
11	120	30	40.2	0.444

[a] No correction was made for fatty acid or *N*-phenyl-β-naphthylamine inclusion. [b] Essentially only crosslinked material was obtained.

Elemental analysis on the soluble portions of these polymers after purification indicated the materials all to be only polybutadiene (see Table II).

TABLE II

COMPOSITION OF PYRENE-BUTADIENE COPOLYMERS

Sample	Elemental Analysis (Average Values) % C	% H	C/H Ratio
6	88.01	10.97	8.023
7	87.51	10.98	7.970
8	88.52	11.15	7.939
9	88.57	11.10	7.979
10	86.95	10.92	7.962
11	87.48	10.91	8.018
Butadiene	88.82	11.18	7.945
Pyrene	95.02	4.98	19.1

These polymers (5–6 g./l. in tetrahydrofuran) showed weak ultraviolet absorption maxima at 335, 318, 300, 271, and 260 mμ, values differing from those observed by Marvel and Anderson,[2] but very similar to the spectrum of pyrene in ethanol. The spectrum of pyrene in tetrahydrofuran (1.86 mg./l.) showed maxima at 334, 318, 305, 271, 260, and 237 mμ. Using the 335-mμ maximum and assuming Beer's law is applicable, it was calculated that each of these polymers contained pyrene as a contamination in the range of 0.031 ± 0.005 weight per cent. This level of pyrene at the end of the purification process is entirely reasonable.

Pyrene-p-chlorostyrene copolymerization. Only one polymer was prepared, using the same recipe as above, except substituting 15.0 ml. of *p*-chlorostyrene for the butadiene, and using 25 mg. of modifier. The polymerization was of 88 hr. duration and the uncorrected conversion was 107%. The inherent viscosity (0.25% in benzene) was 0.842.

Anal. Calcd. for $(C_8H_7Cl)_x$: C, 69.33; H, 5.09; Cl, 25.58. Found: C, 69.51; H, 5.37; Cl, 25.65. C, 68.90; H, 5.23.

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(3) E. F. G. Herington, R. Handley, and A. J. Cook, *Chem. & Ind. (London)*, 292 (1956).

(4) C. S. Marvel and G. L. Schertz, *J. Am. Chem. Soc.*, **65**, 2054 (1943).

A Reexamination of Phthalide Precursors[1]

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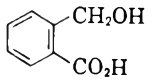
Received March 14, 1958

In the course of a study of the comparative ease of lactonization of various phthalide precursors, it was desired to contrast the chemical properties of *o*-hydroxymethylbenzoic acid (I) and *o*-methoxymethylbenzoic acid (II). While I has long been known,[2] there has been considerable confusion over the physical properties of the ethereal acid II.



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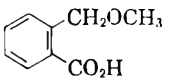

II

Both McGeoch and Stevens[3] and von Braun, Anton, and Weiszbach[4] have reported the preparation of II by treatment of phthalide with alkaline dimethyl sulfate. The recorded melting points of the products, however, were 116–118° and 93–94°, respectively. A melting point of 92–93° was reported by Clemo and Swan[5] for the acid II, which they prepared by an independent route from ethyl *o*-toluate. In another instance[6] a product from metalation and subsequent carbonation of benzyl methyl ether was assigned the structure of *o*-methoxymethylbenzoic acid on the basis of its melting point, 94–95°.

Since the only evidence offered by McGeoch and Stevens for structure II was a neutralization equivalent, it seemed necessary to repeat their work and reexamine the acid product. From combustion analysis, mixture melting point, and a comparison of infrared spectra, it was shown to be *o*-hydroxymethylbenzoic acid (I), which is also formed easily from phthalide by saponification. *o*-Methoxymethylbenzoic acid (II), m.p. 95–96°, prepared for comparison by the method of Clemo and Swan, exhibits a distinctly different infrared spectrum.

The most likely spectral band associated with alcohol or ether C–O stretching is at 1032 cm.$^{-1}$ for I and at 1114 cm.$^{-1}$ for II. While the value for I is considerably higher than that for benzyl alcohol,[7] it is consistent with a similar band at 1032–1033 cm.$^{-1}$ in both *o*-mesitoyl- and *o*-duroylbenzyl alcohol[8]; thus it appears that the bathochromic shift, ordinarily observed as a result of conjugation,[7] is partially counterbalanced by an acyl or carboxy group in the *ortho* position. Analogies for the corresponding assignment in II are to be found in the spectra of ethyl *o*-methoxymethylbenzoate(1115 cm.$^{-1}$) and *o*-duroylbenzyl methyl ether (1110 cm.$^{-1}$).[8]

Chemical evidence for the structure of McGeoch and Stevens' product is the fact that I has been found to be stable under their conditions of alkylation. While it is unusual that dimethyl sulfate is sometimes ineffective as an alkylating agent, it is now clear that their acid should be reassigned structure I.

EXPERIMENTAL[9]

o-Hydroxymethylbenzoic acid (I). Phthalide (10 g.) was heated with 19 g. of sodium hydroxide and 200 ml. of water at 60° for 90 min. After acidification at 5° with dilute hydrochloric acid, the white solid (22 g.) was collected and dried. It was recrystallized from chloroform: ethanol (20:1) in the form of fine needles; m.p. 111–112°.

The infrared spectrum (Nujol mull) contains bands attributable to a primary alcohol (3200 cm.$^{-1}$ broad, 1032 cm.$^{-1}$), to a carboxylic acid group (1670 cm.$^{-1}$ broad), and to *ortho*-disubstituted benzene (740 cm.$^{-1}$).

Attempted methylation of o-hydroxymethylbenzoic acid with dimethyl sulfate. A mixture of 20 g. of the above acid (unrecrystallized), 15 g. of sodium hydroxide, 200 ml. of water, and 25 g. of dimethyl sulfate was heated, with stirring, at 50° for 2 hr. and then stirred an additional 2 hr. By acidification and recrystallization as described above, there was obtained 6 g. (59% based on phthalide) of colorless needles, m.p. 111–112°. A mixture melting point with I showed no depression; and the infrared spectra (Nujol mulls) of the two samples are superimposable.

Attempted direct preparation of o-methoxymethylbenzoic acid (II) *from phthalide.* The procedure, similar to that previously described,[4] was carried out with 10 g. of phthalide, 100 ml. of water, 57 g. of dimethyl sulfate, and 360 ml. of 10% sodium hydroxide. After being washed with ether, the mixture was acidified and the product extracted once with ether and twice with ethyl acetate. By removal of the solvent there was obtained 5.5 g. (48%) of a white solid, m.p. 107–109°. After three recrystallizations from chloroform: ethanol (20:1) the melting point of the *o*-hydroxymethylbenzoic acid (I) was 111.5–112.5°.

Anal. Calcd. for $C_8H_8O_3$: C, 63.15; H, 5.30. Found: C, 63.17; H, 5.49.

From the filtrate there was recovered 2.2 g. (22%) of phthalide.

o-Methoxymethylbenzoic acid (II). The acid was prepared essentially by the method previously described[5] from 33 g. of ethyl *o*-toluate in an over-all yield of 21%. Intermediates were ethyl *o*-bromomethylbenzoate (not purified) and ethyl *o*-methoxymethylbenzoate (b.p. 246–248°/740 mm.; infrared bands (smear) at 1725, 1267, 1140, 1114, and 742 cm.$^{-1}$). The major modification was the use of *N*-bromosuccinimide in carbon tetrachloride rather than molecular bromine for

(1) This work was supported by a Frederick Gardner Cotrell Grant from the Research Corp. of New York and in part by a grant from the University Research Fund of the University of New Hampshire.

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(9) Infrared spectra were determined with a Perkin-Elmer Model 21 spectrophotometer. Microanalyses were performed at Galbraith Laboratories, Knoxville, Tenn.

bromination of the side chain. The acid, after two recrystallizations from benzene, was in the form of white prisms, m.p. 95.0–96.0°.

Anal. Calcd. for $C_9H_{10}O_3$: C, 65.05; H, 6.07. Found: C, 65.33; H, 6.27.

The infrared spectrum (10% chloroform) of *o*-methoxymethylbenzoic acid contains the typical, broad bands attributable to a carboxylic acid function (3525, 1693 cm.$^{-1}$), as well as a strong band at 1114 cm.$^{-1}$

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An Improved Synthesis of *N*-Phenethylnormorphine and Analogs

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N-Phenethylnormorphine (Ia) has been prepared[2] by direct phenylethylation of normorphine and exhibits six to ten times the analgesic potency[3] of morphine. We have had occasion to prepare this compound for addiction studies and wish to report an improved method of synthesis.

In this method normorphine was converted to the *N*-phenylacetyl derivative which, without purification, was reduced to the tertiary amine (Ia) with ethereal lithium aluminum hydride.[4] The isolation of Ia from the reduction mixture (in 90% yield based on normorphine) was rendered simple by reason of the low water solubility of its hydrobromide salt.[5] By a similar sequence, norcodeine and dihydrodesoxynorcodeine-D (the latter prepared by cyanogen bromide *N*-demethylation of dihydrodesoxycodeine-D) were transformed into the corresponding *N*-phenethyl derivatives Ib and IIb. There was no complication in isolation of the bases from the reduction mixture since the phenolic hydroxyl is protected in these instances. Hydrobromic acid demethylation of *N*-phenethyldihydrodesoxynorcodeine-D (IIb) gave the phenolic congener (IIa).

The analgesic potency of IIa is five times that of dihydrodesoxymorphine-D (desomorphine), while the effectiveness of Ib and *N*-phenethylnorheterocodeine is twice that of the parent compounds. The duration of action of Ia and the corresponding heterocodiene derivative is about the same as seen in the parent compounds, while Ib and IIb are analgesic twice as long as the *N*-methyl counterparts. In all cases testing was done in mice.

EXPERIMENTAL

Microanalyses and most of the rotations were performed by the Institutes service analytical laboratory, Dr. William C. Alford, director.

N-Phenethylnormorphine (Ia). Normorphine hydrochloride (5 g.),[6] 8 g. of K_2CO_3, 30 ml. of water, and 80 ml. of methanol were treated (stirring) with 6 ml. (2.8 molar equivalents) of phenylacetyl chloride during 0.4 hr. After stirring for an additional 3 hr., the mixture was diluted with water and extracted three times with ethyl acetate. The combined extracts were washed with a little dilute HCl, dried and evaporated to thorough dryness *in vacuo*. The residue and 50 ml. of dry ether were treated (stirring) with 100 ml. of 1.5*M* ethereal $LiAlH_4$ at such a rate as to cause gentle refluxing (10–15 min.). The mixture was refluxed for 15 hr. and treated gradually (vigorous stirring) with 75 ml. of 48% HBr in 130 ml. of water. All inorganic material gradually dissolved leaving a viscous, ball-like mass which, on cooling, crystallized and was easily pulverized. Filtration gave the gummy hydrobromide which, in warm methanol, was converted to the base (Ia) by addition of dilute NH_4OH; yield 5.5 g. (90%), m.p. 250–253° (dec.); thin prisms from absolute ethanol, $[\alpha]_D^{20}$ −117° (c 0.84 in 2:1 $CHCl_3$-MeOH).

Anal. Calcd. for $C_{24}H_{25}NO_3$: C, 76.76; H, 6.71. Found: C, 76.95; H, 6.54.

The tartrate,[1] prepared from the base in refluxing 95% ethanol, melted at 144–147° (froth) alone or in mixture with authentic material[7] and had $[\alpha]_D^{20}$ −68.9° (c 0.99 in 50% by vol. ethanol); reported[1] $[\alpha]_D^{20}$ −67° (solvent not specified).

N-Phenethylnorcodeine hydrobromide (Ib). The reaction of phenylacetyl chloride (1.2 g.) with norcodeine hydrochloride (2 g.) was carried out as described for normorphine above. Reduction of the resultant amide (1.8 g.) with 20 ml. of 1.5*M* ethereal $LiAlH_4$ gave, after addition of 5–10 ml. of water and drying the ethereal filtrate, 1.5 g. of Ib. Acidification of an ether solution of this base with 33% HBr-AcOH yielded an amorphous hydrobromide which crystallized from acetone in prisms; yield 1.5 g., m.p. 273–275°. It was further purified by dissolving it in 225 ml. of boiling 95% ethanol, concentrating the solution to 50–75 ml. and cooling to 0°; m.p. 290–293° (dec.), $[\alpha]_D^{20}$ −97.0° (c 0.58 in MeOH-H_2O, 3:2).

Anal. Calcd. for $C_{25}H_{28}BrNO_3$: C, 63.83; H, 6.00. Found: C, 63.52, 63.46; H, 5.81, 5.95.

N-Phenethyldihydrodesoxynorcodeine-D hydrobromide (IIb). To 2.0 g. of cyanogen bromide (Eastman) in 13 ml. of dry chloroform was added (stirring) during 1 hr. 5.0 g. of dihydrodesoxycodeine-D[8] in 20 ml. of chloroform. The solution was refluxed for 3 hr. and evaporated to dryness *in vacuo*. The residue and 100 ml. of 6% HCl were refluxed overnight. Cooling and basification gave 4.5 g. of crude secondary base which was phenylacetylated as described for normorphine except that 2 molar equivalents of chloride was used. The amide in 50 ml. of dry ether was treated with 50 ml. of 1.5*M* ethereal $LiAlH_4$ during 10–15 min. and the mixture was refluxed overnight. After addition of 20 ml. of water (stirring)

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(5) In another set of experiments in which norheterocodeine was used, almost equally good yields of the *N*-phenethylnorheterocodeine could be obtained in the same fashion.

(6) Supplied by Merck & Co., Inc., *via* Dr. H. F. Fraser, PHS Hospital, Lexington, Ky.

(7) Supplied by Merck & Co., Inc. *via* Dr. Joseph Cochin of this Institute.

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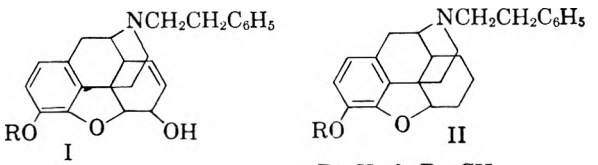
the ether was filtered and dried. The base left from evaporation of the ether was acidified (in acetone) with about 3.0 ml. of 33% HBr-AcOH to give 3.0 g. of IIb hydrobromide, m.p. 243–245°; plates from acetone, m.p. 245–246°, $[\alpha]_D^{20}$ −77.2° (c 1.0 in MeOH).

Anal. Calcd. for $C_{25}H_{30}BrNO_2$: C, 65.79; H, 6.63. Found: C, 65.93; H, 6.60.

N-Phenethyldihydrodesoxynormorphine-D hydrobromide (IIa). Refluxing 2.0 g. of IIb hydrobromide and 12 ml. of 48% HBr for 15 min., cooling and filtering gave a quantitative yield of the IIa hydrobromide, m.p. 285–290°. It crystallized from methanol in plates, m.p. 297–298° (dec.), $[\alpha]_D^{20}$ −74.2° (c 1.0 in MeOH), which analyzed for the hemihydrate; there was, however, no loss in weight of a sample dried for 5 hr. at 135° without vacuum.

Anal. Calcd. for $C_{24}H_{28}BrNo_2 + {}^1/_2\ H_2O$: C, 63.85; H, 6.48. Found: C, 63.92; H, 6.47.



a, R = H, b, R = CH_3

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2-Amino-6-substituted Benzothiazoles as Potential Anthelmintics

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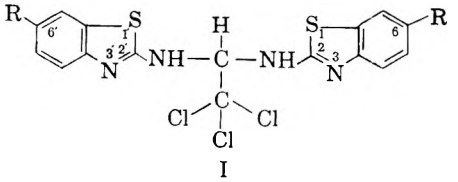
Received March 18, 1958

In an earlier communication Mackie, Stewart and Misra[2] reported the paralysant and lethal action of some benzothiazole compounds toward *Ascaris lumbricoides* and *Fasciola hepatica.* In view of the important physiological properties[3a,b,c] possessed by the 2-amino-6-substituted benzothiazoles, it appeared of interest to prepare the condensation products of these compounds with chloral, of the general structure (I), incorporating a lipoid-solubilizing group (trichloromethyl) which might assist the penetration of the compounds through the cuticle of *Ascaris lumbricoides* and thereby have a deleterious effect on the neuromuscular system of the intestinal nematodes and on other trematodes.



I

Condensation products of aromatic and heterocyclic amines with chloral had previously been reported by Sumerford and Dalton[4] and Nelson *et al.*[5] but no work in this respect seems to have been done with the 2-amino-6-substituted benzothiazoles.

The 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes of the structure I were prepared by refluxing a benzene solution of the 2-aminobenzothiazole with an excess of freshly distilled chloral for 1.5 hr. on a water bath. The precipitate was filtered, washed with a small volume of dry benzene and recrystallized from a suitable solvent. Under the conditions of the experiment, the condensation did not take place with the 6-nitro, 6-carboxy or 6-carbethoxy-2-aminobenzothiazoles. In the case of 6-chloro-2-aminobenzothiazole, a small amount of its hydrochloride was obtained during reflux along with the unreacted base, while with 2-amino-4,5,6,7-tetrahydrobenzothiazole, the hydrochloride of the base was isolated in good yield. This was presumably due to the partial photochemical decomposition of chloral and the liberation of hydrochloric acid.[6]

The details of the *in vivo* biological activity of these compounds toward the dog hookworms and the ascarid infections in poultry and dogs will be reported later.

EXPERIMENTAL

The 2-aminobenzothiazole and its 6-substituted derivatives were prepared by the known methods.[7–11] The data concerning the new 1,1-bis(2-benzothiazolylamino)-2,2,2-trichloroethanes are listed in Table I. 2-Amino-4,5,6,7-tetrahydrobenzothiazole[12] gave its hydrochloride, which recrystallized in colorless rhomboids from benzene. Yield 50%, m.p. 236–237° (dec.).

Anal. Calcd. for $C_7H_{10}N_2S{\cdot}HCl$, C, 44.09%, H, 5.70%, N, 14.60%. Found C, 43.98%, H, 5.80%, N, 14.89%.

Sprague and Kissinger[13] gave the melting point of the hydrochloride, 249–250°.

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TABLE I

1,1-BIS(2-BENZOTHIAZOLYLAMINO)-2,2,2-TRICHLOROETHANES

R	M.P.	Formula	% C		% H		% N		% Cl		Yield, %
			Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
(a) H	203° (dec.)	$C_{16}H_{11}Cl_3N_4S_2$	44.70	45.20	2.56	2.66	13.03	13.00	24.79	24.65	80
(b) CH_3	180–181° (dec.)	$C_{18}H_{15}Cl_3N_4S_2$	47.21	47.60	3.27	3.34	12.24	12.50	23.27	22.89	51
(c) OCH_3	196–197° (dec.)	$C_{18}H_{15}Cl_3N_4O_2S_2$	44.12	44.30	3.06	3.06	11.44	11.56			82
(d) OC_2H_5	168–169° (dec.)	$C_{20}H_{19}Cl_3N_4O_2S_2$	46.37	46.73	3.67	3.67	10.82	10.73			85
(e) $COO.(CH_2)_2—N(C_2H_5)_2$	102–103°	$C_{30}H_{37}Cl_3N_6O_4S_2.2HCl$	45.70	45.93	4.94	4.97	10.65	10.00			75

The analytical samples were: (*a*) recrystallized in colorless needles from benzene; (*b, c, d*) recrystallized in colorless needles from absolute ethanol-light petroleum (40–60°); (*e*) recrystallized from dry benzene, hygroscopic, decomposes if crystallized from hydroxylic solvents.

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An Unusual Reaction of Propargyl Bromide

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When an attempt to alkylate phenothiazine with propargyl bromide failed using the customary conditions of sodamide in xylene, the procedure was changed to one using sodium hydride in dimethylformamide. Under these conditions, alkylation occurred to give a 70% yield of product which turned out to be *N*-(1-propynyl)phenothiazine (I) instead of the desired isomeric *N*-(2-propynyl)phenothiazine.

I

Support for the assigned structure includes the presence of disubstituted acetylenic absorption at 4.48 microns in the infrared, and the absence of ≡C—H and >C=C=C< absorption in the 3 and 5.1 micron regions, respectively. However, a disturbing feature of the infrared spectrum is the absence of C-methyl absorption at 7.25μ. Instead, two strong bands appear at 6.87μ and 6.96μ, more characteristic of *N*-methyl absorption. In view of the chemical evidence, it is assumed, nevertheless, that this shift is caused by attachment of methyl to the polar $\diagdown$N—C≡C— system.

Chemical evidence for structure I was obtained by hydrogenation to known *N*-(*n*-propyl)phenothiazine and by hydrolytic cleavage to unsubstituted phenothiazine.

The anomalous course of this reaction can be rationalized by postulating involvement of the dipolar ion, $CH_2C{\equiv}C^+$, of the type proposed by Hennion and co-workers[1–3] to explain some of the hydrolytic and aminolytic reactions of certain

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tertiary acetylenic chlorides. Resonance stabilization of this ion by the forms, $H:\overset{\overset{H}{\cdot\cdot}}{C}:C:::C: \rightarrow H:C::C::C: \leftrightarrow H:\overset{\overset{H}{\cdot\cdot}}{C}:C:::C$, explains how nucleophilic attack by nitrogen (of the phenothiazine ring) can occur at the acetylenic carbon if one assumes either subsequent or simultaneous attack of a proton or sodium ion at the methylenic carbon atom.

EXPERIMENTAL

N-(1-Propynyl)phenothiazine (I). To a stirred suspension of 7.2 g. (0.3 mole) of sodium hydride in 600 ml. of dry dimethylformamide, protected by an atmosphere of dry nitrogen, was added, in portions, 60 g. (0.3 mole) of phenothiazine. After warming at 50° for an additional 2 hr., the reaction mixture was heated to 70° and a solution of 35.7 g. (0.3 mole) of propargyl bromide in 50 ml. of dimethylformamide was added dropwise. After heating for an additional 2 hr. at 70°, the mixture was stirred overnight at room temperature.

Most of the solvent was removed by distillation at reduced pressure, and the residue was poured into cold water. Insoluble product was taken up in ether, washed with water, and dried over anhydrous magnesium sulfate. Filtration and removal of the ether by distillation gave an oil (52 g.) which solidified on trituration with hexane. Although purification could be accomplished by recrystallization from hexane, it was conveniently found that passing a benzene solution of the product over a column of alumina gave 48 g. of colorless crystals, m.p. 95–96°.

Anal. Calcd. for $C_{15}H_{11}NS$: C, 75.91; H, 4.67; N, 5.90. Found: C, 75.99; H, 4.70; N, 5.85.

Infrared spectrum (μ): 3.3 (w), 3.37 (w), 3.46 (w), 3.55 (vw), 4.48(m), 5.2 (vw), 5.31 (vw), 5.53 (vw), 5.64 (vw), 6.30 (m), 6.39 (m), 6.77 (m), 6.87 (s), 6.96 (s), 7.18 (vw), 7.28 (vw), 7.58 (s), 7.75 (s), 7.83 (m), 7.97 (s), 8.92 (m), 9.31 (w), 9.68 (m), 10.76 (w), 11.01 (w), 11.21 (w).

Substituting *n*-propyl bromide for the propargyl bromide in the above procedure gave a 65% yield of *N-(n-propyl)-phenothiazine*, b.p. 155–165° (0.8 mm.), m.p. 48–49° (from ethanol) (lit.[4] reports m.p. 49–50°).

Hydrogenation of I. A solution of 10.5 g. of N-(1-propynyl)-phenothiazine (I) in 250 ml. of 95% ethanol was treated with 0.53 g. of platinum oxide catalyst and hydrogenated at 30 lb. pressure and room temperature. After 17 hr., hydrogen absorption was 65% complete. The reaction was then warmed to 60° and reaction was complete in 4 hr. After removal of the catalyst by filtration, the filtrate was concentrated to dryness under reduced pressure. Several portions of benzene were distilled from the residue which was then taken up in 25 ml. of warm absolute ethanol. Heating this solution with charcoal followed by filtering, cooling, and seeding gave, after one more recrystallization from absolute ethanol, 4.2 g. of product, m.p. 47–48°, which did not depress the melting point of *N-(n-propyl)phenothiazine*. Furthermore, the infrared spectrum of the hydrogenation product was qualitatively identical with that of the known reference compound.

Hydrolysis of I. A mixture of 500 mg. of *N-(1-propynyl)-phenothiazine* (I) and 5 ml. of 10% hydrochloric acid was refluxed overnight. However, within 5 min. after the beginning of reflux, the oil turned to a solid. The mixture was concentrated to dryness; the black, crystalline residue was taken up in benzene and dried over anhydrous magnesium sulfate. After removal of the drying agent by filtration, the benzene solution was passed through an alumina column (20 × 1 cm.). Concentration of the eluate gave 295 mg. of yellow crystals, m.p. 174–176°. Recrystallization from benzene gave 195 mg., m.p. 177–179°.

Anal. Calcd. for $C_{12}H_9NS$: C, 72.32; H, 4.55; N, 7.03. Found: C, 72.46; H, 4.64; N, 6.95.

The product did not depress the melting point of an authentic sample of phenothiazine.

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Decarboxylation of 2-Vinylcyclopropane-1,1-dicarboxylic Acid to the Lactone of 4-Hydroxy-5-hexenoic Acid

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The synthesis of one of a series of sulfur compounds being prepared in these laboratories involved 3-cyclopentenecarboxylic acid as an intermediate.[1] This acid should readily be obtainable by hydrolysis and decarboxylation of the product of reaction of 1,4-dibromo-2-butene (I) and diethyl disodiomalonate which Skinner *et al.*[2] have described as diethyl 3-cyclopentene-1,1-dicarboxylate. However, the decarboxylation product obtained by this series of reactions did not possess the properties of the required acid. Its properties and infrared spectrum were in fact those to be expected of a vinyl substituted γ-lactone. Decarboxylation at 200° gave only poor yields of this compound, the majority of the product being a higher boiling material, but heating to 170° under a reduced pressure of nitrogen resulted in considerable improvement in the yields of lactone, presumably due to a decrease in the tendency for polymerization.

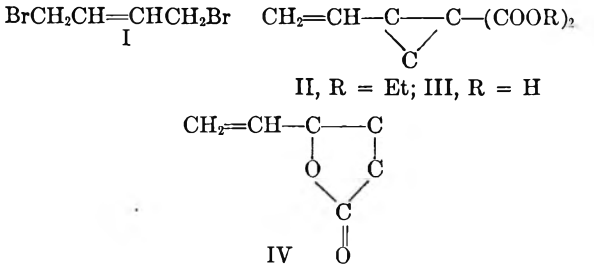
In view of the unexpected course of the preparation, a survey of the literature was made and it was then found that Kierstead *et al.*[3] had reported that condensation of 1,4-dibromo-2-butene and the monosodio-derivative of diethyl malonate gave diethyl 2-vinylcyclopropane-1,1-dicarboxylate (II). Investigation showed that our condensation product had an infrared spectrum not inconsistent with

(1) S. F. Birch, R. A. Dean, N. J. Hunter, and E. V. Whitehead, *J. Org. Chem.*, 22, 1590 (1957).

(2) G. S. Skinner, G. Limperos, and R. H. Pettebone, *J. Am. Chem. Soc.*, 72, 1648 (1950).

(3) R. W. Kierstead, R. P. Linstead, and B. C. L. Weedon, *J. Chem. Soc.*, 3610 (1952).

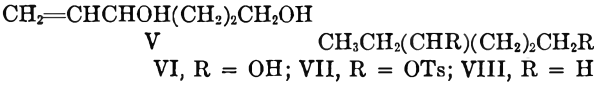
its being a vinylcyclopropane diester and that the melting point of the diacid obtained on hydrolysis was in agreement with that quoted[3] for III. It was therefore concluded that a process similar to that described by Kierstead *et al.*[3] had occurred during our condensation and that the product was not the desired cyclopentene compound, but the diester II. Presumably the 3-cyclopentene-1,1-dicarboxylate described by Skinner *et al.*[2] is also in fact this cyclopropane compound.



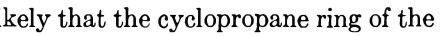
I

II, R = Et; III, R = H

IV



V



VI, R = OH; VII, R = OTs; VIII, R = H

It seemed likely that the cyclopropane ring of the diacid III had undergone fission during the decarboxylation reaction and that the compound[4] subsequently formed was the lactone of either 4-hydroxy-5-hexenoic acid (IV) or 3-hydroxymethyl-4-pentenoic acid. Examination of the reduction products V–VIII not only confirmed that the cyclopropane ring had been ruptured, but showed that the isolated decarboxylation product was IV, since reduction of the alternative lactone would have given 3-methylpentane instead of *n*-hexane as the final product. It may therefore be concluded that fission of the 3-membered ring occurs in the same position on decarboxylation as on hydrogenation.[3]

EXPERIMENTAL

Microanalyses by Dr. Ing. A. Schoeller, Kronach/Oberfranken, Bambergerstrasse 20, Germany. All melting points are corrected. Infrared spectra are for the liquid state and were obtained using a Grubb Parsons double beam recording spectrometer.

Condensation of 1,4-dibromo-2-butene and diethyl disodiomalonate. 1,4-Dibromo-2-butene (393 g.) was treated (in two batches) with diethyl disodiomalonate as described by Skinner *et al.*[2] Distillation of the product gave 255 g. (65%) of diester (II) b.p. 102–110°/4.5 mm., n_D^{20} 1.4522. Maxima assignable to vinyl (991 and 917 cm.$^{-1}$) and cyclopropane (1031 and 866 cm.$^{-1}$)[5] groups were observed in the infrared absorption spectrum. Skinner *et al.*[2] report b.p. 80–81°/0.5 mm. and n_D^{25} 1.4500 for their material; Kierstead *et al.*[3] give b.p. 69–72°/0.5 mm., n_D^{19} 1.4528 for diethyl 2-vinylcyclopropane-1,1-dicarboxylate.

The lactone of 4-hydroxy-5-hexenoic acid (IV). The above diester (254 g.) was refluxed with aqueous ethanolic potash (KOH, 308 g.; EtOH, 1680 ml.; H_2O, 420 ml.) for 6 hr.; the ethanol was removed by distillation and the residual liquor acidified with hydrochloric acid (600 ml.) and extracted with ether to give the crude diacid (III) (178 g., 93%). A specimen of this, crystallized twice from benzene, melted at 109.5–110.5°. Kierstead *et al.*[3] report m.p. 107–108° for 2-vinylcyclopropane-1,1-dicarboxylic acid.

Anal. Calcd. for $C_7H_8O_4$: C, 53.8; H, 5.2. Found: C, 54.1; H, 5.3.

A small quantity (11.5 g.) of the crude diacid was heated in an oil bath at 200°. Only 3.0 g. (35%) of distillate (b.p. 62–68°/1.7 mm.) was obtained there being a considerable resinous residue. The remainder of the crude diacid was heated in four batches under a pressure of 100 mm. of nitrogen to only 170°. In each instance, when the rate of evolution of carbon dioxide moderated, the nitrogen pressure was reduced to 24 mm. and the material which distilled at about 114° was collected. On redistillation the combined products (103 g.) gave 77.5 g. (62%) of IV, b.p. 108–112°/20 mm. A mid-cut from this distillation, taken as analytical specimen, had n_D^{20} 1.4601 and m.p. −15.5°. Reported[6] for the lactone of 4-hydroxy-5-hexenoic acid b.p. 75°/2 mm. and n_D^{25} 1.4603.

Anal. Calcd. for $C_6H_8O_2$: C, 64.3; H, 7.2. Found: C, 64.0; H, 7.3.

The compound IV could not be esterified by the usual techniques and did not react readily with sodium bicarbonate solution. It rapidly decolorized potassium permanganate solution and bromine water. The infrared spectrum contained bands assignable to a γ-lactone (1779 cm.$^{-1}$)[7] and a vinyl group (990 and 908 cm.$^{-1}$).

1-Hexene-3,6-diol (V). The lactone IV (5 g.) in ether (500 ml.) was reduced with lithium aluminum hydride (3.3 g.) in ether (180 ml.) and the product, b.p. 98–100°/1.8 mm., n_D^{20} 1.4633 was isolated in the usual way;[8] yield 1.8 g. (35%, extraction not completed). Its infrared spectrum showed absorption peaks at 3378 cm.$^{-1}$ (hydroxyl; k = 0.976) and at 990 and 920 cm.$^{-1}$ (vinyl); comparative group analysis using *n*-propyl alcohol (hydroxyl; k = 1.04) as a reference material, indicated the presence of 1.8 hydroxyl groups per molecule.

Anal. Calcd. for $C_6H_{12}O_2$: C, 62.0; H, 10.4. Found: C, 61.8; H, 10.5.

1,4-Hexanediol (VI). On hydrogenation at room temperature and atmospheric pressure, the diol V (1.32 g.) in ethanol (15 ml.) absorbed 1 molar equivalent of hydrogen and the product (VI), which was isolated in almost theoretical yield, had b.p. 122–124°/10 mm., n_D^{20} 1.4503 and absorption maxima at 3378 cm.$^{-1}$ (hydroxyl) and 1379 cm.$^{-1}$ (methyl).

Anal. Calcd. for $C_6H_{14}O_2$: C, 61.0; H, 11.9. Found: C, 60.7; H, 11.8.

Di-p-toluenesulfonate of 1,4-hexanediol (VII). The diol VI (0.7 g.) was treated with *p*-toluenesulfonyl chloride and the product VII isolated in the usual way.[9] The crude product (1.1 g., 43%) was crystallized three times from ethanol to give material (0.4 g.) melting constantly at 33–35°.

Anal. Calcd. for $C_{20}H_{26}S_2O_6$: C, 56.3; H, 6.1. Found: C, 56.3; H, 6.4.

Reduction of di-p-toluenesulfonate of 1,4-hexanediol. An ethereal solution of VII (0.3 g. in 0.75 ml.) was reduced with lithium aluminum hydride (0.12 g.) in ether (0.75 ml.), and water (2 ml.) followed by dilute sulfuric acid (H_2SO_4, 0.3 ml.; H_2O, 1.33 ml.) was added dropwise to the reaction mixture. The ethereal layer was removed by means of a hypodermic syringe, and gas liquid chromatography (*n*-hexatriacontane stationary phase at 78°) indicated that the hydrocarbon component was *n*-hexane (retention volume relative

(4) The sharpness of the melting point indicated that the decarboxylation product was essentially one compound.

(5) J. M. Derfer, E. E. Pickett, and C. E. Boord, *J. Am. Chem. Soc.*, 71, 2482 (1949).

(6) R. R. Russell and C. A. VanderWerf, *J. Am. Chem. Soc.*, 69, 11 (1947).

(7) L. J. Bellamy, *Infrared Spectra of Complex Molecules*, John Wiley and Sons, N. Y., 1954, p. 159.

(8) S. F. Birch and R. A. Dean, *J. Chem. Soc.*, 2477 (1953).

(9) C. S. Marvel and V. C. Sekera, *Org. Syntheses*, Coll. Vol. 3, 366 (1955).

to *n*-pentane: observed 2.46; determined for *n*-hexane, 2.42 and for 3-methylpentane, 2.12). Several further portions were chromatographed and the hydrocarbon fractions were collected in a liquid nitrogen trap as they emerged from the column. The cracking pattern of this material confirmed that it was *n*-hexane.

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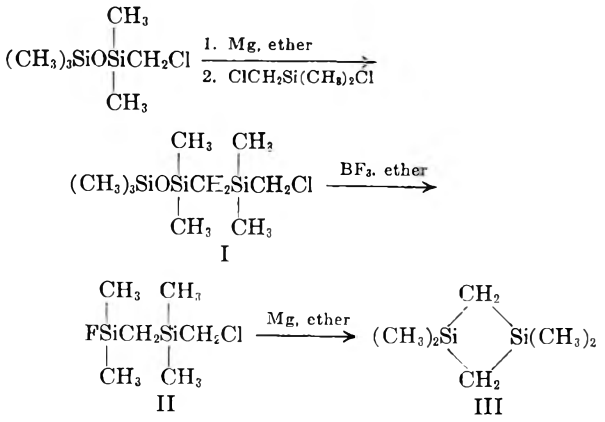
1,1,3,3-Tetramethyl-1,3-disilacyclobutane

W. H. KNOTH, JR., AND R. V. LINDSEY, JR.

Received March 26, 1958

Monosilacyclobutanes have been reported[1,2] only recently and no cyclobutanes containing more than one silicon atom in the ring have been described. Accordingly, it was of interest to prepare such a compound and to compare its properties with those of the monosilacyclobutanes, particularly in view of the reported ease of ring opening of the latter.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane was synthesized in an over-all yield of 25% by a three-step procedure starting with chloromethylpentamethyldisiloxane. The first step, which proceeded



in 73% yield, is analogous to the reported[3] coupling of trimethylsilylmethylmagnesium chloride with chloromethyldimethylchlorosilane. Cleavage of the siloxane linkage with boron trifluoride ethyl etherate gave a 57% yield of II. Cyclization was accomplished in 60% yield by refluxing a solution of II in ether with magnesium turnings.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane is a mobile liquid boiling at 117–119°. It was characterized by elemental analysis, molecular weight determination, and examination of its proton magnetic resonance spectrum, which is in agreement with the assigned structure. The high reactivity of III was demonstrated by its rapid reduction of silver nitrate in alcohol at room temperature, and by its reaction at room temperature with a solution of bromine in carbon tetrachloride. Similar reactions occur with 1,1-dimethyl-1-silacyclobutane and have been shown to involve ring-opening.[4]

EXPERIMENTAL

1-Chloro-2,2,4,4,6,6-hexamethyl-5-oxa-2,4,6-trisilaheptane (I). A Grignard reagent was prepared from chloromethylpentamethyldisiloxane[5] (103 g., 0.52 mole) and magnesium (12.8 g., 0.52 mole) in 250 ml. of ether. To this was added chloromethyldimethylchlorosilane (75 g., 0.52 mole). After the addition, the mixture was heated to reflux and stirred overnight. Saturated ammonium chloride solution was added slowly with stirring until the salts separated to leave a clear, supernatant liquid. The mixture was filtered; the salts were washed with ether; and the ether washings were combined with the filtrate. Distillation gave 103.2 g. (0.38 mole, 73%) of I, b.p. 88–89° (8 mm.).

Anal. Calcd. for $C_9H_{25}ClOSi_3$: C, 40.15; H, 9.31. Found: C, 40.66; H, 9.37.

1-Chloro-4-fluoro-2,2,4-trimethyl-2,4-disilapentane (II). The trisilaheptane (I) (125 g., 0.47 mole) and boron trifluoride ethyl etherate (125 g., 1.06 mole) were mixed and immediately distilled until a head temperature of 125° was reached. The distillation residue was extracted with ether and the extracts were combined with the distillate. This solution was distilled to give 52.5 g. (0.26 mole, 57%) of II, b.p. 173–178°.

Anal. Calcd. for $C_6H_{16}ClFSi_2$: C, 36.36; H, 8.07; Cl, 17.93; Neut. Equiv., 199. Found: C, 36.73; H, 8.29; Cl, 17.85; Neut. Equiv., 195.

1,1,3,3-Tetramethyl-1,3-disilacyclobutane (III). Magnesium (7.2 g., 0.30 mole) and 50 ml. of sodium-dried ether were placed in a 500-ml. flask under an atmosphere of nitrogen. A small amount of II was added and the reaction was started by the addition of three drops of methylmagnesium iodide solution. The reaction mixture was heated to reflux temperature. An additional 225 ml. of ether was added and the remainder of a 58 g. (0.29 mole) sample of II was dissolved in 80 ml. of ether and added over a 95-min. period with rapid stirring. After completion of the addition, stirring and refluxing were continued overnight. Decane (200 ml.) was added and the mixture was distilled rapidly until the head temperature was 170°. Redistillation gave 25 g. (0.17 mole, 60%) of III, b.p. 117–119°, n_D^{27} 1.4380.

Anal. Calcd. for $C_6H_{16}Si_2$: C, 50.00; H, 11.11; Si, 39.00; mol. wt., 144. Found: C, 49.98; H, 11.27; Si, 38.29; mol. wt., 133.

The proton magnetic resonance of this material supports the assigned structure. The product decolorized a carbon

(1) L. H. Sommer and G. A. Baum, *J. Am. Chem. Soc.*, 76, 5002 (1954).

(2) R. West, *J. Am. Chem. Soc.*, 77, 2339 (1955).

(3) L. H. Sommer, G. M. Goldberg, J. Gold, and F. C. Whitmore, *J. Am. Chem. Soc.*, 69, 980 (1947); L. H. Sommer, F. A. Mitch, and G. M. Goldberg, *J. Am. Chem. Soc.*, 71, 2746 (1949).

(4) L. H. Sommer, private communication.

(5) R. H. Krieble and J. R. Elliott, *J. Am. Chem. Soc.*, 67, 1810 (1945).

tetrachloride solution of bromine slowly, and reduced alcoholic silver nitrate rapidly as evidenced by the formation of a silver mirror.

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1,5-Anhydro-β-D-ribofuranose from Phenyl β-D-Ribofuranoside

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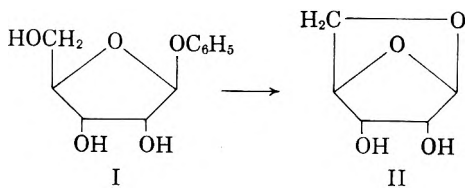
Received April 7, 1958

While the action of strong alkali on aryl glycopyranosides represents a familiar procedure for the synthesis of 1,5-anhydroglycopyranoses[2] and other analogous substances containing this ring system, similar treatment of aryl glycofuranosides has not, to our knowledge, been reported to yield 1,5-anhydroglycofuranoses. In a recent paper,[3] indeed, we stated that an attempt to synthesize 1,5-anhydro-β-D-ribofuranose (II, 1,4-anhydro-α-D-ribopyranose) from phenyl β-D-ribofuranoside (I) had



failed to yield a crystalline product. Subsequent work has now shown, however, that I is converted to II (albeit in low yield) through the action of sodium isopropoxide in 2-propanol.

EXPERIMENTAL[4]

Phenyl β-D-ribofuranoside (158 mg.), prepared as described earlier,[3] was dissolved in 10 ml. of 2-propanol and the solution treated with 6 ml. of 2-propanol in which 32.5 mg. of sodium had been dissolved. The reaction mixture was boiled under reflux for 90 hr., cooled, diluted with a few drops of water and neutralized with carbon dioxide. Solvent was removed *in vacuo* and the residue extracted with acetone. Toluene was added to the extract and the solution concentrated *in vacuo* to a sirup which was freed of the remaining phenol by repeated extraction with benzene. Attempts to crystallize the residue failed and it was therefore benzoylated in the usual fashion to yield a sirup which was partially purified by precipitation from benzene with pentane and then from ethanol with water. On standing for several months at −8° in aqueous ethanol a small deposit of crystalline material was obtained. Recrystallized from methanol this product (*ca.* 15 mg., 6%) showed a double melting point: 132–133° and 146–147°. We reported earlier[3] that 1,5-anhydro-2,3-di-*O*-benzoyl-β-D-ribofuranose melts at 132–133°. Reexamination of the authentic material now reveals that it too shows the double melting point just quoted; a mixture of samples of the compound from the two sources shows the same two melting points. Upon appropriate seeding, either the form with the double melting point or one with the higher melting point only could be obtained from solution.

(1) Chemical Foundation Fellow 1956–58. Present address: Quartermaster Research and Development Center, Natick, Mass.

(2) *Cf.* L. C. Stewart, E. Zissis, and N. K. Richtmyer, *Chem. Ber.*, 89, 535 (1956).

(3) E. Vis and H. G. Fletcher, Jr., *J. Am. Chem. Soc.*, 79, 1182 (1957).

(4) Melting points are corrected.

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Reciprocal Resolution of DL-Tryptophan and DL-α-Phenylethylamine

LACY R. OVERBY

Received April 11, 1958

Our interests in producing large quantities of L-tryptophan from the DL-form by economically feasible methods prompted a study of known methods and a search for new methods of resolution. The availability of *N*-acetyl-DL-tryptophan as an intermediate in commercial synthesis and the ease of racemization of the undesired D-form[1] indicated that this would be the desirable starting compound. Published methods[1–6] for resolving *N*-acetyl-DL-tryptophan suffer from one or more of the usual disadvantages of resolutions; such as, low yields, time consuming and tedious crystallizations, expensive resolving agents, or handling of large volumes. The method of du Vigneaud and Sealock[1] appeared to offer possibilities for attainment of maximum antipodal purity and for large scale use. The main disadvantage was the scarcity of the desired active form of α-phenylethylamine. DL-α-Phenylethylamine is readily available. If one were able to resolve this with the active forms of acetyltryptophan it would be possible to build up large supplies of optically active acid and base by repetition of the reciprocal resolution.

When one mole of *N*-acetyl-DL-tryptophan was combined with 0.5 mole of (−)- α-phenylethylamine and 0.5 mole of potassium hydroxide in ethanol the sparingly soluble diastereoisomeric salt [LA(−)B]

(1) V. du Vigneaud and R. R. Sealock, *J. Biol. Chem.*, 96, 511 (1932).

(2) C. P. Berg, *J. Biol. Chem.*, 100, 79 (1933).

(3) A. C. Shabica, *J. Am. Chem. Soc.*, 71, 3251 (1949).

(4) Usines Chemiques des Laboratoires Francais, Brit. Patent 745,097, Feb. 22, 1956; U. S. Patent 2,797,226, June 25, 1957.

(5) C. Neuberg and I. Mandl, U.S. Patent 2,511,867 (Interchemical Corp.) June 20, 1950.

(6) D. G. Doherty and E. A. Popenoe, Jr., *J. Biol. Chem.*, 189, 447 (1951).

crystallized in 73% yield and of purity greater than 99% without further recrystallization. The soluble *N*-acetyl-D-tryptophan was racemized with acetic anhydride and again resolved. The acetyl derivative was hydrolyzed to L-tryptophan or reserved for resolution of α-phenylethylamine as needed. The diastereoisomeric (−)-amine salt crystallized from ethanol in 99% purity and 83% yield when the DL-form was mixed with 0.5 equivalent of *N*-acetyl-L-tryptophan and 0.5 equivalent of hydrochloric acid.

Our starting materials were 60.5 g. of (−)-α-phenylethylamine[7] and a plentiful supply of *N*-acetyl-DL-tryptophan and DL-α-phenylethylamine. By alternately resolving acid and base with the available quantities of each several times it was easily shown that 12.5 kg. of acetyl-L-tryptophan and 8.6 kg. of (−)-α-phenylethylamine could be realized after 17 reciprocal resolutions. Thus it is rather easy to work up to quite large scale resolutions with no initial large supply of resolving agent.[8]

These particular experiments were directed toward production of L-tryptophan. Through suitable modifications D-tryptophan and derivatives could be made equally readily, if desired.

EXPERIMENTAL

I. Resolution of acetyl-DL-tryptophan. A. Formation and separation of the diastereoisomers. Acetyl-DL-tryptophan[9] (246 g., 1.0 mole) was dissolved in 500 cc. of hot *N* KOH in 95% 3A ethanol. To the warm solution there was added 60.5 g. (0.5 mole) of (−)-alpha-phenylethylamine.[7] The solution was allowed to cool overnight at room temperature. The yield of crystalline salt [LA(−)B] was 134 g. (73%), $[\alpha]_D^{25}$ + 17.8° (C, 2 in water).[10]

B. Decomposition of the less soluble salt [LA(−)B]. The salt (134 g.) was suspended in about 250 cc. of water and about 50 cc. of benzene. The mixture was made alkaline to phenolphthalein with sodium hydroxide. The aqueous phase was separated and washed three times with 50-cc. portions of benzene. The combined benzene extracts were washed once with water which was combined with the aqueous phase.

C. Preparation of L-tryptophan. The aqueous solution of the sodium salt obtained as in Ib was adjusted with water and 3 equivalents of hydrochloric acid to be 2*N* with respect to acidity. After heating under reflux for 4 hr. the solution was decolorized with carbon and evaporated to dryness under reduced pressure. The residue was extracted with 95% 3A ethanol to separate the tryptophan hydrochloride from the sodium chloride. The alcoholic solution was neutralized with ammonium hydroxide to precipitate the L-tryptophan. This was removed by filtration, washed on the funnel with water followed by alcohol, and dried. The yield was 95%; $[\alpha]_D^{25}$ −31.2° (C, 1 in water).

D. Recovery of acetyl-L-tryptophan. The aqueous solution from Ib was decolorized with activated carbon as necessary and acidified to *p*H 3 with hydrochloric acid. About 96% of the acetyl-L-tryptophan precipitated. This was removed by filtration, washed with water and dried. $[\alpha]_D^{25}$ + 29.1° (C, 1 in H_2O + 1 equivalent NaOH).

E. Decomposition of the more soluble salt and racemization of acetyl-D-tryptophan. The alcoholic solution from Ia was evaporated to dryness and the residue dissolved in about 250 cc. of water and the salt decomposed with NaOH as in Ib. The aqueous solution was decolorized with activated carbon as necessary and 150 cc. of acetic anhydride added. The solution was seeded with *N*-aectyl-DL-tryptophan and kept at 40° overnight, whereupon acetyl-DL-tryptophan crystallized in about 92% yield. After chilling the mixture, the crystalline product was removed by filtration, washed with water, and dried. Specific rotation was zero, m.p. 205–206° (uncorr.). The yield of product was increased to 97% by combining similar filtrates and obtaining additional crops after evaporation of solvent.

II. Resolution of DL-α-phenylethylamine. *N*-Acetyl-L-tryptophan (123 g., 0.5 mole) was dissolved in 250 cc. of warm 95% 3A ethanol. To this solution there was added 0.5 mole of concentrated hydrochloric acid followed by 121 g. (1.0 mole) of DL-α-phenylethylamine (prepared from acetophenone using formamide and formic acid as described by Moore[11]). The solution was seeded and allowed to crystallize at room temperature overnight. The yield of LA(−)B salt was 151 g. (83%), $[\alpha]_D^{25}$ +17.7° (C, 2 in water).[7] The salt was decomposed as in Ia. The (−)-amine was recovered by drying the benzene extracts over sodium hydroxide pellets and distilling the benzene and amine through a short column; b.p. 185–187°, $[\alpha]_D^{25}$ −38.8° to −39.3° (without solvent) depending upon whether the salt was recrystallized before decomposition.

The more soluble material from the original alcohol filtrate was decomposed as in Ie to recover *N*-acetyl-L-tryptophan and the amine rich in the dextro-rotatory form.

ABBOTT LABORATORIES
NORTH CHICAGO, ILL.

(7) We are indebted to Professor A. W. Ingersoll of Vanderbilt University for this initial supply of active amine.

(8) Although it was not investigated in this study it is also possible to obtain an initial large supply of (−)-α-phenylethylamine through the method of DeWitt and Ingersoll using easily available *N*-acetyldibromo-L-tyrosine, *J. Am. Chem. Soc.*, 73, 5782 (1951).

(9) Purchased from the Winthrop Chemical Co.

(10) Recrystallization from water increased the specific rotation of the salt to +18.8°, which was unchanged by further crystallization. The over-all yield of salt was reduced to 64%. Unless a product of exceptional antipodal purity was desired recrystallization was normally omitted.

(11) M. L. Moore, *Org. Reactions*, 5, 321 (1949).

Preparation of 3-(1,1,2-Trifluoro-2-chloroethoxy)propanol and Some of Its Derivatives

J. D. PARK, J. G. ABRAMO,[1] AND J. R. LACHER

Received February 28, 1958

The preparation of ethers of the general formula RO—CF_2—CX_2H where R is an alkyl radical and X is halogen or hydrogen has received a good deal of attention in recent years.[2–4] However, very little has been done in the preparation of ethers of the type, $OH(CH_2)_n$-O-CF_2CX_2H. Coffman *et al.*[5]

(1) Abstracted from a thesis submitted by J. G. Abramo in partial fulfillment of the requirements for the Ph.D. degree, University of Colorado, June 1956.

(2) J. D. Park, D. K. Vail, and J. R. Lacher, *J. Am. Chem. Soc.*, 70, 1550 (1948).

(3) J. D. Park, C. M. Snow, and J. R. Lacher, *J. Am. Chem. Soc.*, 73, 861 (1951).

(4) Hanford and Rigby, U. S. Patent 2,409,274 [*Chem. Abstr.*, 41, 982 (1942)].

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have prepared $HOCH_2CH_2$-O-CF_2CF_2H by the base-catalyzed addition of ethylene glycol to tetrafluoroethylene. The diether, CF_2H-CF_2-O-CH_2CH_2-O-CF_2CF_2H was also isolated. Lawson[6] reported the preparation of $HOCH_2CH_2$-O-CF_2CFClH and Chaney[7] prepared a series of derivatives of 1,1,1,-4,4,4-hexafluorobut-2-yne with ethylene glycol and trimethylene glycol through a base-catalyzed reaction. This paper presents our findings concerning the addition of trimethylene glycol to trifluorochloroethylene and the preparation of some of its derivatives obtained thereform.

The nucleophilic addition of trimethylene glycol to chlorotrifluoroethylene has been found to proceed in the presence of potassium hydroxide under autogenous pressure. The dispersion of the olefin through the solution of potassium hydroxide and trimethylene glycol under atmospheric conditions was unsuccessful.

Two products were obtained from the pressure reaction in the form of an azeotrope—a mixture of $CFClHCF_2$-$O(CH_2)_3OH$ (I) and $CFClHCF_2$-O-$(CH_2)_3$-OCF_2CFClH (II) which was not separable by ordinary fractional distillation.

Refractive index data later indicated that the mixture had the following composition: 59 mole per cent of I and 41 mole per cent of II.

Separation was achieved by conversion of I to the benzoate followed by purification of the benzoate and subsequent saponification of the benzoate (C_6H_5-$CO_2(CH_2)_3$-O-CF_2CFClH) to the ether-alcohol. The diether II was isolated by oxidation of the azeotrope (in which the ether-alcohol is converted to the ether-acid) and distillation of the solution remaining after extraction of the acid. Another product was obtained from the oxidation mixture, namely $CFClH$-$CF_2OCH_2CH_2$-$COO(CH_2)_3OCF_2C$-$FClH$, which would be expected from the oxidation of an ether-alcohol in an acid medium.

EXPERIMENTAL

The base catalyzed addition of trimethylene glycol to trifluorochloroethylene. A gas-tight 500-ml. Parr hydrogenation bomb was charged with 153 g. (2.0 moles) of trimethylene glycol in which 56 g. (1 mole) of potassium hydroxide had been dissolved. The bomb was then cooled to −78° and charged with 230 g. (2 moles) of trifluorochloroethylene, after which it was rocked for 36 hr. at room temperature. After removal of the unreacted olefin, the bomb was opened and the contents washed with water until neutral to litmus paper, and dried over anhydrous sodium sulfate. Fractionation on a "Helipak"-packed column yielded 175 g. of product distilling at 76–77° at 7-mm. Hg pressure. This product was found to be a mixture of the monoadduct, $CFClH$-CF_2-$O(CH_2)_3$-OH (I) and the di-adduct, $CFClH$-CF_2-$O(CH_2)_3O$-CF_2CFClH (II), which was not separable by simple distillation. The refractive index of this mixture at 20° was found to be 1.3852.

3-(1,1,2-Trifluoro-2-chloroethoxy)-1-propyl benzoate. About 170 g. of the mixture of the mono- and di-ether, I and II, was treated with 120 g. of benzoyl chloride and 100 ml. of pyridine under reflux conditions for about 1 hr. The reaction mixture was washed three times with water and then three times with a 10% solution of sodium hydroxide. Distillation at 3-mm. pressure yielded two fractions with the desired benzoate distilling over at 128–129°; n_D^{20} 1.4710; d_4^{20} 1.313. Molecular refraction: Calcd. for $C_{12}H_{12}O_3F_3Cl$ 62.6. Found, 63.16.

Anal. calcd. for $C_{12}H_{12}O_3F_3Cl$: C, 48.6; H, 4.27, Cl, 12.01. Found: C, 48.79; H, 4.18; Cl, 11.96.

Saponification of $C_6H_5CO_2(CH_2)_3O$-CF_2CFClH. About 53 g. (0.2 mole) of $C_6H_5CO_2(CH_2)_3O$-CF_2CFClH and 22 g. (0.4 mole) of potassium hydroxide pellets were dissolved in 200 milliliters of 75% aqueous ethanol and refluxed for about 0.5 hr. The reaction mixture was then poured into 200 ml. of water and extracted with three 100-ml. portions of ether. The ether fractions were combined and dried over anhydrous sodium sulfate. Distillation in a helix-packed column yielded 15 g. (39%) of $CFClH$-CF_2-$O(CH_2)_3OH$ boiling at 57–58° at 3 mm. of Hg pressure. n_D^{20} 1.3916; d_4^{20} 1.379. Molecular refraction: Calcd. for $C_5H_8O_2F_3Cl$, 33.11. Found, 33.11.

Anal. Calcd. for $C_5H_8O_2F_3Cl$: C, 31.01; H, 4.15; Cl, 18.50. Found: C, 30.8; H, 4.00; Cl, 18.80.

3-(1,1,2-Trifluoro-2-chloroethoxy)propionic acid. About 39 g. of the mixture of the mono- and diether, I and II, was charged to a three-neck flask with 70 g. of magnesium sulfate and 240 ml. of water. To this mixture was added 30 g. of potassium permanganate in 300 ml. of water over a 6-hr. period with constant stirring. The stirring was continued an additional 8 hr. to ensure completeness of reaction after which time, the reaction mixture was then treated with sodium bisulfite until the color of the permanganate was discharged and the manganese dioxide allowed to settle. After filtering and washing the manganese dioxide precipitate, the aqueous solution was treated with 50% sulfuric acid until acid to litmus paper. The aqueous solution was then extracted with 4-250-ml. portions of ether and the ether extracts combined and dried over anhydrous sodium sulfate. Distillation yielded 15 g. of $CHClFCF_2$-$O(CH_2)_2COOH$ boiling at 114–115° at 7 mm. of Hg pressure. n_D^{20} 1.3953; d_4^{20} 1.477. Molecular refraction: Calcd. for $C_5H_6ClF_3O_3$, 33.33. Found, 33.55. Neutralization equivalent: Calcd., 206.6; Found, 208.

The acid-catalyzed oxidation of the mixture of I and II was carried out through the courtesy of Mr. Wayne Severson, Minnesota Mining & Manufacturing Co., St. Paul, Minn.

Isolation of $CFClHCF_2$-$O(CH_2)_2COO(CH_2)_3O$-CF_2CF-ClH and $CFClH$-CF_2—$O(CH_2)_3OCF_2CFClH$. After the acid had been extracted from the oxidation mixture, distillation of the organic residue gave two main fractions, the first boiling at 73–73.5° (3 mm.) and the second boiling at 136–137° (3 mm.) The physical properties and analyses of the two fractions are given.

(1) $CFClH$-CF_2-$O(CH_2)_3OCF_2CFClH$. B.p. 73–73.5°/3 mm.; n_D^{20} 1.3758; d_4^{20} 1.476. MR_D: Calcd. 47.55; Found, 48.01.

Anal. Calcd. for $C_7H_8F_6Cl_2O_2$: Cl, 23. Found: Cl, 23.1.

(2) $CFClH$-CF_2-$O(CH_2)_3COO(CH_2)_3O$—CF_2CFClH. B.p. 136–137°/3 mm.; n_D^{20} 1.400; d_4^{20} 1.460. MR_D: Calcd. 63.1; Found, 63.1.

Anal. Calcd. for $C_{10}H_{12}F_7Cl_2O_4$: C, 31.42; F, 29.85. Found: C, 31.70; F, 29.90.

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Synthesis and Properties of Some Fluorinated Ketones[1]

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Ketones containing one perfluoroalkyl group have been prepared[2] by the reactions of perfluorinated acids with Grignard reagents. In this study, a variety of ketones of the type $Cl(CF_2—CFCl)_n$-CF_2-CO-R where n = 1, 2, and 3 and R = methyl and ethyl groups were prepared by the action of RMgBr on $Cl(CF_2CFCl)_nCF_2COOH$. Ketones of the type $R_F—CO—R$, where $R_F = -CF_3$ and $-C_2F_5$ and R = methyl, ethyl, and allyl groups, were also prepared by the action of RMgX on R_FCOOH or R_FCOONa. The results are given in Table I.

The formation of secondary alcohols also accompanied the formation of ketones in many cases. These will be reported in a later paper.

EXPERIMENTAL

The method of Dishart and Levine[2b] was used in which three moles of the Grignard reagent was treated with one mole of the fluorinated acid (or salt) at temperatures around 0–15° for about 5–8 hr. The reaction products were hydrolyzed in hydrochloric acid solution, extracted with ether, dried, and then subjected to fractional distillation.

I. Reaction of $CH_2=CHCH_2MgBr$ and CF_3COONa yielded a mixture of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$ and $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$ (37.1% yield) collected over a temperature range of 55–80°/623 mm. This was dried over P_2O_5, decanted, and then distilled over fresh P_2O_5 whereupon the following fractions were obtained:

Both fractions (A) and (C) gave a positive Baeyer unsaturation test and a positive haloform reaction with concd. sodium hydroxide. Both are strong lachrymators, but found to have no effect on the respiration or blood pressure of a dog. On standing, fractions (A) and (B) reverted almost entirely to fraction (C) as observed by index of refraction, density, and infrared measurements. A 2,4-dinitrophenylhydrazone of fraction (A) with m.p. 140–141° was also prepared (yellow crystals).

Anal. Calcd. for $C_{11}H_9F_3N_4O_4$ (2,4 D.N.P. of Fraction (A)): C, 41.52; H, 2.85; F, 17.91. Found: C, 41.30; H, 2.91; F, 18.03.

Infrared absorption spectra of fraction (A) showed one strong carbonyl peak at 5.64 μ and a very weak one at 5.78 μ; that of fraction (B) showed two strong peaks in the carbonyl region, one at 5.64 μ and another at 5.78 μ; that of fraction (C) showed one strong peak at 5.78 μ with a very weak one at 5.64 μ. Furthermore, fraction (A) and (B) on standing reverted in all properties (index of refraction, density, infrared spectral data) to those of fraction (C). Hence, we propose fraction (A) is comprised almost entirely of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$, fraction (B) of a mixture of $CF_3—\overset{O}{\overset{\|}{C}}—CH_2$-$CH=CH_2$ and $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$, and fraction (C) almost entirely of $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$. The shift in the carbonyl peak from 5.64 μ to 5.78 μ in going from the β, γ to the α, β isomer is understandable in view of the fact that this results in a shift of the double bond to the conjugate position, hence to greater polarizability of the electrons. Similarly, the higher index of refraction of the α, β isomer over the β, γ isomer is thus accounted for. All three fractions showed strong carbon-carbon double bond absorption at about 6.13 μ. Fraction (A) and (B) also showed absorption in the —OH region (2.85 μ). This might find explanation in the fact that some of the β, γ ketone may exist in the enol form, $CF_3—\overset{OH}{\overset{|}{C}}=CH—CH=CH_2$. This —OH absorption disappears for the α,β ketone where enolization is not possible. This, in effect, substantiates the infrared interpretations of Rausch *et al.*,[2d] who did not obtain and characterize $CF_3COCH_2CH=CH_2$.

Fraction	Component	B.P./ 623 Mm.	n_D^{20}	d_4^{20}	MR_D Calcd.	MR_D Found	Amount, G.
(A)	$CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$	60–61°	1.3544	1.1769	24.83	25.53	5.0
(B)	$CF_3—\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$ + $CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$	61–79°	1.3480	—	—	—	11.0
(C)	$CF_3—\overset{O}{\overset{\|}{C}}—CH=CHCH_3$	79–80°	1.3585	1.1891	24.83	25.52	4.0

A higher boiling material still remained from the original distillation, and at a pressure of 33-mm. Hg 8.0 g. of a product boiling at 93.0° was obtained. Analysis showed this fraction to be comprised of a higher polymer of the original ketone, $(C_5H_5F_3O)_n$.

This product was yellow in color and possessed a fairly

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(2) Presented in partial fulfillment of the requirements for the Ph.D. degree at the University of Colorado, 1956. E. I. du Pont de Nemours & Co., Inc., Pre-Doctoral Fellow, 1955–56.

TABLE I

PHYSICAL PROPERTIES OF KETONES PREPARED

Compound	B.P., °C./Mm. Hg	d_4^{20}	n_D^{20}	% C		% F		% Cl		% H		Yield, %
				Calcd.	Found	Calcd.	Found	Calcd.	Found	Calcd.	Found	
$CF_2Cl—CFClCF_2\overset{O}{\overset{\|}{C}}—CH_3$	80–81/150	1.4967	1.3685	24.5	25.4	38.78	38.45					23
$CF_2ClCFClCF_2\overset{O}{\overset{\|}{C}}—C_2H_5$	106–108/150	1.4607	1.3881	27.82	27.58	36.67	36.37	27.38	26.6	1.94	2.09	8
$Cl(CF_2CFCl)_2CF_2\overset{O}{\overset{\|}{C}}—CH_3$	67.5–68.5/9	1.6530	1.3882	23.26	23.67	42.05	42.26					24
$CF_2=CFCF_2CFClCF_2\overset{O}{\overset{\|}{C}}—CH_3$	30/10	1.5991	1.3648	28.93	28.94	52.31	52.05					
$Cl(CF_2CFCl)_3CF_2\overset{O}{\overset{\|}{C}}—CH_3$	106–107/3	1.7600	1.3938	22.62	23.60	43.73	43.33					22
$CF_3\overset{O}{\overset{\|}{C}}—C_2H_4Cl$	86–87/623	1.3932	1.3619	29.93	29.8	35.50	35.12			2.78	2.91	24
$CF_3\overset{O}{\overset{\|}{C}}—CH_2CH=CH_2$	60–61/623	1.1769	1.3544	43.48	43.16					3.65	4.0	
$CF_3\overset{O}{\overset{\|}{C}}—CH=CH—CH_3$	79–80/623	1.1891	1.3585	43.48	43.30	41.28	41.45			3.65	3.43	37.1
$(C_5F_6F_3O)_n$	93/33	1.3195	1.3886	43.48	43.38	41.28	41.45			3.65	3.84	
$CF_2=CF—\overset{O}{\overset{\|}{C}}—C_6H_5$	100–102/5											
$CF_2=CF\diagdown\atop C_6H_5\diagup C=NNHC_6H_3(NO_2)_2\text{-}2,4$	M.p. 232–234			49.19	49.72	15.56	15.80					

sweet odor. It gave a positive Baeyer unsaturation test, decolorized aqueous bromine solution, and gave a positive haloform reaction with concd. sodium hydroxide.

II. Reaction of CH_2=$CHCH_2MgBr$ and CF_3COOH yielded results similar to that obtained in I. Reaction of C_6H_5MgBr and CF_2=$CFCN$ yielded about 1 g. of material boiling at 100–102° at 5-mm. Hg pressure. This product gave a positive test for unsaturation with 5% permanganate solution and decolorized bromine solution. It formed a 2,4 dinitrophenylhydrazone instantaneously which after two recrystallizations from ethanol-water mixture showed an m.p. 232–234°C.

Anal.: Calculated for $C_{15}H_9F_3N_4O_4$: C, 49.19; F, 15.56. Found: C, 49.72; F, 15.80.

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A Qualitative Test for Mono-, Di-, and Tri-substituted Silanes

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The reducing properties of Group IVB metal hydrides have been known and recognized for a long time, but only recently has any use been made of this information.

Buchner[1] reported that silane reduced aqueous silver nitrate to metallic silver. Later, Stock and Somieski[2] reported the reduction of iron(III), copper(II), and mercury(II) salts to iron(II), copper (I), and copper(0), and mercury(I) and mercury(0), respectively, the degree of reduction being dependent on the original metal ion to silane ratio in the aqueous solution.

Ruff and Albert,[3] while investigating the properties of silicochloroform, found it also could function as a reducing agent. They report the reduction of chromium(VI) oxide to chromium(III) oxide, sulfur trioxide to sulfur dioxide, sulfur dioxide to sulfur, arsenic(III) to arsenic(0), and antimony(III) oxide to antimony(0), the latter two in the presence of catalytic amounts of sodium hydroxide. Quite similar results are recorded by Besson and Fournier.[4]

Concomitant with these reductions is the evolution of hydrogen gas. Kipping[5] devised a method of quantitative analysis for Si-H compounds which involves measurement of the volume of hydrogen produced. His technique entails the dissolution of the silane in an organic base, such as pyridine or piperidine, and measurement of the hydrogen evolved as the mixture is warmed.

The evolution of hydrogen has also served as a means of monitoring the kinetics of the reaction of Si-H compounds with base. Price[6] examined the rate of hydrolysis of trialkylsilanes in aqueous alcoholic potassium hydroxide, and found his data agreed satisfactorily with a pseudo first order kinetic expression during the first three fourths of the reaction. In a similar study,[7] the effect of substituents on the rate of hydrolysis of triarylsilanes in wet piperidine was found to agree well with the values of Hammett's for carbon compounds. The rates of hydrolysis of triphenylsilane-*d* and triphenylsilane-*t* have also been investigated.[8]

The most recent studies of the reducing power of the Group IVB metal hydrides are those reporting the reduction of fourteen different transition metal salts and seven organic acids with triethylgermane;[9] and the reduction of certain halides and oxides of seven regular group elements and thirteen transitional elements to a lower oxidation state or, in certain cases, to the free element with triethyltin hydride.[10] Another recent publication[11] reports the reaction of Si-H compounds with alcohols in the presence of metallic copper. In light of the low yields reported, there exists the possibility that the reaction is indeed catalyzed by oxides of copper and not the metal itself.

In this laboratory, we have had the occasion to synthesize a large number of partially substituted silanes and, while investigating their chemical and physical properties, have developed a sensitive test for the degree of substitution at the silicon atom. Essentially, the test entails treatment of a mixture of one milliliter of a basic solvent, such as pyridine, and two drops of an approximately 5% aqueous solution of copper(II) chloride with one drop of the silane. Monosubstituted silanes discharge the blue color of the test solution within a few seconds and very rapidly thereafter develop a yellow coloration. Disubstituted silanes are somewhat slower in discharging the blue color, giving a final green coloration. The trisubstituted silanes do not discharge the blue color over a period of three minutes. In all cases where color changes were observed, the aryl compound underwent these changes at a more rapid rate than the similarly substituted alkyl compounds. It is possible to differentiate between monoalkyl and monoarylsilanes using nickel(II) salts. Mercury(II) chloride, potassium permanganate, and silver nitrate, more powerful

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TABLE I

RATE OF REACTION IN PYRIDINE

Oxidant	Color of Complex	Phenylsilane Color	Phenylsilane Time, Sec.	Diphenylsilane Color	Diphenylsilane Time, Sec.	Triphenylsilane Color	Triphenylsilane Time, Min.	*n*-Hexylsilane Color	*n*-Hexylsilane Time, Sec.	Di-*n*-butylsilane Color	Di-*n*-butylsilane Time, Sec.	Triethylsilane Color	Triethylsilane Time, Min.
$CuCl_2 \cdot 2H_2O$	Dk. blue	Green	4	Green	50	Dk. blue	3	Green	6	Green	80	Dk. blue	3
		Yellow	11					Yellow	70				
$Cu(NO_3)_2 \cdot 3H_2O$	Blue	Lt. green	13	Lt. blue	60	Blue	3	Lt. blue	15	Lt. blue	3 (min.)	Blue	3
		Yellow	30					Lt. green	60				
$CuAc_2 \cdot H_2O$	Blue	Brown	2	Green	4								
				Yellow	6	Blue	3	Green	2	Green	50		
				Brown	10			Brown	4	Yellow	60	Blue	3
										Brown	65		
$NiCl_2 \cdot 6H_2O$	Lt. blue	Brown	12	Blue	3 (min.)	Blue	3	Blue	3 (min.)	Blue	3 (min.)	Blue	3
$Ni(NO_3)_2 \cdot 6H_2O$	Lt. blue	Brown	6	Blue	3 (min.)	Blue	3	Brown	40	Blue	3 (min.)	Blue	3
$HgCl_2$	Colorless	Grey	1	Grey	1	Grey	2	Grey	1	Grey	1	Grey	5 (sec.)
$AgNO_3$	Colorless	Brown	1	Brown	2	Brown	5 (sec.)	Brown	1	Brown	2	Brown	6 (sec.)
$KMnO_4$	Deep purple	Brown	2	Brown	2	Brown	5 (sec.)	Brown	2	Brown	2	Brown	5 (sec.)

TABLE II

RATE OF REACTION WITH $CuCl_2$ IN OTHER SOLVENTS

Solvent	Color of Complex	Phenylsilane Color	Phenylsilane Time, Sec.	Diphenylsilane Color	Diphenylsilane Time, Min.	Triphenylsilane Color	Triphenylsilane Time, Min.	*n*-Hexylsilane Color	*n*-Hexylsilane Time, Sec.	Di-*n*-butylsilane Color	Di-*n*-butylsilane Time, Min.	Triethylsilane Color	Triethylsilane Time, Min.
Tetrahydrofuran	Lt. green	Color-less	4	Color-less	3	Lt. green	3	Color-less	9	Lt. green	3	Lt. green	3
		Yellow	30					Yellow	34				
		Turbid	60					Turbid	70				
Ethylene glycol di-methyl ether	Green	Color-less	5	Green	5	Green	3	Color-less	6	Green	3	Green	3
		Yellow	22					Yellow	22				
		Turbid	30					Turbid	32				3
1,4-Dioxane	Lt. blue	Color-less	9	Lt. blue	3	Lt. blue	3	Color-less	13	Lt. blue	3	Lt. blue	
		Yellow	15					Yellow	21				
		Turbid	25					Turbid	30				
Piperidine	Dk. green	Brown	1	Brown	2 (sec.)	Brown	2.5	Brown	1	Brown	10 (sec.)	Dk. green	3

oxidants, give positive tests with trisubstituted silanes. Further differentiations are also possible if the time for color change is observed as well as the final color attained.

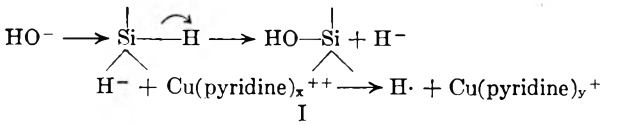
As could be predicted from the previously mentioned kinetic studies,[6,7] there is a slight substituent effect on the rate of reaction. In the tables, the times recorded are for the specific compounds mentioned. However, time variations due to the substituent effect are small when compared with the variations due to degree of substitution at the silicon atom itself and this factor does not, therefore, reduce the applicability of the test. This was demonstrated more precisely when, after testing a total of seventy-two silanes containing either one, two or three hydrogen atoms attached to silicon, all were found to conform to the specifications of this test.[12]

In Table I are listed the various oxidants tested as possible indicators. In addition to those shown, copper(II) sulfate, vanadium(IV) sulfate, nickel(II) sulfate, iron(III) chloride, sodium chromate, chromium(VI) oxide, chromium(III) chloride, and cobalt(II) chloride were also investigated. The first three, all sulfates, and the iron(III) chloride gave precipitates in pyridine which obscured the color changes. The other four compounds underwent little or no color change over the three-minute period.

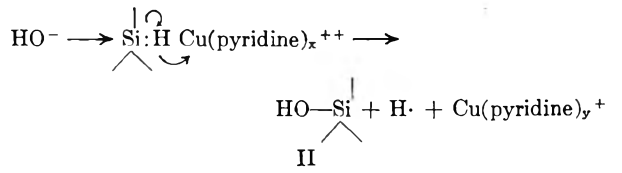
Other polar solvents were investigated as well, and the results, using copper(II) chloride as the oxidant, are assembled in Table II. All are capable of complexing the copper(II) ion somewhat, as evidenced by the various colors observed. It appears that a solvent of basicity and polarity close to that of pyridine is necessary. Piperidine, with its high basicity, is too reactive to be selective; while tetrahydrofuran, ethylene glycol dimethyl ether, and dioxane are not basic and/or polar enough. For intensity of original color and sharpness of color changes, none was as good as pyridine.

Completely nonaqueous systems were investigated also. Suspensions of chloranil, quinone, and azobenzene in pyridine underwent no reaction when treated with the various silanes. However, upon the addition of two drops of water, the evolution of hydrogen was observed and the colors of the solutions were slowly discharged.

These results indicate that hydroxide ion attack on the silane is the first step of the reaction, and the resultant reduction of the oxidant is either by hydride ion in a two step reaction (I) or by a concurrent one electron transfer (II). No attempt



I



II

was made to ascertain which mode of reduction is actually followed.

(12) Some correlations between infrared spectra and the number of hydrogens attached to a silicon atom in organosilanes will be reported later

EXPERIMENTAL

Oxidant solutions. Approximately 5% by weight solutions of all salts were prepared by dissolving 0.5 g. of the hydrated salt in 9.5 ml. of distilled water.

Solvents. All the solvents used were distilled and dried over sodium metal before use, except the pyridine and piperidine. The pyridine employed was a fresh bottle of Baker and Adamson purified grade and the piperidine was Eastman White Label.

Silanes. The times recorded in Tables I and II are for the silanes indicated. In the experiments involving pyridine, the triphenylsilane was added as a 50% by weight solution in pyridine. For the reactions involving other sovents a 50% solution of triphenylsilane in benzene was used for convenience.

Procedure. To one milliliter of the organic solvent was added 2 drops of the oxidant solution and the mixture was shaken until the color became uniform. One drop of the silane or silane solution was then introduced with shaking after which the reaction mixture was allowed to stand while the color changes were observed. The results are summarized in Tables I and II.

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o-(2,4-Dihydroxybenzhydryl)benzyl Alcohol

Max H. Hubacher

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Since *o*-(4,4′-dihydroxybenzhydryl)benzyl alcohol, which Baeyer called phenolphthalol, was found to be a good laxative,[1] it was decided to prepare and test its isomer, the *o*-(2,4-dihydroxybenzhydryl)-benzyl alcohol (VI).

The starting material for its synthesis, the 3-phenyl-3-(2,4-dihydroxyphenyl)phthalide (I) has already been described, but neither of the two methods of preparation is satisfactory. Pech-

(1) M. H. Hubacher, S. Doernberg, and A. Horner, *J. Am. Pharm. Assoc.*, 42, 23 (1953); O. E. Schultz and L. Geller, *Arch. Pharm.*, 287/59, 584 (1954); 288/60, 239 and 244 (1955).

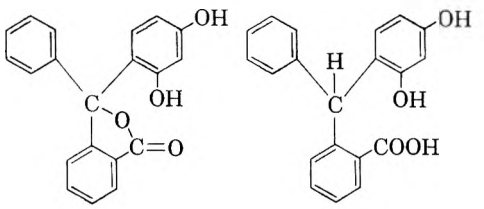
mann's[2] I has a very low melting point and shows color reactions which the pure I does not exhibit. Baeyer's[3] procedure lacks important details, thus giving low yields and erratic results. The procedure described here gives consistent and good yields of pure I.

A second compound (II) melting at 290° is always formed along with I in the reaction between resorcinol and *o*-benzoylbenzoic acid. So far, our investigation has shown that II is not the anhydride of I, as Pechmann[2] thought. This interesting compound is now being investigated further.

The reduction of I leads to the *o*-(2,4-dihydroxybenzhydryl)benzoic acid (III), briefly mentioned by Pechmann.[2] Derivatives of this acid were prepared. One which forms by the elimination of one mole of water on heating of III, is most likely the ϵ-lactone of the α-(2,4-dihydroxyphenyl)-α-(phenyl)-*o*-toluic acid (V), reconverting to III on hydrolysis. This lactone also forms a monoacetyl derivative (Va) and a monomethyl ether (Vb). The latter forms an oily acid on hydrolysis which, on heating to 200°, again yields the monomethylether Vb. Dr. B. Katlavsky of Monsanto Chemical Co., who studied the infrared spectrum of V, reported that V could possibly be a lactone but that the infrared evidence could not in itself confirm or deny this possibility.

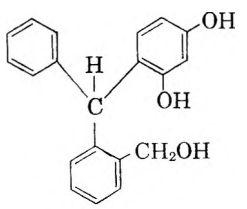
The formation of ϵ-lactones from similarly constituted compounds, such as from 2-carboxy-2′-hydroxydiphenylmethane, has been described by Baker, *et al.*[4]

The *o*-(2,4-dihydroxybenzhydryl)benzyl alcohol (VI) obtained by $LiAlH_4$ reduction of III, was found to possess distinct laxative properties. The pharmacological tests will be described elsewhere.



I

III



VI

EXPERIMENTAL[5]

3-Phenyl-3-(2,4-dihydroxyphenyl)phthalide (I). Attempts to obtain I free from the by-product II, by changing the type of condensing agent, temperature, etc., were unsuccessful. In the absence of a condensing agent, no reaction takes place. Purification of the crude I by precipitation from its alkaline solution by carbon dioxide gives lower yields because it is not as stable in alkaline solution as are most other phthaleins.

A mixture of 22.0 g. (0.2 mole) of resorcinol, 45.2 g. (0.2 mole) of *o*-benzoylbenzoic acid, and 5.0 g. anhydrous zinc chloride was stirred for 2.5 hr. at 120°. Ethanol (150 ml.) was added to the hot, sticky, orange colored reaction mass and refluxed until it had dissolved. The solution, containing some white suspended II, was poured into 1200 ml. slightly acidic water. The precipitated pliable mass was treated with boiling water, hardening slowly on cooling: 53.5–62.3 g. (m.p. 130–148°) of a gray powder was obtained.

This crude I was refluxed with 1600 ml. absolute ether. The insoluble part was II (9.8–15.4 g; m.p. 276–285°). Crystals formed when the ethereal filtrate was evaporated to a volume of 200 ml. These were found to contain one mole solvate ether which was easily lost at 100°.

Anal. Calcd. for $C_{20}H_{14}O_4 \cdot (C_2H_5)_2O$: Ether, 18.9%. Found, loss in weight: 19.2 ± 0.5%.

Additional crystals were obtained by partial evaporation of the filtrate. The total yield of I, dried at 120°, was 30.5–39.0 g., m.p. 195–199° (48–61%). Sometimes, when no crystals are forming, the solvent is evaporated, leaving a gummy residue. On refluxing with chloroform, this residue first dissolves and then crystals containing one mole of chloroform form. These are the solvate crystals described by Baeyer.[3]

Pure 3-phenyl-3-(2,4-dihydroxyphenyl)phthalide (I) melts at 199.0–200.0° (Pechmann[2] 175–176° and Baeyer[3] 198–199°).

Anal. Calcd. for $C_{20}H_{14}O_4$: C, 75.46; H, 4.47; mol. wt. 318. Found: C, 75.34; H, 4.36; mol. wt. 315.

I is very soluble in acetone and ethanol; soluble in absolute ether, but soon crystals containing solvate ether will form in such a solution.

A 0.001-molar solution of I in 0.1*N* sodium hydroxide is of strong reddish orange color[6] which fades slowly when such a solution is exposed to the air, becoming yellow after one week.

A solution of 10 g. of I in 100 ml. *N* sodium hydroxide, heated for 30 min. to 100°, yielded 4.3 g. *o*-benzoylbenzoic acid and 2.2 g. resorcinol. When 5.0 g. of I was stirred in 50 g. molten KOH at 220° for 5 min., benzoic acid and some 2,4-dihydroxybenzophenone were obtained.

The deep orange solution of 0.1 g. of I in 5 ml. concd. sulfuric acid, when heated for 10 min. to 100°, yielded 0.042 g. anthraquinone.

When I was subjected to the oxime splitting of Friedlaender,[7] a small quantity of a compound was obtained, which crystallized from ethanol in needles melting at 163.0–163.5°.

Anal. Calcd. for $C_{14}H_9O_2N$: C, 74.88; H, 4.04; N, 6.27; mol. wt. 223. Found: C, 75.24; H, 3.88; N, 6.85; mol. wt. 228.

A mixture of this compound with 4-phenyl-1*H*-2,3-benzoxazin-1-one (m.p. 162.5–163.0°) prepared by the method of Thorp[8] melted at 162.7–163.1°.

Diacetylderivative of I. Purified by crystallizations from ethanol, it melted at 141.0–141.9° (v. Pechmann 137°).

Anal. Calcd. for $C_{24}H_{18}O_6$: C, 71.63; H, 4.50; —$COCH_3$, 21.40. Found: C, 71.60; H, 4.55; —$COCH_3$, 21.27.

(2) H. v. Pechmann, *Ber.*, **14**, 1860 (1881).

(3) A. Baeyer, *Ann.*, **372**, 91 (1910).

(4) W. Baker, D. Clark, W. D. Ollis, and T. S. Zeally, *J. Chem. Soc.*, 1452 (1952).

(5) All melting points are corrected. Molecular weights were determined by the Signer method as described by E. P. Clark, *Ind. Eng. Chem., Anal. Ed.*, **13**, 820 (1941).

(6) Color designation according to the Munsell Color System *Method of Designating Colors*, National Bureau of Standard Research Paper PR 1239, September 1939.

(7) M. H. Hubacher, *J. Am. Chem. Soc.*, **68**, 718 (1946).

(8) F. H. Thorp, *Ber.*, **26**, 1262, 1795 (1893).

Dimethylether of I. Prepared by heating 3.18 g. of I, 3.8 ml. of methyl iodide, 2.8 g. K_2CO_3, and 50 ml. acetone for 6 hr. at 60°, and recrystallized from ethanol (1 g. in 16 ml.), it formed six-sided plates melting at 157.0–158.5°.

Anal. Calcd. for $C_{22}H_{18}O_4$: C, 76.27; H, 5.20; mol. wt. 346. Found: C, 76.12; H, 5.71; mol. wt. 346.

o-(2,4-dihydroxybenzhydryl)benzoic acid (III). The reduction of I to the acid was best accomplished as follows: 5 g. Raney alloy was added over a period of 20 min. to a stirred solution of 15.9 g. of I in 60 ml. 2.5*N* sodium hydroxide. The temperature rose to 55–60°. As soon as the orange color disappeared, the mixture was filtered to remove the nickel. The light orange filtrate, on acidification, yielded a gummy precipitate which was then treated with hot water. On cooling overnight, it became hard (14.7–15.5 g., m.p. 175–181°).

This acid was purified by dissolving it in absolute ether (1 g. in 30 ml.), and evaporating the filtrate to a small volume (5 ml.). The crystals thus obtained contained one mole of solvate ether, which was lost at 120°. (Calcd. for $C_{20}H_{16}O_4 \cdot (C_2H_5)_2O$: Ether, 18.8%. Found, loss in weight: 19.0 ± 0.3%). The yield, in the form of two crops, was 7.6–10.4 g., m.p. 184–186° (47–65%).

This same acid may be prepared by the zinc dust reduction of I in 80% acetic acid, in which case some V is obtained as the part which is insoluble in 2*N* sodium carbonate.

The pure III melts at 186.9–187.4° (Pechmann,[2] 184°).

Anal. Calcd. for $C_{20}H_{16}O_4$: C, 75.00; H, 5.00; mol. wt. 320. Found: C, 75.03; H, 5.75; neut. equiv. 318.

This acid is very soluble in acetone, ethanol, ethyl acetate, and acetic acid; insoluble in chloroform or benzene. It may also be recrystallized from 20% acetic acid (1 g. in 6 ml.).

I dissolves in concd. sulfuric acid with yellow color, becoming dark green. Its solution in dilute alkalies, initially colorless, slowly turns orange.

Methyl ester of III. Diazomethane, made from 5.2 g. nitrosomethylurea, was distilled into a solution of 8.0 g. of III in 200 ml. pure ether. On evaporation of most of the solvent, white crystals (m.p. 186–194°) formed. Sometimes, an oil is left which, on treatment with benzene, becomes crystalline.

The ester was purified by dissolving it in a large volume of ether and then distilling off most of the ether; or from a mixture of 1 vol. of methanol and 5 vol. of benzene. The pure ester forms white crystals melting at 203.6–204.4°.

Anal. Calcd. for $C_{21}H_{18}O_4$: C, 75.45; H, 5.39. Found: C, 75.24; H, 5.70.

Triacetylderivative of 10-(o,p-dihydroxyphenyl)-9-anthrol (IV). By heating 3.2 g. of III in 5 ml. acetic anhydride and 0.03 ml. of concd. sulfuric acid for 30 min. to 120°, and recrystallizing the crude product from 230 ml. ethanol, 3.1–3.5 g. of IV, m.p. 181–185° were obtained. After crystallizations from ethyl acetate (1 g. in 12 ml.), the pure compound melted at 183.4–184.0°. Solutions of IV in organic solvents exhibit blue fluorescence.

Anal. Calcd. for $C_{26}H_{20}O_6$: C, 72.89; H, 4.67. Found: C, 72.78; H, 4.39.

A mixture of this compound with the acetyl derivatives (m.p. 179–181°) of the condensation product obtained from resorcinol and 9-bromo-10-anthrone by the procedure of Liebermann and Mamlock[9] melted at 182–183°.

The ε-lactone of α-(2,4-dihydroxyphenyl)-α-(phenyl)-o-toluic acid (V). When III (1.60 g.) was heated to 220°, it gave off one mole water (85 mg.) and a trace of carbon dioxide (2 mg.). The resulting compound, obtained in practically quantitative yield, was crystallized from ethanol (1 g. in 12 ml.). It may also be purified by sublimation at 200° and 10 microns pressure. The pure V melts at 242.0–242.5° and dissolves in *N* sodium hydroxide to a colorless solution.

Anal. Calcd. for $C_{20}H_{14}O_3$: C, 79.46; H, 4.76; mol. wt. 302. Found: C, 79.41; H, 4.71; mol. wt. 315.

When a suspension of 0.75 g. of V in 10 ml. of *N* sodium carbonate is refluxed under nitrogen for 5 hr. and the resulting solution is acidified, then III will precipitate out.

Acetyl derivative of V (Va). On heating 1.0 g. of V, 1.5 ml. acetic anhydride, and 0.02 ml. concd. sulfuric acid for 30 min. to 120° and recrystallizing the product from 12 ml. ethyl acetate, 0.78 g. (m.p. 174–175°) was obtained.

This same acetyl derivative is obtained as the main product by direct acetylation of III with acetic anhydride and sodium acetate.

The pure Va melts at 174.6–175.3°.

Anal. Calcd. for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68; mol. wt. 344. Found: C, 76.70; H, 4.73; mol. wt. 345.

The methyl ether of V *or the ε-lactone of α-(2-hydroxy-4-methoxyphenyl)-α-(phenyl)-o-toluic acid* (Vb). A mixture of 3.02 g. of V, 1.4 g. of K_2CO_3, and 50 ml. acetone were heated for 8 hr. on a water bath of 60°. The resulting compound, recrystallized from ethanol (1 g. in 80 ml.), melted at 191.9–192.7°.

Anal. Calcd. for $C_{21}H_{16}O_3$: C, 79.73; H, 5.09; $-OCH_3$, 9.8. Found: C, 79.29; H, 5.25; $-OCH_3$, 10.0.

On heating this methylether with *N* sodium hydroxide, it gradually dissolved. On acidification, an oil separated, which could not be made to crystallize. When heating this amorphous acid to 200°, it was transformed back into Vb.

o-(2,4-dihydroxybenzhydryl)benzyl alcohol (VI). This alcohol was prepared according to the procedure given for phenolphthalol.[10] The extraction thimble was charged with 12.8 g. of III, and the flask with a solution of 5.0 g. of $LiAlH_4$ in 500 ml. pure ether. The thimble content was dissolved during the first 2 to 3 hr. of a total of 24 hr. of refluxing. The quantity of unreacted III was negligible. The oily residue, left after the evaporation of the ether, was dissolved in 200 ml. of 20% ethanol, stirring the solution while slowly cooling. The 10.4–11.2 g. of crystals (m.p. 168–169°; yield 85–91% based on III) were recrystallized from water (1 g. in 450 ml.; recovery 75–81%). The pure VI melts at 169.8–170.4°.

Anal. Calcd. for $C_{20}H_{18}O_3$: C, 78.42; H, 5.92; mol. wt. 306. Found: C, 78.47; H, 6.16; mol. wt. 320.

This alcohol is very soluble in acetone, ethanol, n-butanol, cyclohexanone; soluble in ether; insoluble in chloroform. As expected, its solution in *N* sodium hydroxide is colorless.

Triacetyl derivative of VI. A mixture of 3.06 g. of VI, 6 ml. acetic anhydride, and 0.02 ml. concd. sulfuric acid was heated for 1 hr. to 100°. The 4.1–4.4 g. dry crude acetyl derivative was placed in a thimble and extracted with pure ether. The compound crystallized from the ether in the form of fine white needles after standing for several days at 5° (yield 3.1–3.6 g., m.p. 103–105°). The pure triacetyl derivative melted at 104.1–105.5°.

Anal. Calcd. for $C_{26}H_{24}O_6$: C, 72.22; H, 5.56; mol. wt. 432. Found: C, 72.19; H, 5.29; mol. wt. 422.

Tribenzoyl derivative of VI. To a solution of 1.0 g. of VI in 2 ml. of pyridine was added 2 ml. of benzoyl chloride. The mixture was kept for 0.5 hr. at 120°, and was then poured into ice water. The gummy precipitate, washed free of pyridine, very slowly became crystalline. Recrystallized from a large amount of ethanol, it formed colorless needles, m.p. 141.1–142.2°.

Anal. Calcd. for $C_{41}H_{30}O_6$: C, 79.60; H, 4.89; mol. wt. 618. Found: C, 79.82; H, 5.07; mol. wt. 592.

Acknowledgment. The author is indebted to D. Curtin and A. Horner for experimental assistance.

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(9) C. Liebermann and L. Mamlock, *Ber.*, **38**, 1798 (1905).

(10) M. H. Hubacher, *J. Am. Chem. Soc.*, **74**, 5216 (1952).

2-Chloroprocaine Amide and 2-Chlorothiocaine

DAVID B. REISNER AND MICHAEL G. CORDASCO

Received March 21, 1958

In connection with our investigations on the biological effect of substituting halogens on the benzene ring of procaine and related compounds, we have prepared 2-chloroprocaine amide and 2-chlorothiocaine. These were secured *via* the reaction of 2-chloro-4-nitrobenzoyl chloride with β-diethylaminoethylamine and with β-diethylaminoethanethiol, respectively, and subsequent reduction with iron.

Both, 2-chloroprocaine amide and 2-chlorothiocaine, are as active as procaine as local anesthetics. 2-Chloroprocaine amide is approximately four times as potent as procaine amide in blocking artificial fibrillation in the dog.

EXPERIMENTAL[1]

N-(β-Diethylaminoethyl)-2-chloro-4-nitrobenzamide hydrochloride (I). To a solution of 0.25 mole of 2-chloro-4-nitrobenzoyl chloride, secured from the acid and thionyl chloride, in 150 ml. of dry benzene 58 g. of β-diethylaminoethylamine was added with stirring and cooling. The mixture was stirred for 20 min. at room temperature and then allowed to stand overnight at room temperature. It was stirred and heated under reflux for 1 hr., cooled, and poured into a mixture of ice and concd. hydrochloric acid (50 ml.). The aqueous layer was separated and washed with benzene. The aqueous solution was then cooled, made alkaline with sodium carbonate trihydrate (*ca.* 120 g.) and extracted with one 200-ml. and three 100-ml. portions of ether. The combined ether solutions were washed thoroughly with water, dried over anhydrous magnesium sulfate, and saturated with dry hydrogen chloride. The solid was removed by filtration, washed with ether, and air-dried. It weighed 70 g. and melted at 167–170°. Recrystallization from a mixture of ethanol and ether provided an analytical sample melting at 169–170°.

Anal. Calcd. for $C_{13}H_{19}Cl_2N_3O_3$: N, 12.50. Found: N 12.53, 12.35.

N-(β-Diethylaminoethyl)-2-chloro-4-aminobenzamide(2-chloroprocaine amide) dihydrochloride (II). A suspension of 50 g. of powdered iron in 100 ml. of water was heated to 65°, and a warm solution of 20.2 g. of I in 100 ml. of water was added slowly with stirring. The mixture was then stirred and heated for 2 hr. at *ca.* 75° and filtered while hot. The filtrate was chilled, made alkaline with 10% sodium carbonate and extracted with one 300-ml. and three 150-ml. portions of chloroform. The chloroform solutions were combined, washed with water, and dried over anhydrous magnesium sulfate. Ethanol (100 ml.) was added and mixture was treated with dry hydrogen chloride. Ether was added to the cloud point, and after chilling overnight the solid was removed and dried. It weighed 16.2 g. and melted at 190–193°. After recrystallization from ethanol with charcoal, the white crystals melted at 193–195°.

Anal. Calcd. for $C_{13}H_{22}Cl_3ON_3$: N, 12.26; Cl, 31.04. Found: N, 12.26; Cl, 31.04.

Free base (III). An aqueous solution of 25 g. of II was made alkaline with sodium carbonate and extracted with ether. The ether solution was dried over anhydrous sodium sulfate and evaporated to dryness. Recrystallization of the residue (18.7 g.) from ether gave white glistening crystals that melted at 79.5–80.5°.

Anal. Calcd. for $C_{13}H_{20}ClN_3O$: C, 57.86; H, 7.47. Found: C, 57.81; H, 7.50.

Monohydrochloride (IV). This was prepared by mixing a solution of II (3.06 g.) in 50 ml. of methanol and a solution of III (2.70 g.) in 5 ml. of benzene. The product melting at 139.5–141° was recrystallized from a mixture of methanol and ether to provide an analytical sample melting at 142–143°.

Anal. Calcd. for $C_{13}H_{21}Cl_2N_3O$: N, 13.72. Found: N, 13.70, 13.72.

Formate (V). A solution of III (2.70 g.) in 5 ml. of benzene was mixed with a solution of 0.46 g. of 98% formic acid in 5 ml. of isopropyl alcohol and ether was added to induce crystallization. The product weighing 2.40 g. and melting at 99.5–100° was recrystallized from a mixture of ethanol and ether to give an analytical sample melting at 100–100.5°.

Anal. Calcd. for $C_{14}H_{22}ClN_3O_3$: N, 13.31. Found: N, 13.34, 13.37.

N-(β-Diethylaminoethyl)-2-chloro-4-nitrothiolbenzoate hydrochloride (VI). To a solution of 2-chloro-4-nitrobenzoyl chloride, prepared from 12.1 g. of acid and 14.3 g. of thionyl chloride, in 25 ml. of dry benzene a solution of 7.98 g. of β-diethylaminoethanethiol[2] in 20 ml. of dry benzene was added with stirring and cooling. The mixture was stirred 0.5 hr. longer and then allowed to stand overnight at room temperature. It was transferred to a mixture of 150 ml. of water and 50 g. of ice. Ether (50 ml.) and benzene (50 ml.) were added, and mixture was made alkaline with ammonium hydroxide. The organic layer was separated, and the aqueous solution was washed twice with 50 ml. of ether. The combined organic solutions were washed with one 100-ml. and four 50-ml. portions of water, dried over anhydrous magnesium sulfate, and treated with dry hydrogen chloride. The hydrochloride was removed and dried. It weighed 11.85 g. and melted at 120.5–122.5°. After recrystallization from a mixture of ethanol and ether, the melting point was raised to 125–126°.

Anal. Calcd. for $C_{13}H_{18}Cl_2N_2O_3S$: N, 7.93. Found: N, 8.00.

N-(β-Diethylaminoethyl) 2 chloro-4-aminothiolbenzoate (2-chlorothiocaine) hydrochloride (VII). A solution of 2.7 g. of VI (m.p. 120.5–122.5°) in 20 ml. of distilled water was added with stirring to a mixture of 7.5 g. of iron powder and 10 ml. of distilled water preheated to 45°. The resulting mixture was stirred and heated for 1 hr. at 45° and then allowed to stand for 1 hr. at room temperature. While cooling, the *p*H was adjusted to 11 with concd. ammonium hydroxide, and the mixture was filtered. The filtrate was extracted with 50 ml. of ethyl acetate and the sludge was washed with 200 ml. of hot ethyl acetate. The combined ethyl acetate solutions were washed with three 100-ml. portions of water, dried over anhydrous magnesium sulfate, and evaporated to dryness *in vacuo*. Absolute ethanol (10 ml.) and anhydrous ether (50 ml.) were added and solution was charged with dry hydrogen chloride. The crude hydrochloride weighed 1.4 g. An analytical sample, after recrystallization from aqueous ethanol, melted at 218–219°.

Anal. Calcd. for $C_{13}H_{20}Cl_2N_2OS$: N, 8.67; Cl, 21.93. Found: N, 8.60; Cl, 21.82.

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BELLEVILLE, N. J.

(1) All melting points are uncorrected.

(2) N. F. Albertson and R. O. Clinton, *J. Am. Chem. Soc.*, 67, 1222 (1945).

Chromium Trichloride Tetrahydrofuranate[1]

W. Herwig and H. H. Zeiss

Received April 9, 1958

The reaction of anhydrous chromium trichloride and phenylmagnesium bromide in ether[2] or in tetrahydrofuran[3] is necessarily a heterogeneous one owing to the extreme insolubility of this metallic halide in organic solvents. Inorganic salts of chromium are in fact generally insoluble in all nonhydroxylic solvents; and this property presents difficulties in promoting their reactions in organic solvents with organic reagents. We have now found that the trichloride may be made soluble by complexing it with tetrahydrofuran and that its reactions with Grignard reagents proceed rapidly, quantitatively, and homogeneously in this form.

The conversion of anhydrous chromium trichloride into its tetrahydrofuranate is achieved by the continuous extraction with anhydrous tetrahydrofuran of its solid form admixed with catalytic amounts of zinc dust. In this manner the halide is quantitatively extracted by the solvent from which the violet tetrahydrofuranate is crystallized. The zinc metal which is recovered unchanged is considered to behave as a reducing agent, solubilizing chromium in its divalent form, followed by subsequent reduction itself and concurrent formation of $CrCl_3(THF)_3$.[4] The coordinating tetrahydrofuran molecules are very tightly bound in the complex, for they are not lost even upon heating of the complex to 100° at 20 mm., and the tetrahydrofuranate may be kept in the open air several hours without appreciable hydrolysis, since the crystals are only slightly hygroscopic and deliquesce quite slowly to a green hydrate. Consequently, as a reagent it may be stored indefinitely without decomposition so long as it is kept dry.

EXPERIMENTAL

Chromium trichloride tri-tetrahydrofuranate. The tetrahydrofuran (Mathieson, Coleman and Bell, b.p. 64–66°) used in this preparation was purified and dried by refluxing over sodium ribbon with fresh ribbon being added until new ribbon maintained a clean surface after 5 hr. of refluxing. Just prior to use the THF was distilled, treated with fresh sodium ribbon and with lithium aluminum hydride, and then redistilled in a stream of dry, oxygen-free nitrogen (GE lamp grade is suitable for this purpose without further drying and/or purification).

Anhydrous chromium trichloride (Fisher), 12.21 g., mixed with 0.15 g. of zinc dust, is placed in the thimble of a Soxhlet extraction apparatus and then extracted overnight with 140 ml. of boiling THF or until no further color is observable in the cycling liquid (10–15 hr.). After complete extraction only zinc dust remains in the extraction thimble, while the pot flask contains the solution of the tetrahydrofuranate (2.8 g./100 ml. of hot THF) together with the crystalline chromium trichloride tri-tetrahydrofuranate which has crystallized during extraction. Concentration, cooling, and filtration are employed to isolate the crystalline form in essentially quantitative yield.

Anal. Calcd. for $CrCl_3(C_4H_8O)_3$: Cr, 13.88; Cl, 28.39. Found: Cr, 13.42; Cl, 28.57, 28.19.

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(1) Paper VI, "π-Complexes of the Transition Metals"; Paper V, H. H. Zeiss and W. Herwig, *J. Am. Chem. Soc.*, 80, 2913 (1958).

(2) H. H. Zeiss and M. Tsutsui, *J. Am. Chem. Soc.*, 79, 3062 (1957).

(3) W. Herwig and H. H. Zeiss, *J. Am. Chem. Soc.*, 79, 5959 (1957).

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Preparation of a New Class of Steroids with Unnatural Configuration. The 19-Nor-5α,10α Series

Richard T. Rapala and Eugene Farkas

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There are four possible steric arrangements of the A/B rings of the 19-nordihydrosteroid nucleus (the *trans-syn-trans* conformation requires a boat form for ring B), all other centers of asymmetry being kept constant. The allo configurational series (5α,10β) was reported by Bowers, Ringold, and Dorfman[1] while the normal series (5β,10β) was described recently from this Laboratory.[2]

This communication reports the synthesis of a third and hitherto unknown series of 19-norsteroids, and evidence is presented which permits assignment of structure and classification as 19-nor-5α,10α-dihydrosteroids.

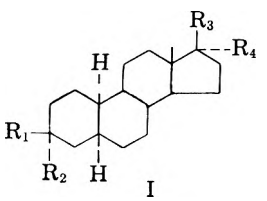
Hydrogenation of 17α - ethinyl - or 17α - ethyl-17β - estradiol with ruthenium dioxide catalyst at elevated pressures afforded a crystalline product, 17α-ethyl-5α,10α-estrane-3β,17β-diol (Ia) (m.p. 143–145°; $[\alpha]_D^{25}$ −20.9° ($CHCl_3$). Found for $C_{20}H_{34}O_2$: C, 78.11; H, 11.27) in excellent yield. Oxidation of this diol with chromic anhydride - pyridine gave 17α-ethyl-5α,10α-estran-17β-ol-3-one (IIa) (m.p. 205–207°; $[\alpha]_D^{25}$ −66.4°. Found for $C_{20}H_{32}O_2$: C, 78.67; H, 10.99).[3] Sodium and pro-

(1) A. Bowers, H. J. Ringold, and R. I. Dorfman, *J. Am. Chem. Soc.*, 79, 4556 (1957).

(2) R. T. Rapala and E. Farkas, *J. Am. Chem. Soc.*, 80, 1008 (1958).

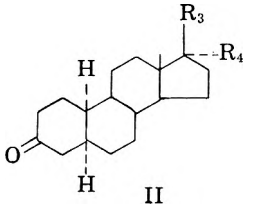
(3) All melting points are uncorrected. We gratefully acknowledge valuable technical assistance by Messr. W. Scanlon, hydrogenation experiments; Messrs. G. M. Maciak, W. L. Brown, and H. L. Hunter, elemental analysis. All rotations are done in methanol unless otherwise specified.

panol reduction of this ketone furnished 17α-ethyl-5α,10α-estrane-3α,17β-diol (Ic) (m.p. 221–223°. Found for $C_{20}H_{34}O_2$: C, 77.93; H, 11.50) (3-monoacetate, m.p. 146–147°; $[\alpha]_D^{25}$ −30.1°. Found for $C_{22}H_{36}O_3$: C, 75.59; H, 10.23) while reduction with sodium borohydride gave the original diol (Ia) (3-monoacetate, m.p. 126–127°. Found for $C_{22}H_{36}O_3$: C, 75.48; H, 10.34).



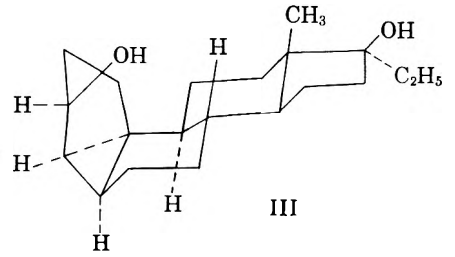
I

(a) $R_1 = R_3 = OH$, $R_2 = H$, $R_4 = C_2H_5$
(b) $R_1 = R_3 = OH$, $R_2 = R_4 = H$
(c) $R_2 = R_3 = OH$, $R_1 = H$, $R_4 = C_2H_5$



II

(a) $R_3 = OH$, $R_4 = C_2H_5$
(b) $R_3, R_4 = O$
(c) $R_3 = COCH_3$, $R_4 = H$
(d) $R_3 = OH$, $R_4 = H$



III

These assignments are supported by the following considerations: (*a*) Assuming a single period of adsorption, catalytic hydrogenation of the benzenoid ring[4] would allow for only two stereochemical products, 5β,10β and 5α,10α. (*b*) Reduction of ketone IIa with sodium - alcohol gave the more stable 3α-alcohol with the equatorial configuration. This is borne out by the fact that the 3 - monoacetate of this diol shows the simple infrared band in the 8μ region typical of equatorial acetoxy steroids.[5] (*c*) Furthermore, the 3 - monoacetate derived from the borohydride reduced ketone and the original diol (Ia) shows a complex band indicative of axial orientation. (*d*) The rotatory dispersion curve of ketone IIa is distinctive and quite different from the curves of the 3-keto allo and the normal estrane series.[2] Using an all chair conformation these results are consistent only with structure III involving an unnatural configuration at C_{10}[6] for the diol Ia.

High yields of 5α,10α-estrane-3β,17β-diol (Ib) (m.p. 179–181°. Found for $C_{18}H_{30}O_2$: C, 77.95; H, 11.09) were obtained from similar hydrogenations (RuO_2) of estrone, β-estradiol or $\Delta^{5:10}$-estraene - 17β - ol - 3 - one. Oxidation with *N* - bromoacetamide gave the corresponding dione, 5α,10α-estrane-3,17-dione (IIb) (m.p. 163-165°; $[\alpha]_D^{25}$ +27.5° (dioxane). Found for $C_{18}H_{26}O_2$: C, 78.66; H, 9.78).

Reduction of 3-hydroxy-17β-acetyl-1,3-5-estratriene gave a diol which upon oxidation yielded the related 5α,10α-dione (IIc)(m.p. 140–142°; $[\alpha]_D^{25}$ −1.0° ($CHCl_3$). Found for $C_{20}H_{30}O_2$: C, 79.22; H, 10.19).

Selective ketalization[7] of diones IIb and IIc followed by reduction and then hydrolysis gave 5α,-10α-estran-17β-ol-3-one (IId) (m.p. 192–194°; $[\alpha]_D^{25}$ −31.1°. Found for $C_{18}H_{28}O_2$: C, 77.95; H, 10.28) and 5α,10α-19-norpregnan-20β-ol-3-one (m.p. 152–154°). Found for $C_{20}H_{32}O_2$: C, 79.02; H, 10.88.

The rotatory dispersion curves[8] of the 3-monoketone derivatives are essentially identical. They differ, however, from the curves of the 3-keto, *cis* A/B (5β,10β) and the *trans* A/B (5α,10β) steroids as well as from the curves of lumistanone A, B, and C.[9]

The results of hydrogenations of 11-oxygenated 1,3,5-estratrienes, equilenin and ring B aromatic steroids to complete the series of 5α,10α analogs of the major classes of natural steroids will be reported shortly.

Added in proof. Careful R. D. determinations of these 3-keto-5α,10α-steroids in methanol, 2-propanol and dioxane confirmed the absence of any Cotton-effect while infrared analysis in methanol showed intense carbonyl absorption. Thus, this is the first example of a monoketosteroid containing the usual asymmetric centers which lacks the Cotton-effect commonly occurring in rotatory dispersion studies.

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(4) R. P. Linstead, W. E. Doering, S. B. Davis, P. Levine, and R. R. Whetstone, *J. Am. Chem. Soc.*, 64, 1985 (1942).

(5) D. H. R. Barton, *J. Chem. Soc.*, 1036 (1953).

(6) The only reported unnatural configurations at C_{10} are the C_{10}—CH_3 isomers, lumisterol and pyrocalciferol, and their reduced products. For leading references, see I. M. Heilbron, T. Kennedy, F. S. Spring, and G. Swain, *J. Chem. Soc.*, 869 (1938); J. Castells, E. R. H. Jones, R. W. J. Williams, and G. Meakins, *Proc. Chem. Soc.*, 7 (1958).

(7) E. Oliveto, C. Gerold, and E. B. Hershberg, *J. Am. Chem. Soc.*, 76, 6114 (1954).

(8) Kindly performed by M. Marsh and J. Carson of these Laboratories. Duplicate curves were obtained from two samples submitted for comparison to Wayne State University through the courtesy of Dr. E. J. Eisenbraun.

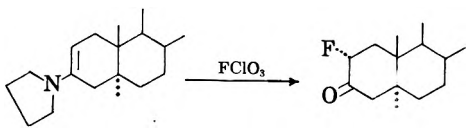
(9) We are indebted to Drs. E. R. H. Jones, G. Meakins, and C. Djerassi for making the curves available to us prior to publication.

Communications TO THE EDITOR

2α-Fluorocholestanone

Sir:

We wish to report the synthesis of a 2α-fluoro-3-ketosteroid by a novel chemical reaction, the treatment of a 3-ketosteroid enamine with perchloroyl fluoride.



Cholestan-3-one pyrrolidyl enamine[1] (3.0 g.) was dissolved in dry thiophene-free benzene (900 ml.), and perchloroyl fluoride[2] was bubbled into the orange-colored solution until the color was discharged (about 30 sec.). After washing with saturated sodium bicarbonate and then with water, the benzene was removed by evaporation at reduced pressure, and the residual yellow crystals were taken up in 100 ml. of a 1:1 mixture of benzene and petroleum ether. This solution was filtered through 10 g. of Florisil and the filtrate evaporated to dryness *in vacuo*. Recrystallization of the residue from *n*-hexane afforded 2α-fluorocholestan-3-one as colorless glistening plates, 2.0 g., 72%, m.p. 170–173° (uncorr.), $[\alpha]_D^{25}$ + 60° (c = 1.00, $CHCl_3$). *Anal.* Calcd. for $C_{27}H_{45}OF$: C, 80.15; H, 11.21; F, 4.70. Found: C, 79.83; H, 11.20; F, 4.93

The infrared spectrum of 2α-fluorocholestan-3-one (KBr pellet) was compared with that of cholestan-3-one. The position of the carbonyl band was found to have shifted from 5.88μ for cholestanone to 5.79μ for the fluorocholestanone. A rather strong band at 9.23μ was shown by the fluorocholestanone but was completely absent in the spectrum of cholestanone; this 9.23μ band, therefore, was assigned to the C—F stretching of the fluoro ketone. Otherwise the spectrum of 2α-fluorocholestan-3-one was quite similar to that of cholestan-3-one.

2α-Fluorocholestanone can be sublimed without decomposition at its melting point (170°) under 0.1 mm. Hg. pressure. This remarkable thermal stability, as well as the shift in the position of the carbonyl band by 0.09μ (26 $cm.^{-1}$),[3] indicates that the fluorine atom at position 2 is equatorial (α) and not axial (β).

Syntheses of other steroidal α-fluoroketones by the foregoing method are in progress, and the results will be discussed more completely in a forthcoming publication.

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Received August 6, 1958

(1) F. W. Heyl and M. E. Herr, *J. Am. Chem. Soc.*, 75, 1918 (1953).

(2) Pennsylvania Salt Manufacturing Co., Three Penn Center Plaza, Philadelphia 2, Pa.

(3) R. N. Jones, D. A. Ramsay, F. Herling, and K. Dobriner, *J. Am. Chem. Soc.*, 74, 2828 (1952).